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Development and Usability Testing of HEARTPA♀N: Protocol for An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

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Title: Development and Usability Testing of HEARTPA♀N: Protocol for An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

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ABSTRACT

Introduction More women experience cardiac pain related to coronary artery disease (CAD) and cardiac procedures compared to men. The overall goal of this program of research is to develop and evaluate an integrated smartphone and web-based intervention (HEARTPA♀N) to help women self-manage cardiac pain.

Methods and analysis This protocol outlines the mixed methods strategy used for the development of the HEARTPA♀N architecture (Phase 2A), usability testing (Phase 2B) and evaluation of the pilot randomized controlled trial (RCT) (Phase 3). We are using the individual and family self-management theory, mobile device functionality and pervasive information architecture of mHealth interventions, and following a similar sequential phased approach recommended by the Medical Research Council (MRC) to develop HEARTPA♀N. The Phase 3 pilot RCT will enable us to refine the prototype, inform the methodology, and calculate the sample size for a larger multi-site RCT (Phase 4, future work). Patient partners have been actively involved in setting the HEARTPA♀N research agenda, including defining patient-oriented outcome measures (PROMs) for the pilot RCT: pain and health-related quality of life (HRQoL). As such, the guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols (SPIRIT-PRO) are used to report the protocol for the pilot RCT (Phase 3). Quantitative data will be summarized using descriptive statistics (Phases 2AB, 3) and a thematic content analysis will be used to identify themes that emerge from the data (Phase 2AB). A process evaluation will be used to assess the feasibility of implementation of the intervention and a preliminary efficacy evaluation will be undertaken focusing on the outcomes of pain and HRQoL (Phase 3).

Ethics and dissemination Ethics approval was obtained from the University of Toronto (36415, November 26th, 2018). We will disseminate knowledge of HEARTPA♀N through publication,

conference presentation and national public forums (Café Scientifiques), and through fact sheets, Tweets, and webinars.

Trial Registration Number NTC03800082, containing all items from the World Health Organization Trial Registration Data Set

Strengths and limitations of this study

- Patient partners have helped to define the HEARTPA♀N research agenda
- We are using the individual and family self-management theory, mobile device functionality and the pervasive information architecture of mHealth interventions, and following the sequential phased approach recommended by the Medical Research Council (MRC) to develop and evaluate the HEARTPA♀N application
- There is a co-intervention risk, but we will track and report other strategies women use to manage their pain at home

INTRODUCTION

Coronary artery disease (CAD) differs between women and men in terms of pathophysiology/ risk, clinical presentation, diagnosis and prognosis.[1] The clinical presentation of CAD in women is much more subtle and varied compared to that of men;[1,2] this makes it difficult for women and healthcare providers (HCPs) to interpret and diagnose.[3-6] Women describe cardiac pain as sharp or burning with symptoms of breathlessness, fatigue, and discomfort in the jaw and/or shoulders.[3] Gendered roles and responsibilities for family/children cause delays in diagnosis for women and many women prefer to discuss their symptoms with family and friends before seeking assessment with their HCP or at the emergency department (ED).[7] Compared to men, women have more non-obstructive CAD[5] and a higher prevalence of clinically relevant cardiac pain/cardiac pain symptoms after PCI[8] and cardiac surgery.[9-12] Women who present with persistent and recurrent cardiac pain/cardiac pain symptoms are frequent users of health care services[13] and at risk for impaired function, depression, poor health-related quality of life (HRQoL), and death.[14]

Supporting women to recognize and manage cardiac pain and symptoms associated with CAD is vital to lower risk of major adverse cardiac events.[15] Self-management programs allow people to take an active part in the management of their own conditions[16] and are important predictors of successful behavior change.[17] In addition to reducing pain, self-management programs improve HRQoL.[18-23] A current mixed methods systematic review of self-management programs (HEARTPA♀N, *Phase 1*), which included women greater than 18 years of age with cardiac pain, found self-management interventions for cardiac pain were more effective if they included a greater proportion of women (p=0.02), goal setting (p=0.03) and collaboration/support from HCPs (p=0.01).[24] Mobile health (mHealth) technologies have been developed to help women self-manage weight,[25-29] increase physical activity,[30] monitor for perinatal depression, and assist with postpartum smoking cessation.[31] Many women view mobile health technologies as

novel and supportive,[25] and indicate these technologies motivate healthy behaviors, reduce symptoms,[32] and improve HRQoL.[32] Health app usage is on the rise,[33] yet there is little objective rigorous research evaluating outcomes of smartphone-based interventions.[34,35] The benefits of mHealth interventions in healthcare are compelling; smartphones are portable, they offer connectivity, and they provide access to women who are difficult to reach, yet no smartphone or web-based self-management program has been developed and tested with women who have cardiac pain.

OBJECTIVES

The overall goal of this program of research is to develop and systematically evaluate an integrated smartphone and web-based intervention (HEARTPA♀N) to provide evidence-informed symptom triage and self-management support to reduce pain and increase HRQoL in women with cardiac pain and cardiac pain symptoms. Specific objectives for each phase of development/evaluation include: 1) develop the HEARTPA♀N architecture (*Phase 2A*), 2) conduct usability testing (*Phase 2B*), and 3) assess feasibility in terms of implementation (accrual rates, acceptability and level of engagement) and determine an initial estimation of effectiveness outcomes (estimates of magnitude of effect) in a pilot RCT (*Phase 3*). The Phase 3 pilot study will enable us to refine the prototype, inform the methodology, and calculate the sample size for a larger multi-site RCT (*Phase 4*, future work).

METHODS AND ANALYSIS

Phases 2A and 2B

We are using the individual and family self-management theory,[36,37] mobile device functionality and the pervasive information architecture of mHealth interventions,[38] and following the sequential phased approach recommended by the Medical Research Council (MRC)[39-41] and used by Stinson and others[41,42] to develop HEARTPA♀N. We will develop the HEARTPA♀N

architecture and conduct usability testing (*Phases 2A* and *2B*) to ensure it is easy to use, efficient and satisfying to operate.

Study design

Focus group interviews in *Phase 2A* will assist to: 1) learn about the experiences and health care needs of women with cardiac pain from the perspectives of women and their HCPs, and 2) design content and the core architecture of HEARTPA♀N. This core architecture will include evidence-informed symptom triage algorithms to help women recognize their cardiac pain and cardiac pain symptoms and seek appropriate care. Additional functionalities will also include symptom tracking, SMART goal-setting, interactive coping skills toolbox of self-management strategies, and social support that is peer-based and/or provided by a health coach. The usability testing in *Phase 2B* will focus on user performance (ease of use, efficiency, ease of learning, and errors) and satisfaction with program content and functionality (reports, goal setting)[43]. HEARTPA♀N will be developed using key input from women with cardiac pain and cardiac pain symptoms.

Eligibility criteria for Phases 2A and 2B

Women greater than 18 years of age with obstructive/non-obstructive CAD pain and/or pain/symptoms post PCI/cardiac surgery lasting greater than 3 months are eligible to participate. All women will be required to speak and read English and will be excluded if they have severe cognitive impairment assessed using the Six-Item Screener administered by telephone or in face-to-face interview,[44,45] or major comorbid medical or psychiatric illness that could preclude their ability to participate in an interview. HCPs such as physicians and nurses who have worked in cardiology, cardiac surgery and adult multidisciplinary chronic pain clinics for at least one year will be excluded, as well as trainees, whose presence in the clinical setting is often transient.

Study setting

Phase 2A one-hour focus group interviews will be scheduled at a mutually convenient time for participants, and conducted by telephone, using ZOOM online video conferencing, or face-to-face in a location suitable to participants and free from distractions.[46] *Phase 2B* participants will complete a one-on-one observation for 60-90 minutes in a quiet room within the labs at Healthcare Human Factors in Toronto, Ontario, Canada.

Procedures

Phase 2A. Following ethics approval, a purposive sample of 30 women with obstructive (n=10)/non-obstructive (n=10)] CAD pain and post PCI/cardiac surgery pain (n=10) will be recruited for focus group interviews through cardiology, cardiac surgery and pain clinics, social media platforms (e.g., Twitter, Facebook), and through database mailouts. HCPs (n=10) will also be recruited for a separate focus group interview via letters and emails. Interested participants will contact the project coordinator, who will screen all participants as per the eligibility criteria and when eligibility is confirmed, informed consent will obtained either via mail or using a secure link to the online consent form available from the secure Hosted in Canada Surveys server (Appendix). We will use a semi-structured interview guide to explore the views, experiences and beliefs/motivations[46] of women with cardiac pain/cardiac pain symptoms and their HCPs. Interviews will be conducted by two team members experienced in conducting interviews and techniques will be used to minimize power differentials, such as establishing rapport, active listening, and relaxed body language.[47]

Phase 2B. A purposive sample of 15 women will be recruited through cardiology, cardiac surgery and pain clinics, social media platforms (e.g., Twitter, Facebook), and through database mailouts. Interested participants will contact the project coordinator, who will screen all participants as per the eligibility criteria and when eligibility is confirmed, informed consent will obtained either via mail or using a secure link to the online consent available from the Hosted in Canada Surveys

server (Appendix). Based on previous experience[48-50] and recommendations that usability testing by 3 - 5 users finds approximately 85% of interface usability problems,[51,52,74] each usability cycle will include 5 end-users (per pain type – obstructive [n=5]/non-obstructive [n=5] CAD, and pain post PCI/cardiac surgery [n=5]). Women will be provided with a brief explanation of the HEARTPA♀N intervention and then asked to move through standardized scenarios and list of features including the about you, diary, goal setting features, graphics, audio and video clips, and interactive components (reporting, symptom triage algorithms, self-management skills). We will employ a 'think aloud' approach[53] to gather insight into the way users solve problems as they move through the application and the website in a systematic way. Comments will be recorded, and the project coordinator will make field notes about any problems encountered on the Usability Testing Error and Efficiency Documentation Form. At the end of the session, participants will be asked to complete the System Usability Scale (SUS).[54] The SUS has been used across a wide range of user interfaces, including Web pages and Web applications.[55] The ten 5-point Likert questions can be scored to provide a point estimate of usability with a reported reliability of 0.85.[55] In addition, four semi-structured questions will be asked to determine users' overall impression of HEARTPA♀N, what they liked and why, what could be improved, and if anything was missing.[50] Observations will be conducted in iterative cycles. After the first cycle, changes will be made to the interface based on comments from the content analysis of the audiotapes and field notes. The revised user interface will then be evaluated in a subsequent cycle. These iterations usually require 2-3 testing cycles with each end-user group until no further comments are identified.[50,51,56]

Outcomes

We will use the information obtained from our integrated mixed methods systematic review (*Phase 1,* previously published)[24,57,58] and the results from focus group interviews (*Phase 2A*) to

discuss HEARTPA♀N design concepts with HCPs and women who have cardiac pain in four 3-4 hour consensus conference workshops with our Human Factors Designers. HEARTPA♀N will be designed for a consistent experience for women, and developed on a web-based platform, with easy access on any device with a web-browser, including smartphones and tablets.[59,60] HEARTPA♀N's web-based approach will allow for faster maintenance, easier updates to content, as well as improved accessibility for users.[61] All HEARTPA♀N content will be written at a grade 5 to 6 reading level.[62] Women with cardiac pain/cardiac pain symptoms will participate in realistic scenarios in a simulated environment (*Phase 2B*) in order to assess the appropriateness and ease of use of HEARTPA♀N prior to the *Phase 3* pilot RCT.

Phase 3

The HEARTPA♀N intervention is the first of its kind; there are no previous trials of the efficacy of such an intervention to decrease pain and improve HRQoL in women with cardiac pain. We will undertake a process and preliminary effect evaluation of the HEARTPA♀N intervention for women with cardiac pain, as guided by the MRC framework.[39-41] The guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols (SPIRIT-PRO)[63] are used to report the protocol for this pilot RCT; trial registration number NTC03800082, containing all items from the World Health Organization Trial Registration Data Set (Appendix).[64]

Study design

A two group parallel single blind pilot RCT.

Eligibility criteria

Inclusion/ exclusion criteria have been previously described (*Phases 2A and 2B*). Additional exclusion criteria will include women who participated in Phase 2A or 2B studies.

Study setting

Participants will attend one in-person session to learn about the trial, obtain informed written consent, and complete demographic, clinical and baseline measures (T1). Participants allocated to the intervention group will also learn how to use the HEARTPA♀N intervention. The intervention will be delivered on restricted password-protected applications.

Procedures

Following ethics approval, a single coordinating center (University of Toronto) will recruit women using methods described previously (*Phases 2A and 2B*). Interested participants will contact the project coordinator by telephone or email. Eligibility criteria will be confirmed, mailed or online consent (using a secure link sent to Hosted in Canada surveys server) obtained (Appendix), and an appointment for an initial study visit will be made. The project coordinator will track the number of eligible participants approached and reasons for refusal using a study log. We will use multiple methods to promote recruitment and retention, such as reimbursing participants for travel costs related to the initial study visit and reimbursing for use of their smartphone and data plan ($85) for the duration of the study. The project coordinator will send email and postcard reminders and at 3 months, participants will be telephoned (standardized script) to complete post-test measures online at home. Gift cards will be provided at study completion ($25). We anticipate minimal loss to follow-up as reported in previous pilot studies.[65] However, daily reporting for 3 months may be burdensome for women, which we will assess in our process evaluation. The project coordinator will also be available to address questions, issues, and concerns without delay and all T2 assessments will be completed online, eliminating the need for participants to return to the study center.

Randomization. Following completion of baseline measures, participants will be randomized to the control or intervention group at a 1:1 ratio in blocks of four stratified by type of cardiac pain[66,67] (obstructive CAD, non-obstructive CAD, and post PCI/cardiac surgery).

Randomization will be managed centrally using a web-based randomization service (www.randomize.net/).

Allocation. Participants allocated to the control group will receive the usual care and supports provided to women with cardiac pain, including usual clinic appointments and follow-up. With detailed informed consent procedures, it is expected that women will accept their group allocation following randomization. Participants randomized to the intervention group will consist of daily use of the HEARTPA♀N intervention, in addition to usual care, for a period of 3 months. The HEARTPA♀N intervention will be delivered on restricted password-protected applications that will permit tracking of adherence (number of logins to app and website using Google Analytics). Participants will be encouraged to log-in to the pain diary app daily (via automated alerts) over the 3-month period to complete pain diary entries and develop and track their goals related to their pain, activities, sleep, emotions and medications. Participants will be directed to the project coordinator for technical problems.

Blinding. It is not possible to blind the participants to group allocation due to the specific nature of the HEARTPA♀N intervention; however, a data analyst at the University of Toronto's Faculty of Nursing who is blinded to treatment allocation will conduct the analysis ensuring neutrality of the outcome assessment.

Outcomes

A process evaluation will be used to assess the feasibility of the implementation of the intervention. Recruitment and retention will be determined through the use of the study log, which will document each potential participant contacted, whether or not they chose to participate in the trial, reasons for non-participation, whether or not they completed follow-up assessments and reasons for dropout. Issues and/or difficulties encountered during trial implementation will be tracked. Adverse events will be recorded on an Adverse Event Form and

engagement will be assessed using Google Analytics. We will assess acceptability and satisfaction at the end of the 3-month period in all participants in the intervention group using a modified Acceptability e-Scale (AES)[68]. A preliminary efficacy evaluation will also be undertaken focusing on the outcomes of pain and HRQoL. Pain will be measured using the Brief Pain Inventory-Short Form (BPI-SF), which rates pain severity and the degree to which pain interferes with mood, sleep, and other physical activities such as work, social activity and relations with others. It has good construct validity,[69,70] reliability is reported at 0.86 to 0.91,[69] and it has detected clinically important differences.[9,65,71] HRQoL will be measured using the SF-36v2™, which contains 36 items and yields a score for each of the 8 domains of health: physical functioning, role limitations due to physical health (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (role emotional), and mental health.[72] It has an internal consistency of 0.76 to 0.94[73,74] with construct, criterion and predictive validity.[74] A participant flow diagram is included in Figure 1.

-Insert Figure 1-

Sample size

As this is a pilot trial focused on feasibility and primary evaluation of efficacy, we are not testing for statistical significance.[75] To decide on a sample size, we used the confidence interval approach based on the feasibility outcomes of recruitment and retention. For a one-sided 95% confidence interval for the proportion of women recruited and a margin of error of 0.05 (the lower bound) we would need at least 81 participants to estimate an overall recruitment rate of 0.70. A sample of n=49 would be needed to estimate an overall retention rate of 85%; however, to estimate retention separately in the intervention and control groups, we will need a total sample size of 98 (49*2). As attrition is one of our measured feasibility outcomes, we have not accounted for it in the sample size calculations.

Data management

Data will be collected using surveys and the HEARTPA♀N application, and stored on password-protected servers. The trial steering committee includes all research and Patient Advisory Committee (PAC) team members. As this is a pilot trial, there is not a separate data monitoring and safety committee.

Statistical methods

Process Evaluation. Prevalence of refusal, retention, engagement with the intervention and technical difficulties reported will be calculated, along with their 95% confidence intervals. Mean acceptability and satisfaction will be calculated from the total score of the Acceptability e-Scale, along with its standard deviation. We will record symptom descriptions and use of the symptom triage algorithms, what women did as a result of this recommendation (e.g., self-management, contact with primary HCP, ED visit). Qualitative process data collected will be analyzed using methods appropriate to the data obtained.

Primary Effect Evaluation. We will investigate the variability and sensitivity to change for outcomes of pain and HRQoL (T2-T1). We will calculate the number of participants who report clinically meaningful decreases in pain, which has been defined for the BPI-SF as a two-point difference in worst pain.[76] Variability will be estimated using the mean/median scores and standard deviation, in each group separately, at pre and post-test. Similarly, sensitivity to change will be assessed by determining the number of participants who had a clinically meaningful increase in HRQoL scores over time. Although the study will not be powered to detect significant differences, we will use multiple regression to estimate the effect of group allocation on each outcome (separately) at post-test, adjusting for baseline scores. This will help determine the magnitude and direction of effect and provide a signal of the intervention's effectiveness. The

analysis will be conducted using an intent-to-treat approach. As this is a pilot trial, no interim analyses are planned.

PATIENT AND PUBLIC INVOLVEMENT

Seven women (LC, CA, CF, DP, MP, BR, VSD) with cardiac pain form the HEARTPA♀N Patient Advisory Committee (PAC). They were actively involved in *Phase 1* of this research program (e.g., defining search terms for our systematic review) and continue to be actively involved in setting the HEARTPA♀N research agenda for *Phases 2A, 2B and 3*. This includes assisting to define the scope of the project (e.g., defining patient-reported outcome measures [PROMs] for the pilot RCT), active involvement in recruitment activities, assisting to write project quarterly newsletters, and participation in all team meetings. They will be invited to be co-presenters at scientific conference meetings and public forums (Café Scientifiques) and will assist to write lay summaries and fact sheets for each phase of our project.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the University of Toronto (36415, November 26th, 2018). Any protocol modifications will be submitted as an amendment to the University of Torontor research ethics board and to the NIH clinical trials registry NTC03800082. This is a 3-year study, Phase 2A recruitment began in March 2019. Informed consent will be obtained from all participants. To ensure privacy during the pilot RCT, all personally identifying information will be stored on a separate database from health data on the HEARTPA♀N application. Information that is sent to the smartphone or used by the reporting system will be independent of participants' personal information. No personal information will be transmitted after the initial set-up. For security issues, information that is transmitted will be sent securely via encrypted HTTPS connection, preventing interception by a third party. All electronic entries will be backed up on a central server and communication with the central database server will occur through secure Internet

connections. Only the principal investigator and project coordinator will have access to the data. We will disseminate knowledge of HEARTPA♀N through publication, conference presentation and educational national public forums (Café Scientifiques), and through fact sheets, Tweets, and webinars posted in the Women's Xchange Knowledge Translation and Exchange Centre as well as to key stakeholders and programs.

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Author Contributions The PI (Parry) and Co-PI (Clarke) will provide day-to-day oversight of the trial. The remaining co-applicants will assist as follows: REB submissions (Dhukai, Patterson, Price), recruitment (Dhukai, Cooper, Harvey, Norris, Patterson, PAC members), data collection (Bjoernnes, Dhukai, Pink, Patterson, Price), data analyses (Bjoernnes, Leegaard, Parry, Victor), and KTE (publication – trial steering committee; conference and public presentations - Parry, Bjoernnes, Clarke, Dhukai, PAC Members; website [Women's Xchange - Harvey, Price]; Tweets/Fact Sheets/Webinars – project coordinator, HSFC). The project coordinator (Leyden) will provide day-to-day management throughout all phases of this program of research. Authorship will be determined by substantive contribution to the design, conduct, interpretation across all phases of this program of research as per the International Committee of Medical Journal Editors.[77] There is no plan to utilize a professional writer.

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Competing interests None declared.

Supplemental material Consents for Phases 2A, 2B and 3.

Data sharing statement The trial protocol and full study report will be made publicly available through open access publication.

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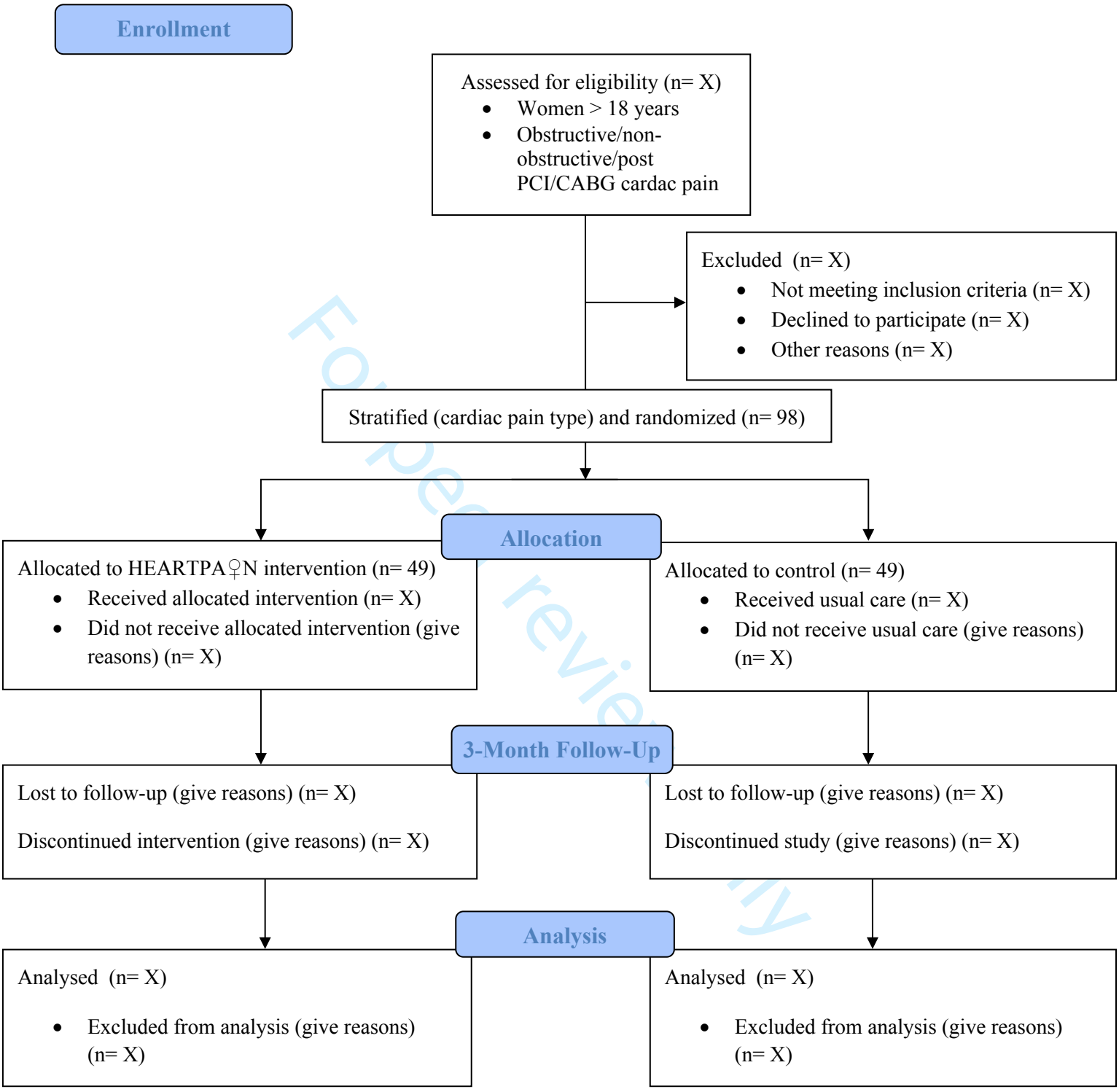
Figure 1. Anticipated participant flow through in pilot RCT.



Participant Information and Consent Form
Study 1

Principal Investigator:
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Co-Investigators:
Dr. Hance Clarke - University Health Network
Dr. Ann Kristin Bjørnnes – Oslo Metropolitan University
Dr. Joseph Cafazzo – University Health Network
Ms. Abida Dhukai – University of Toronto
Dr. Paula Harvey – Women's College Hospital
Dr. Joel Katz – York University
Dr. Chitra Lalloo – Hospital for Sick Children
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Ms. Marianne Park – Patient Advisor
Ms. Beatrice Rickard – Patient Advisor
Ms. Vincenza Spiteri DeBonis – Patient Advisor

Title of Project: Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Purpose and Background
More women die of coronary artery disease (CAD) than cancer, chronic lower respiratory disease, Alzheimer's disease, and accidents combined. Coronary artery disease is also the leading cause of death of women across all ages, and recent data show an increase in CAD incidence and deaths in

women younger than 55 years of age. Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from women is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will participate in a discussion group session (face-to-face or by free video/web conferencing) for approximately one hour that may involve 4 to 9 other women who have cardiac pain. Their cardiac pain may be similar or different from the cardiac pain that I experience. The session will be audiotaped and to protect my privacy and anonymity, my last name will not be used. All audio and transcribed files will be kept on the secure server at Bloomberg Nursing and only the PI (Parry) and Project Coordinator (Leyden) will have access to the password-protected server. Study data will be kept for seven years and then destroyed.

3. I understand that I can volunteer to participate in the 2-day consensus conference.

4. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study that there may be no direct benefits. However, I understand that by participating in this study I may have a better understanding of my cardiac pain. I may also become more aware of cardiac pain in other women.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. If I find that the discussion group upsets me, I can discuss this with the researchers who are conducting this study. I can have the option of a one-to-one telephone interview.

If you experience medical distress during a discussion group session, we ask that you let the facilitator know about your distress and medical attention will be sought.

Cost
I understand that there is no charge for participating in this study. I may incur transportation and/or parking costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation
I understand that if I need to travel within the GTA to participate in a discussion group my transportation costs will be reimbursed (e.g., TTC tokens, parking), in accordance with University of

Toronto's reimbursement to participant guidelines. I also understand if I attend the 2-day consensus conference that my transportation costs will be covered (e.g., TTC tokens, parking, economy travel), in accordance with University of Toronto's reimbursement to participant guidelines. [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided.

Confidentiality

I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.
I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

I understand that I must respect the privacy and confidentiality of other study participants. The names of others involved in this study, and any personal information discussed during the group session are to be kept strictly confidential.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw

I understand that my participation in this study is entirely voluntary and I am free to refuse to take part in the discussion group or to withdraw at any time prior to the discussion group without penalty. During the discussion group, I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly request this to be done. I also understand that during and after the discussion groups, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have questions about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and

technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____
(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____
(Signature of study personnel) (Date)

Health Care Provider Information and Consent Form
Study 1

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Phone: (416) 946 – 3561
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death of women across all ages, and recent data show an increase in CAD incidence and deaths in women younger than 55 years of age. Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from health care providers is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, and employment etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will participate in an interview session for approximately one hour, which may involve other health care providers who manage women who have cardiac pain. In this session I will be asked to describe the women I see with cardiac pain symptoms, and how I assess, manage and make decisions about their symptoms. The session will be audiotaped and to protect my privacy and anonymity, my last name will not be used.

3. I understand that I can volunteer to participate in the 2-day consensus conference.

4. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study I may have a better understanding of how others assess, manage and make decisions about cardiac pain in women. I may also become more aware of cardiac pain and cardiac pain symptoms in women.

I understand that by participating in this study that there may be no direct benefits. However, I may have a better understanding of how others assess, manage, and make decisions about cardiac pain in women. I may also become more aware of cardiac pain and cardiac pain symptoms in women.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that the focus group is difficult for me to attend, I can discuss this with the researchers who are conducting this study. I can have the option of a one-to-one telephone interview.

Cost
I understand that there is no charge for participating in this study.

Financial Compensation
I understand there is no financial compensation provided for participation in this study.

Confidentiality
I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

I understand that I must respect the privacy and confidentiality of other study participants. The names of others involved in this study, and any personal information discussed during the group session are to be kept strictly confidential.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw
I understand that my participation in this study is entirely voluntary and I am free to refuse to take part in the discussion group or to withdraw at any time prior to the discussion group without penalty. During the discussion group, I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly request this to be done. I also understand that during and after the discussion groups, it will not be possible for me to withdraw my data from the study.

Contact
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SUBJECT STATEMENT AND SIGNATURE SECTION
I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____
(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

Participant Information and Consent Form
Study 2

Principal Investigator:
Dr. Monica Parry, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto
Phone: (416) 946 – 3561
Email: women.heartpain@utoronto.ca

Co-Investigators:
Dr. Hance Clarke - University Health Network
Dr. Ann Kristin Bjørnnes – Oslo Metropolitan University
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Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will be asked to use the HEARTPAIN app and website as I work through cardiac pain scenarios and describe my experiences with HEARTPAIN. I will be observed during the session that will last for 1-1.5 hours and take place in a quiet room at the Centre for Global eHealth Innovation. At the end of the session I will be asked four short questions and asked to complete a short questionnaire. The session will be video and audio-recorded and to protect my privacy and anonymity, my last name will not be used. All video/audio and transcribed files will be kept on the secure server at Bloomberg Nursing and only the PI (Parry) and Project Coordinator (Leyden) will have access to the password-protected server. Study data will be kept for seven years and then destroyed.

3. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
Although there is no guarantee of direct benefits, I do understand that by participating in this study that I may have a better understanding of my cardiac pain.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that s cardiac pain scenario upsets me, I can discuss this with the researchers who are conducting this study. A mutually agreeable alternative scenario will be given to me.

If you experience medical distress during a scenario session, we ask that you let the facilitator know about your distress and medical attention will be sought.

Cost
I understand that there is no charge for participating in this study. I may incur transportation, parking and/or out-of-pocket costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation

I understand that my transportation and out-of-pocket expenses will be reimbursed, in accordance with University of Toronto's reimbursement to participant guidelines. Out-of-pocket expenses include, but are not limited to: ground transportation to/from session, accommodation if necessary, meals as required. [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided.

If the study results in the commercialization of this intervention, I understand that I will not be entitled to any financial benefits resulting from it.

Confidentiality

I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw

I understand that my participation in this study is entirely voluntary and I am free to refuse to take part in the usability testing or to withdraw at any time prior to the usability testing without penalty. During the usability testing, I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly request this to be done. I also understand that during and after the usability testing, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have question about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

Participant Information and Consent Form
Study 3

Principal Investigator:
Dr. Monica Parry, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto
Phone: (416) 946 – 3561
Email: women.heartpain@utoronto.ca

Co-Investigators:

Dr. Hance Clarke - University Health Network
Dr. Ann Kristin Bjørnnes – Oslo Metropolitan University
Dr. Joseph Cafazzo – University Health Network
Ms. Abida Dhukai – University of Toronto
Dr. Paula Harvey – Women's College Hospital
Dr. Joel Katz – York University
Dr. Chitra Lalloo – Hospital for Sick Children
Dr. Marit Leegaard – Oslo Metropolitan University
Dr. France Légaré - Université Laval
Dr. Judith McFetridge-Durdle – Florida State University
Dr. Michael McGillion – McMaster University
Dr. Colleen Norris – University of Alberta
Ms. Rose Patterson – Anishnawbe Health Toronto
Dr. Louise Pilote – Research Institute of the McGill University Health Centre
Ms. Leah Pink – Sinai Health System
Dr. Jennifer Price – Women's College Hospital
Dr. Jennifer Stinson – Hospital for Sick Children
Mr. J. Charles Victor – University of Toronto
Dr. Judy Watt-Watson – Lawrence S. Bloomberg Faculty of Nursing
Ms. Carol Auld – Patient Advisor
Ms. Lynn Cooper – Patient Advisor
Ms. Christine Faubert – Patient Advisor
Ms. Deborah Park – Patient Advisor
Ms. Marianne Park – Patient Advisor
Ms. Beatrice Rickard – Patient Advisor
Ms. Vincenza Spiteri DeBonis – Patient Advisor

Title of Project: Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Purpose and Background

More women die of coronary artery disease (CAD) than cancer, chronic lower respiratory disease, Alzheimer's disease, and accidents combined. Coronary artery disease is also the leading cause of

death of women across all ages, and recent data show an increase in CAD incidence and deaths in women younger than 55 years of age.Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from women is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to attend one in-person session to learn about the study, provide consent, and complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will be asked to complete two questionnaires that relate to my pain and health-related quality of life. In addition, I will be asked to fill out these same questionnaires at the end of the 3-month study. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the questionnaires.

3. I understand that there will be two groups of participants in this study: HEARTPAIN group and a control group. I will be randomly assigned (e.g., like flipping a coin) to one of these two groups. I understand that if I am assigned to the control group, I will receive the usual care and supports given to women with cardiac pain, including usual clinic appointments and follow-up. If I am assigned to the HEARTPAIN group, I will also receive the usual care and supports given to women with cardiac pain, including usual clinic appointments and follow-up. In addition, I will log-in to the pain diary app daily for 3 months to complete pain diary entries and develop and track my goals. I can also use the HEARTPAIN website to learn more about cardiac pain.

4. To ensure privacy, all my personal information (e.g., name, address, phone number) will be stored separately from the health data (e.g., risk factors, pain descriptors) that I enter on the HEARTPAIN app/website. Information that is entered in the smartphone app/website or used by the reporting system will be separate from my personal information (e.g., name, address, phone number). No personal information (e.g., name, address, phone number) will be transmitted. For security issues, I will access the app/website using a study number and all health information that is transmitted will be sent securely through an encrypted HTTPS connection that prevents interception by a third party.

5. I understand that my attendance in the HEARTPAIN study is not meant to replace my regular ongoing health care. I should not change any aspect of my regular treatment without first talking to my doctor.

6. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study I may have a better understanding of my cardiac pain.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that it is difficult for me to attend the in-person session, I can discuss this with the researchers who are conducting this study.

If you experience medical distress during the three-month app trial phase, please contact your local family doctor. If your medical distress is urgent, please call 911.

Cost
I understand that there is no charge for participating in this study. I may incur transportation, parking and/or out-of-pocket costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation
I understand that if I need to travel to attend the in-person session my transportation costs will be reimbursed, in accordance with University of Toronto's reimbursement to participant guidelines. I also understand that a gift card will be provided at study completion ($25). [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided. If I am assigned to the HEARTPAIN group I will log-in to the pain diary app daily for 3 months to complete pain diary entries and develop and track my goals. This will be done using a Smartphone. If I need a Smartphone to participate in the study, one will be provided for the duration of the study. The study will also pay for data on the phone ($85 each month). If the Smartphone gets lost/stolen/broken during the 3-month study, it will be replaced at no charge.

If the study results in the commercialization of this intervention, I understand that I will not be entitled to any financial benefits resulting from it.

Confidentiality
I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw
I understand that my participation in this study is entirely voluntary and I am free to withdraw at any time without penalty. I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly

request this to be done. I also understand that after I receive my group assignment, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have question about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

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I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

January/Janvier 22, 2018

DC0190GP

Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Notice of Decision / Avis de décision

Application Number/Numéro de la demande: 389044

Committee Code/Code du comité: KTR

Applicants/Candidats: Dr. Monica J.E. Parry Dr. Hance Alex Clarke

With/Avec:

Dr. A. Bjoernnes	Dr. J. Cafazzo	Ms. L. Cooper	Ms. A. Dhukai
Dr. P. Harvey	Dr. J. Katz	Dr. C. Lalloo	Mrs. M. Leegaard
Docteure F. Légaré	Dr. J. Mcfetridge-Durdle	Dr. M. Mcgillion	Dr. C. Norris
Ms. R. Patterson	Dr. L. Pilote	Ms. L. Pink	Dr. J. Price
Dr. J. Stinson	Mr. J. Victor	Dr. J. Watt-Watson	

Institution paid/ Établissement payé: University of Toronto

Title/Titre: Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Primary Inst./ Inst. principal: Gender and Health / Santé des femmes et des hommes

Other Related Inst./ Autres inst. connexes: Circulatory and Respiratory Health / Santé circulatoire et respiratoire

Competition Outcome/Résultats du concours: Project Grant / Subvention Projet

September/Septembre 15, 2017

Number in competition/Nbre de demandes dans le concours: 3415

Number approved/Nbre de demandes approuvées: 512

Decision on your application/ Décision sur votre demande: Approved / Approuvée

Total Funding Amount:/ Montant total du financement: $566,099

Term/Durée: **3** **yrs/ans** **0** **months/mois**

Peer Review Committee Recommendation, for your information and use/ Recommandation du comité d'examen par les pairs, pour fins d'information et d'utilisation:

Committee/Comité: Knowledge Translation Research / Recherche sur l'application des connaissances

Number reviewed/ Nbre de demandes examinées: 50

Number approved in that committee/ Nbre de demandes approuvées dans ce comité: 7

Application rank within the committee/ Rang de la demande dans ce comité: 5

Percent Rank Within the Committee/ Rang en pourcentage au sein du comité: 91.84%

Rating/ Cote: 4.38

This document is for information only. Official payment is stated on the CIHR Authorization for Funding.
Document à titre d'information seulement. Le paiement officiel est indiqué sur l'autorisation de financement des IRSC.

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Ottawa, Ontario K1A 0W9

Instituts de recherche en santé du Canada
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Ottawa (Ontario) K1A 0W9

January 22, 2018

Dr. Monica J.E. Parry
Lawrence S. Bloomberg Faculty of Nursing
University of Toronto
155 College Street, Suite 130
Toronto, Ontario M5T 1P8

Dear Dr. Parry,

On behalf of the Canadian Institutes of Health Research (CIHR), I am pleased to inform you that your application entitled "Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain", submitted to the Project Grant – Fall 2017 competition, has been approved for funding.

Your application reviews and competition results can be accessed through ResearchNet. If you are unable to view these documents, please contact us at support@cihr-irsc.gc.ca. Your Authorization for Funding will follow in the mail.

As CIHR does not notify co-applicants of the decision, we ask that you inform those individuals involved, along with their research institutions (if different from your own) of the outcome of this application.

Should you have any questions, please do not hesitate to communicate with a Processing Officer in the Contact Centre at 613-954-1968 or by e-mail: support@cihr-irsc.gc.ca.

Congratulations on your success in this competition.

Sincerely,

Martine Lafrance

Martine Lafrance, Ph.D.
Manager, Project Grant Program
Program Design and Delivery Branch

466593-201709PJT-KTR-389044-102113-DLPJT

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January 22, 2018

Dr. Monica J.E. Parry
Lawrence S. Bloomberg Faculty of Nursing
University of Toronto
155 College Street, Suite 130
Toronto, Ontario M5T 1P8

Dear Dr. Parry,

Congratulations on your success in the recent Canadian Institutes of Health Research (CIHR) Project Grant - Fall 2017 competition.

Your application was reviewed by your peers and considered to be of exceptionally high quality. You should take great pride in this achievement, particularly given the highly competitive nature of CIHR funding. As you know, peer review is the cornerstone of our research funding system. This process is made possible because of the volunteerism of individuals who generously gave their time to review your application. We are continuously recruiting and retaining the most accomplished innovative and creative scientists to review health research proposals. As a CIHR-funded researcher, you are encouraged to participate should you be invited to serve in the peer review process for future competitions.

To highlight your achievements and to communicate the value of health research to Canadians, we encourage you to work with your institution to promote your research. To support you in this activity, CIHR has developed guidelines on public communication available at: www.cihr-irsc.gc.ca/e/30789.html.

Once again, I offer you my congratulations and best wishes for success in your research.

Yours sincerely,

Roderick R. McInnes

Roderick R. McInnes, CM, OOnt, MD, PhD
Acting President

466667-201709PJT-KTR-389044-102113-CLPJT

SPIRIT and SPIRIT-PRO reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	11
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors. **SPIRIT-PRO Elaboration/Extension**: Specify individual(s) responsible for the PRO content of the trial protocol	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 17
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15, 18

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention. **SPIRIT-PRO Elaboration/Extension:** Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies	6-7, 11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	13
Objectives	#7	Specific objectives or hypotheses. **SPIRIT-PRO Elaboration/Extension:** State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	11
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). **SPIRIT-PRO Elaboration/Extension:** Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample	8, 11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13, 14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. **SPIRIT-PRO Elaboration/Extension:** Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest	13, 14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended. **SPIRIT-PRO Elaboration/Extension:** Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized	13, 14 Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. **SPIRIT-PRO Elaboration/Extension:** When a PRO is the primary endpoint, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample is not established based on the PRO endpoint, then discuss the power of the principal PRO analyses	14

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9, 11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12, 13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12, 13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12, 13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. **SPIRIT-PRO Elaboration/Extension:** Justify the PRO	13, 14

		instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned. Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other). Specify if more than one language version will be used and state whether translated versions have been developed using currently recommended methods. When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. **SPIRIT-PRO Elaboration/Extension:** Specify PRO data collection and management strategies for minimizing avoidable missing data. Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. **SPIRIT-PRO Elaboration/Extension:** State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error	15, 16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods	

missing data		to handle missing data (eg, multiple imputation). **SPIRIT-PRO Elaboration/Extension:** State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15, 16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct. **SPIRIT-PRO Elaboration/Extension:** State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form	13, 14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 10, 12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15, 16, 17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Appendix
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Appendix 17
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

Calvert M, Kyle D, Mercieca-Bebber R, Slade A, Chan AW, King MT, and the SPIRIT-PRO Group. Guidelines for the Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols, The SPIRIT-PRO Extension. JAMA. 2018; 319(5):483-494.

BMJ Open

Development and Usability Testing of HEARTPA♀N: Protocol for a Mixed Methods Strategy to Develop an Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033092.R1
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Title: Development and Usability Testing of HEARTPA♀N: Protocol for a Mixed Methods Strategy to Develop an Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

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ABSTRACT

Introduction More women experience cardiac pain related to coronary artery disease (CAD) and cardiac procedures compared to men. The overall goal of this program of research is to develop an integrated smartphone and web-based intervention (HEARTPA♀N) to help women recognize and self-manage cardiac pain.

Methods and analysis This protocol outlines the mixed methods strategy used for the development of the HEARTPA♀N content/core feature-set (Phase 2A), usability testing (Phase 2B) and evaluation with a pilot randomized controlled trial (RCT) (Phase 3). We are using the individual and family self-management theory, mobile device functionality and pervasive information architecture of mHealth interventions, and following a sequential phased approach recommended by the Medical Research Council (MRC) to develop HEARTPA♀N. The Phase 3 pilot RCT will enable us to refine the prototype, inform the methodology, and calculate the sample size for a larger multisite RCT (Phase 4, future work). Patient partners have been actively involved in setting the HEARTPA♀N research agenda, including defining patient-oriented outcome measures (PROMs) for the pilot RCT: pain and health-related quality of life (HRQoL). As such, the guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols (SPIRIT-PRO) are used to report the protocol for the pilot RCT (Phase 3). Quantitative data (e.g., demographic and clinical information) will be summarized using descriptive statistics (Phases 2AB, 3) and a content analysis will be used to identify themes (Phase 2AB). A process evaluation will be used to assess the feasibility of the implementation of the intervention and a preliminary efficacy evaluation will be undertaken focusing on the outcomes of pain and HRQoL (Phase 3).

Ethics and dissemination Ethics approval was obtained from the University of Toronto (36415, November 26th, 2018). We will disseminate knowledge of HEARTPA♀N through publication, conference presentation and national public forums (Café Scientifiques), and through fact sheets,

Tweets, and webinars.

Trial Registration Number NCT03800082 (Date of Registration January 11, 2019)

Strengths and limitations of this study

- Robust methods guided by the individual and family self-management theory, mobile device functionality, and the sequential phased approach recommended by the Medical Research Council (MRC)
- Sustainable HEARTPA♀N design and development based on the real needs of women with oversight by a Patient partner Advisory Committee (PAC)
- Extensive recruitment and solid retention strategies using gender and culturally sensitive research methods
- Larger pilot RCT focused on feasibility and primary evaluation of efficacy will increase precision of estimates and provide robust data to inform the design of a future full-scale RCT

INTRODUCTION

Cardiac pain is a key symptom of coronary artery disease (CAD) and acute coronary syndrome (ACS). Women have a varied pattern and distribution of cardiac pain and/or cardiac pain symptoms associated with both obstructive (macrovascular) and non-obstructive (microvascular) CAD. Women with obstructive CAD are usually 7 to 10 years older than men[1] and present with coronary atherosclerosis and risk of atherosclerotic plaque rupture and/or erosion[2]. Compared to men, women with obstructive CAD who undergo a percutaneous coronary intervention (PCI)[3] and/or cardiac surgery[4-6] have more persistent pain of moderate to severe intensity[7]. The origin of this pain is complex, and thought to be pathophysiologic (e.g., scar tissue, damage to intercostal nerves) and/or psychological (e.g., anxiety) in origin[8]. Non-obstructive CAD is cardiac pain without evidence of coronary artery obstruction[9], defined as less than a 50% epicardial coronary lesion on angiography[10]. Coronary microvascular dysfunction/coronary spasm and coronary micro embolism also contribute to ischemia in non-obstructive CAD[11]. Recent evidence suggests that up to 67% of women who present with cardiac pain and/or cardiac pain symptoms have ischemia related to non-obstructive CAD[12]. Non-obstructive CAD is more prevalent in younger, middle-aged women and evidence suggests that more extensive, non-obstructive CAD is associated with major adverse events (MACE) similar to those with obstructive CAD[13]. Obstructive/non-obstructive CAD is the leading cause of death of women across all ages, and recent data show an increase in CAD incidence and deaths among women 45 to 54 years of age[14].

Many women describe typical obstructive and non-obstructive cardiac pain as tight, heavy and dull with additional symptoms that include nausea and palpitations[15], and/or dyspnea, weakness and unusual fatigue[16]. Women also report that their cardiac pain is more likely to radiate to their left arm, back and/or jaw and neck[15]. Women describe persistent post-sternotomy pain as aching, tender and exhausting[17]. This varied pattern and distribution of symptoms make it

difficult for women to interpret as cardiac-related (i.e., obstructive/non-obstructive or post PCI/cardiac surgery)[13,18,19]. Women also minimize symptoms, prefer to consult with family and friends, have caring responsibilities and concerns for their family[20]. As a result, women delay seeking appropriate care for their cardiac pain[21]. The time from symptom onset to emergency department (ED) arrival for women is 85 to 320 minutes, this has not changed in the last decade[22].

Women with cardiac pain due to obstructive/non-obstructive CAD and/or post PCI/cardiac surgery pain are frequent users of health care services[23] and at risk for impaired function, depression, poor health-related quality of life (HRQoL), and death[24]. Women have been historically underrepresented in cardiovascular clinical trials[25,26], with much of the current evidence comparing cardiac pain and/or cardiac pain symptoms in women to men. There is little evidence focused on interventions to assist women to recognize and manage cardiac pain and/or cardiac pain symptoms[27]. Self-management interventions allow people to take an active part in the management of their own conditions[28] and are important predictors of successful behavior change[29]. In addition to reducing pain, self-management interventions improve HRQoL[30-35]. A current mixed methods systematic review of self-management programs (HEARTPA♀N, *Phase 1*), which included women greater than 18 years of age with cardiac pain, found self-management interventions for cardiac pain were more effective if they included a greater proportion of women (p=0.02), goal setting (p=0.03) and collaboration/support from health care providers (HCPs) (p=0.01)[36]. Mobile health (mHealth) technologies have been developed to help women self-manage weight[37-41], increase physical activity[42], monitor for perinatal depression, and assist with postpartum smoking cessation[43]. Many women view mobile health technologies as novel and supportive[37], and indicate these technologies motivate healthy behaviors, reduce symptoms[44], and improve HRQoL[44]. Health app usage across all ages is on the rise[45,46], yet there is little objective

rigorous research evaluating outcomes of smartphone-based interventions[47]. The benefits of mHealth interventions in healthcare are compelling; smartphones are portable, they offer connectivity, and they provide access to women who are difficult to reach, yet no smartphone or web-based self-management program has been developed and tested with women who have cardiac pain and/or cardiac pain symptoms.

OBJECTIVES

The overall goal of this program of research is to develop and systematically evaluate an integrated smartphone and web-based intervention (HEARTPA♀N) to provide evidence-informed symptom triage and self-management support to reduce pain and increase HRQoL in women with cardiac pain and/or cardiac pain symptoms. Specific objectives for each phase of development/evaluation include: 1) develop the HEARTPA♀N content and core feature-set (*Phase 2A*), 2) conduct usability testing (*Phase 2B*), and 3) assess feasibility in terms of implementation (accrual rates, acceptability and level of engagement) and determine an initial estimation of effectiveness outcomes (estimates of magnitude of effect) in a pilot RCT (*Phase 3*). The Phase 3 pilot study will enable us to refine the prototype, inform the methodology, and calculate the sample size for a larger multisite RCT (*Phase 4*, future work).

METHODS AND ANALYSIS

Phases 2A and 2B

We are using the individual and family self-management theory[48,49], mobile device functionality and the pervasive information architecture of mHealth interventions[50], and following the sequential phased approach recommended by the Medical Research Council (MRC)[51-53] and used by Stinson and others[53,54] to develop HEARTPA♀N. We will develop the HEARTPA♀N content/core feature-set and conduct usability testing (*Phases 2A* and *2B*) to ensure it is easy to use, efficient and satisfying to operate.

Study design

Focus group interviews in *Phase 2A* will assist to: 1) learn about the experiences and health care needs of women with cardiac pain/cardiac pain symptoms from the perspectives of women, 2) design content and the core feature-set of HEARTPA♀N, and 3) validate the HEARTPA♀N triage algorithms with health care providers (HCPs). This feature-set will include evidence-informed symptom triage algorithms to help women recognize their cardiac pain/cardiac pain symptoms and seek appropriate care. The usability testing in *Phase 2B* will focus on user performance (ease of use, efficiency, ease of learning, and errors) and satisfaction with program content and functionality (reports, goal setting)[55].

Eligibility criteria

Women living in Canada greater than 18 years of age with obstructive/non-obstructive CAD pain and/or pain post PCI/cardiac surgery lasting greater than 3 months. All women will be required to speak and read English and will be excluded if they have severe cognitive impairment assessed using the Six-Item Screener administered by telephone or in face-to-face interview[56,57], or major comorbid medical or psychiatric illness that could preclude their ability to participate in an interview. HCPs will include physicians and nurses/nurse practitioners who have worked in cardiology, family medicine, or in an emergency department (ED) for at least one year; trainees, whose presence in the clinical setting is often transient will be excluded.

Study setting

Phase 2A one-hour focus group interviews will be scheduled at a mutually convenient time for participants, and conducted by telephone, using ZOOM online video conferencing technology, or face-to-face in a location suitable to participants and free from distractions[58]. *Phase 2B* participants will complete a one-on-one observation for 60-90 minutes in a quiet room within the labs at Healthcare Human Factors in Toronto, Ontario, Canada.

Procedures

Phase 2A. Following ethics approval, a purposive sample of women with obstructive (n=10)/non-obstructive (n=10)] CAD pain and post PCI/cardiac surgery pain (n=10) will be recruited for focus group interviews through cardiology, cardiac surgery and pain clinics, and using social media platforms (e.g., Twitter, Facebook). HCPs (n=10) will also be recruited for a separate focus group interview via letters and emails. We will use a semi-structured interview guide to explore the views, experiences and beliefs/motivations[58] of women with cardiac pain. We will also use a semi-structured interview guide to validate the triage algorithms with HCPs. Interviews will be conducted by two team members experienced in conducting interviews and techniques will be used to minimize power differentials, such as establishing rapport, active listening, and relaxed body language[59].

Phase 2B. Based on previous experience[60-62] and recommendations that usability testing by 3 - 5 users finds approximately 85% of interface usability problems[63,64], each usability cycle will include 5 end-users (per pain type – obstructive [n=5]/non-obstructive [n=5] CAD, and pain post PCI/cardiac surgery [n=5]). Women will be provided with a brief explanation of the HEARTPA♀N intervention and then asked to move through standardized scenarios and list of features including the about you, event profile, goal setting features, graphics, audio and video clips, and interactive components (reporting, symptom triage algorithms, self-management skills). We will employ a 'think aloud' approach[65] to gather insight into the way users solve problems as they move through the application in a systematic way. Comments will be recorded, and the project coordinator will make field notes about any problems encountered on the Usability Testing Error and Efficiency Documentation Form. At the end of the session, participants will be asked to complete the System Usability Scale (SUS)[66]. The SUS has been used across a wide range of user interfaces, including Web pages and Web applications[67]. The ten

5-point Likert questions can be scored to provide a point estimate of usability with a reported reliability of 0.85[67]. In addition, four semi-structured questions will be asked to determine users' overall impression of HEARTPA♀N, what they liked and why, what could be improved, and if anything was missing[62]. Observations will be conducted in iterative cycles. After the first cycle, changes will be made to the interface based on comments from the content analysis of the audiotapes and field notes. The revised user interface will then be evaluated in a subsequent cycle. These iterations usually require 2-3 testing cycles with each end-user group until no further comments are identified[62,63,68].

Outcomes

We will use the summary matrix from our integrated mixed methods systematic review (*Phase 1*)[36] and the results from focus group interviews (*Phase 2A*) to discuss HEARTPA♀N designs with women who have cardiac pain in a consensus workshop with our Human Factors Designers. HEARTPA♀N will be designed for a consistent experience for women, and developed on a web-based platform, with easy access on any device with a web-browser, including smartphones and tablets[69,70]. HEARTPA♀N's web-based approach will allow for faster maintenance, easier updates to content, as well as improved accessibility for users[71]. All HEARTPA♀N content will be written at a grade 5 to 6 reading level[72], and communication with a central database server will occur through secure Internet connections. Women with cardiac pain will be able to participate in realistic scenarios in a simulated environment (*Phase 2B*) in order to assess the appropriateness and ease of use of HEARTPA♀N prior to the *Phase 3* pilot RCT.

Phase 3

The HEARTPA♀N intervention is the first of its kind; there are no previous trials of the efficacy of such an intervention to decrease pain and improve HRQoL in women with cardiac pain/cardiac pain symptoms. We will undertake a process and preliminary effect evaluation of the

HEARTPA♀N intervention for women with cardiac pain, as guided by the MRC framework[51-53]. The guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols (SPIRIT-PRO) are used to report the protocol for this pilot RCT.

Study design

A two group parallel single blind pilot RCT.

Eligibility criteria

Inclusion/ exclusion criteria have been previously described (*Phases 2A and 2B*). Additional exclusion criteria will include women who participated in Phase 2A or 2B studies.

Study setting

Participants will attend one in-person session to learn about the trial, obtain informed written consent, and complete demographic, clinical and baseline measures (T1). Participants allocated to the intervention group will also learn how to use the HEARTPA♀N intervention. The intervention will be delivered on restricted password-protected applications.

Procedures

Following ethics approval, a single coordinating center (University of Toronto) will recruit women using methods described previously (*Phases 2A and 2B*). Interested participants will contact the project coordinator by telephone or express their interest using the HEARTPA♀N website. Eligibility criteria will be confirmed, verbal consent obtained, and an appointment for an initial study visit will be made. The project coordinator will track the number of eligible participants approached and reasons for refusal using a study log. We will use multiple methods to promote recruitment and retention, such as reimbursing participants for travel costs related to the initial study visit and reimbursement for use of their smartphone and data plan ($85) for the duration of the study. The project coordinator will send email and postcard reminders and at 3 months, participants will be telephoned (standardized script) to complete post-test measures

online at home. Gift cards will be provided at study completion ($25). We anticipate minimal loss to follow-up as reported in previous pilot studies[73]. However, logins every one to two days for 3 months may be burdensome for women, which we will assess in our process evaluation. The project coordinator will also be available to address questions, issues, and concerns without delay and all T2 assessments will be completed online, eliminating the need for participants to return to the study center.

Randomization. Following completion of baseline measures, participants will be randomized to the control or intervention group at a 1:1 ratio in blocks of four stratified by type of cardiac pain[74,75] (obstructive CAD, non-obstructive CAD, and post PCI/cardiac surgery). Randomization will be managed centrally using a web-based randomization service (www.randomize.net/).

Allocation. Participants allocated to the control group will receive the usual care and supports provided to women with cardiac pain/cardiac pain symptoms, including usual clinic appointments and follow-up. With detailed informed consent procedures, it is expected that women will accept their group allocation following randomization. Participants randomized to the intervention group will consist of use of the HEARTPA♀N intervention every one to two days, in addition to usual care, for a period of 3 months. The HEARTPA♀N intervention will be delivered on restricted password-protected applications that will permit tracking of adherence (number of logins to app and website using Google Analytics). Participants will be encouraged to log-in to HEARTPA♀N every one to two days (via automated alerts) over the 3-month period to develop and track goals related to pain, activities, sleep, and emotions. Participants will be directed to the project coordinator for technical problems.

Blinding. It is not possible to blind the participants to group allocation due to the specific nature of the HEARTPA♀N intervention; however, a data analyst at the University of Toronto's

Faculty of Nursing who is blinded to treatment allocation will conduct the analysis ensuring neutrality of the outcome assessment.

Outcomes

A process evaluation will be used to assess the feasibility of the implementation of the intervention. Recruitment and retention will be determined through the use of the study log, which will document each potential participant contacted, whether or not they chose to participate in the trial, reasons for non-participation, whether or not they completed follow-up assessments and reasons for dropout. Issues and/or difficulties encountered during trial implementation will be tracked. Adverse events will be recorded on an Adverse Event Form and engagement will be assessed using Google Analytics. We will assess acceptability and satisfaction at the end of the 3-month period in all participants in the intervention group using a modified Acceptability e-Scale (AES)[76]. A preliminary efficacy evaluation will also be undertaken focusing on the outcomes of pain and HRQoL. Pain will be measured using the Brief Pain Inventory-Short Form (BPI-SF), which rates pain severity and the degree to which pain interferes with mood, sleep, and other physical activities such as work, social activity and relations with others. It has good construct validity[77,78], reliability is reported at 0.86 to 0.91[77], and it has detected clinically important differences[4,73,79]. HRQoL will be measured using the SF-36v2™, which contains 36 items and yields a score for each of the 8 domains of health: physical functioning, role limitations due to physical health (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (role emotional), and mental health[80]. It has an internal consistency of 0.76 to 0.94[81,82] with construct, criterion and predictive validity[82]. A participant flow diagram is included in Figure 1.

-Insert Figure 1-

Sample size

As this is a pilot trial focused on feasibility and primary evaluation of efficacy, we are not testing for statistical significance[83]. To decide on a sample size , we used the confidence interval approach based on the feasibility outcomes of recruitment and retention. For a one-sided 95% confidence interval for the proportion of women recruited and a margin of error of 0.05 (the lower bound) we would need at least 81 participants to estimate an overall recruitment rate of 0.70. A sample of n=49 would be needed to estimate an overall retention rate of 85%; however, to estimate retention separately in the intervention and control groups, we will need a total sample size of 98 (49*2). As attrition is one of our measured feasibility outcomes, we have not accounted for it in the sample size calculations.

Data management

Data will be collected using the HEARTPA♀N application, as well as surveys and stored on a password-protected server. The trial steering committee includes all research and PAC team members. As this is a pilot trial, there is not a separate data monitoring and safety committee.

Statistical methods

Process Evaluation. Prevalence of refusal, retention, engagement with the intervention and technical difficulties reported will be calculated, along with their 95% confidence intervals. Mean acceptability and satisfaction will be calculated from the total score of the Acceptability e-Scale, along with its standard deviation. We will record symptom descriptions and use of the symptom triage algorithms, what women did as a result of this recommendation (e.g., self-management, contact with primary HCP, ED visit). Qualitative process data collected will be analyzed using methods appropriate to the data obtained.

Primary Effect Evaluation. We will investigate the variability and sensitivity to change for outcomes of pain and HRQoL (T2-T1). We will calculate the number of participants who report clinically meaningful decreases in pain, which has been defined for the BPI-SF as a two-

point difference in worst pain[84]. Variability will be estimated using the mean/median scores and standard deviation, in each group separately, at pre and post-test. Similarly, sensitivity to change will be assessed by determining the number of participants who had a clinically meaningful increase in HRQoL scores over time. Although the study will not be powered to detect significant differences, we will use multiple regression to estimate the effect of group allocation on each outcome (separately) at post-test, adjusting for baseline scores. This will help determine the magnitude and direction of effect and provide a signal of the intervention's effectiveness. The analysis will be conducted using an intent-to-treat approach. As this is a pilot trial, no interim analyses are planned.

PATIENT AND PUBLIC INVOLVEMENT

Seven women (LC, CA, CF, DP, MP, BR, VSD) with cardiac pain formed the HEARTPA♀N PAC. They were actively involved in *Phase 1* of this research program (e.g., defining search terms for our systematic review) and continue to be actively involved in setting the HEARTPA♀N research agenda for *Phases 2A, 2B and 3*. This includes assisting to define the scope of the project (e.g., defining patient-reported outcome measures [PROMs] for the pilot RCT), active involvement in recruitment activities, assisting to write project quarterly newsletters, and participation in all team meetings. They will be invited to be co-presenters at scientific conference meetings and public forums (Café Scientifiques) and will assist to write lay summaries and fact sheets for each phase of our project.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the University of Toronto (36415, November 26th, 2018). This is a 3-year study, Phase 2A recruitment began in March 2019. Informed consent will be obtained on participants (Supplementary material). To ensure privacy during the pilot RCT, all personally identifying information will be stored on a separate database from health data on the app.

Information that is sent to the smartphone or used by the reporting system will be independent of their personal information. No personal information will be transmitted after the initial set-up. For security issues, information that is transmitted will be sent securely via encrypted HTTPS connection, preventing interception by a third party. All electronic entries will be backed up on a central server and communication with the central database server will occur through secure Internet connections. Only the principal investigator and project coordinator will have access to the data. We will disseminate knowledge of HEARTPA♀N through publication, conference presentation and educational national public forums (Café Scientifiques), and through fact sheets, Tweets, and webinars posted in the Women's Xchange Knowledge Translation and Exchange Centre as well as to key stakeholders and programs.

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Contributors The PI (Parry) and Co-PI (Clarke) conceived the study. Co-PIs (Bjørnnes, Cafazzo, Cooper, Dhukai , Harvey, Katz, Lalloo, Leegaard, Légaré, McFetridge-Durdle, McGillion, Norris, Patterson, Pilote, Pink, Price, Stinson, Victor, Watt-Watson, Auld, Faubert, D Park, M Park, Rickard, Spiteri DeBonis) contributed to the study design and are assisting with study implementation across Phases 2A, 2B and 3. All authors are grant holders except our Human Factors Designers: Lovas, Parent and Uddin. Our Human Factors Designers (Lovas, Parente and Uddin) are involved in Phases 2A/2B (HEARTPA♀N content and core feature-set/usability testing) and have contributed to writing these components of the manuscript. Cafazzo, Lalloo and Stinson provided methodological expertise on mobile device functionality and the sequential phased approach to developing the HEARTPA♀N application. Leegaard, Bjørnnes and Victor provided methodological expertise: Leegaard and Bjørnnes will lead all qualitative analyses and Victor will lead the primary statistical analysis of the pilot RCT. Seven women (Cooper, Auld, Faubert, D Park, M Park, Rickard, Spiteri DeBonis) with cardiac pain formed the HEARTPA♀N PAC and are Co-PIs. Harvey, Légaré, Norris, Price and Pilote will inform and assist to validate our triage algorithms. All other authors will assist to build and/or approve content for the HEARTPA♀N application (Parry, Clarke, Dhukai, Katz, McFetridge-

Durdle, McGillion, Patterson, Pink, Watt-Watson). All authors approved the final manuscript prior to submission and are accountable for all aspects in ensuring accuracy and integrity of work across all phases of the study.

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Competing interests None declared.

Supplemental material. Model consent form.

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FIGURE LEGEND

Figure 1 Anticipated participant flow through in pilot RCT.

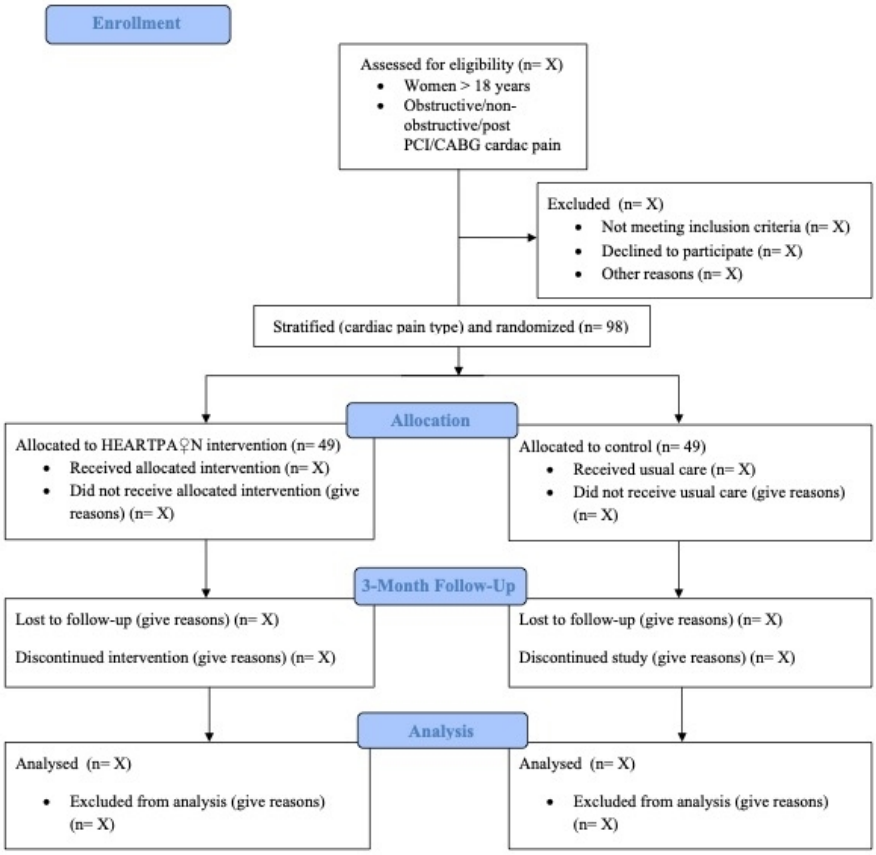

Figure 1 Anticipated participant flow through in pilot RCT.

215x279mm (72 x 72 DPI)

Participant Information and Consent Form
Study 1

Principal Investigator:
Dr. Monica Parry, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto
Phone: (416) 946 – 3561
Email: women.heartpain@utoronto.ca

Co-Investigators:

Dr. Hance Clarke - University Health Network
Dr. Ann Kristin Bjørnnes – Oslo Metropolitan University
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Ms. Abida Dhukai – University of Toronto
Dr. Paula Harvey – Women's College Hospital
Dr. Joel Katz – York University
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Ms. Deborah Park – Patient Advisor
Ms. Marianne Park – Patient Advisor
Ms. Beatrice Rickard – Patient Advisor
Ms. Vincenza Spiteri DeBonis – Patient Advisor

Title of Project: Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Purpose and Background

More women die of coronary artery disease (CAD) than cancer, chronic lower respiratory disease, Alzheimer's disease, and accidents combined. Coronary artery disease is also the leading cause of death of women across all ages, and recent data show an increase in CAD incidence and deaths in

women younger than 55 years of age. Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from women is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will participate in a discussion group session (face-to-face or by free video/web conferencing) for approximately one hour that may involve 4 to 9 other women who have cardiac pain. Their cardiac pain may be similar or different from the cardiac pain that I experience. The session will be audiotaped and to protect my privacy and anonymity, my last name will not be used. All audio and transcribed files will be kept on the secure server at Bloomberg Nursing and only the PI (Parry) and Project Coordinator (Leyden) will have access to the password-protected server. Study data will be kept for seven years and then destroyed.

3. I understand that I can volunteer to participate in the 2-day consensus conference.

4. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study that there may be no direct benefits. However, I understand that by participating in this study I may have a better understanding of my cardiac pain. I may also become more aware of cardiac pain in other women.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. If I find that the discussion group upsets me, I can discuss this with the researchers who are conducting this study. I can have the option of a one-to-one telephone interview.

If you experience medical distress during a discussion group session, we ask that you let the facilitator know about your distress and medical attention will be sought.

Cost
I understand that there is no charge for participating in this study. I may incur transportation and/or parking costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation
I understand that if I need to travel within the GTA to participate in a discussion group my transportation costs will be reimbursed (e.g., TTC tokens, parking), in accordance with University of

Toronto's reimbursement to participant guidelines. I also understand if I attend the 2-day consensus conference that my transportation costs will be covered (e.g., TTC tokens, parking, economy travel), in accordance with University of Toronto's reimbursement to participant guidelines. [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided.

Confidentiality

I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.
I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

I understand that I must respect the privacy and confidentiality of other study participants. The names of others involved in this study, and any personal information discussed during the group session are to be kept strictly confidential.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw

I understand that my participation in this study is entirely voluntary and I am free to refuse to take part in the discussion group or to withdraw at any time prior to the discussion group without penalty. During the discussion group, I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly request this to be done. I also understand that during and after the discussion groups, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have questions about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and

technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

Health Care Provider Information and Consent Form
Study 1

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death of women across all ages, and recent data show an increase in CAD incidence and deaths in women younger than 55 years of age. Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from health care providers is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, and employment etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will participate in an interview session for approximately one hour, which may involve other health care providers who manage women who have cardiac pain. In this session I will be asked to describe the women I see with cardiac pain symptoms, and how I assess, manage and make decisions about their symptoms. The session will be audiotaped and to protect my privacy and anonymity, my last name will not be used.

3. I understand that I can volunteer to participate in the 2-day consensus conference.

4. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study I may have a better understanding of how others assess, manage and make decisions about cardiac pain in women. I may also become more aware of cardiac pain and cardiac pain symptoms in women.

I understand that by participating in this study that there may be no direct benefits. However, I may have a better understanding of how others assess, manage, and make decisions about cardiac pain in women. I may also become more aware of cardiac pain and cardiac pain symptoms in women.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that the focus group is difficult for me to attend, I can discuss this with the researchers who are conducting this study. I can have the option of a one-to-one telephone interview.

Cost
I understand that there is no charge for participating in this study.

Financial Compensation
I understand there is no financial compensation provided for participation in this study.

Confidentiality

I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

I understand that if I participate in a discussion group, my anonymity will be preserved through the use of my first name only.

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I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

Participant Information and Consent Form
Study 2

Principal Investigator:
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Phone: (416) 946 – 3561
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Co-Investigators:
Dr. Hance Clarke - University Health Network
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Title of Project: Development and Usability Testing of HEARTPAIN: An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain

Purpose and Background
More women die of coronary artery disease (CAD) than cancer, chronic lower respiratory disease, Alzheimer's disease, and accidents combined. Coronary artery disease is also the leading cause of

death of women across all ages, and recent data show an increase in CAD incidence and deaths in women younger than 55 years of age. Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from women is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will be asked to use the HEARTPAIN app and website as I work through cardiac pain scenarios and describe my experiences with HEARTPAIN. I will be observed during the session that will last for 1-1.5 hours and take place in a quiet room at the Centre for Global eHealth Innovation. At the end of the session I will be asked four short questions and asked to complete a short questionnaire. The session will be video and audio-recorded and to protect my privacy and anonymity, my last name will not be used. All video/audio and transcribed files will be kept on the secure server at Bloomberg Nursing and only the PI (Parry) and Project Coordinator (Leyden) will have access to the password-protected server. Study data will be kept for seven years and then destroyed.

3. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
Although there is no guarantee of direct benefits, I do understand that by participating in this study that I may have a better understanding of my cardiac pain.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that s cardiac pain scenario upsets me, I can discuss this with the researchers who are conducting this study. A mutually agreeable alternative scenario will be given to me.

If you experience medical distress during a scenario session, we ask that you let the facilitator know about your distress and medical attention will be sought.

Cost
I understand that there is no charge for participating in this study. I may incur transportation, parking and/or out-of-pocket costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation

I understand that my transportation and out-of-pocket expenses will be reimbursed, in accordance with University of Toronto's reimbursement to participant guidelines. Out-of-pocket expenses include, but are not limited to: ground transportation to/from session, accommodation if necessary, meals as required. [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided.

If the study results in the commercialization of this intervention, I understand that I will not be entitled to any financial benefits resulting from it.

Confidentiality

I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw

I understand that my participation in this study is entirely voluntary and I am free to refuse to take part in the usability testing or to withdraw at any time prior to the usability testing without penalty. During the usability testing, I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly request this to be done. I also understand that during and after the usability testing, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have question about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

Participant Information and Consent Form
Study 3

Principal Investigator:
Dr. Monica Parry, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto
Phone: (416) 946 – 3561
Email: women.heartpain@utoronto.ca

Co-Investigators:

Dr. Hance Clarke - University Health Network
Dr. Ann Kristin Bjørnnes – Oslo Metropolitan University
Dr. Joseph Cafazzo – University Health Network
Ms. Abida Dhukai – University of Toronto
Dr. Paula Harvey – Women's College Hospital
Dr. Joel Katz – York University
Dr. Chitra Lalloo – Hospital for Sick Children
Dr. Marit Leegaard – Oslo Metropolitan University
Dr. France Légaré - Université Laval
Dr. Judith McFetridge-Durdle – Florida State University
Dr. Michael McGillion – McMaster University
Dr. Colleen Norris – University of Alberta
Ms. Rose Patterson – Anishnawbe Health Toronto
Dr. Louise Pilote – Research Institute of the McGill University Health Centre
Ms. Leah Pink – Sinai Health System
Dr. Jennifer Price – Women's College Hospital
Dr. Jennifer Stinson – Hospital for Sick Children
Mr. J. Charles Victor – University of Toronto
Dr. Judy Watt-Watson – Lawrence S. Bloomberg Faculty of Nursing
Ms. Carol Auld – Patient Advisor
Ms. Lynn Cooper – Patient Advisor
Ms. Christine Faubert – Patient Advisor
Ms. Deborah Park – Patient Advisor
Ms. Marianne Park – Patient Advisor
Ms. Beatrice Rickard – Patient Advisor
Ms. Vincenza Spiteri DeBonis – Patient Advisor

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death of women across all ages, and recent data show an increase in CAD incidence and deaths in women younger than 55 years of age.Women with CAD have cardiac pain that differs from that of men. The overall goal of this program of research is to develop and assess a HEARTPAIN app and website that will help women self-manage cardiac pain. Feedback from women is a necessary step to designing HEARTPAIN.

Procedures
If I agree to participate in this study, I understand that the following things will happen:

1. I will be asked to attend one in-person session to learn about the study, provide consent, and complete a baseline demographic form describing my age, education, employment, type and duration of cardiac pain etc. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the form.

2. I will be asked to complete two questionnaires that relate to my pain and health-related quality of life. In addition, I will be asked to fill out these same questionnaires at the end of the 3-month study. To protect my privacy and confidentiality, I will have a study ID number instead of my name on the questionnaires.

3. I understand that there will be two groups of participants in this study: HEARTPAIN group and a control group. I will be randomly assigned (e.g., like flipping a coin) to one of these two groups. I understand that if I am assigned to the control group, I will receive the usual care and supports given to women with cardiac pain, including usual clinic appointments and follow-up. If I am assigned to the HEARTPAIN group, I will also receive the usual care and supports given to women with cardiac pain, including usual clinic appointments and follow-up. In addition, I will log-in to the pain diary app daily for 3 months to complete pain diary entries and develop and track my goals. I can also use the HEARTPAIN website to learn more about cardiac pain.

4. To ensure privacy, all my personal information (e.g., name, address, phone number) will be stored separately from the health data (e.g., risk factors, pain descriptors) that I enter on the HEARTPAIN app/website. Information that is entered in the smartphone app/website or used by the reporting system will be separate from my personal information (e.g., name, address, phone number). No personal information (e.g., name, address, phone number) will be transmitted. For security issues, I will access the app/website using a study number and all health information that is transmitted will be sent securely through an encrypted HTTPS connection that prevents interception by a third party.

5. I understand that my attendance in the HEARTPAIN study is not meant to replace my regular ongoing health care. I should not change any aspect of my regular treatment without first talking to my doctor.

6. I understand that I can volunteer to participate in future studies as HEARTPAIN is developed/tested.

Potential Benefits
I understand that by participating in this study I may have a better understanding of my cardiac pain.

I understand that I can get a plain language summary of the study results by checking the box below:

☐ I would like a copy of a plain language summary of the study results sent to me in an email link.

Potential Risks
I understand that there are no known risks to participating in this study. However, there may be unforeseeable risks. If I find that it is difficult for me to attend the in-person session, I can discuss this with the researchers who are conducting this study.

If you experience medical distress during the three-month app trial phase, please contact your local family doctor. If your medical distress is urgent, please call 911.

Cost
I understand that there is no charge for participating in this study. I may incur transportation, parking and/or out-of-pocket costs and these will be reimbursed as outlined in the financial compensation section.

Financial Compensation
I understand that if I need to travel to attend the in-person session my transportation costs will be reimbursed, in accordance with University of Toronto's reimbursement to participant guidelines. I also understand that a gift card will be provided at study completion ($25). [Participant guidelines for study reimbursements: http://www.research.utoronto.ca/policies-and-procedures/compensation-and-reimbursement-of-research-participants/]. Original receipts and/or paid invoices will be required before payment is provided. If I am assigned to the HEARTPAIN group I will log-in to the pain diary app daily for 3 months to complete pain diary entries and develop and track my goals. This will be done using a Smartphone. If I need a Smartphone to participate in the study, one will be provided for the duration of the study. The study will also pay for data on the phone ($85 each month). If the Smartphone gets lost/stolen/broken during the 3-month study, it will be replaced at no charge.

If the study results in the commercialization of this intervention, I understand that I will not be entitled to any financial benefits resulting from it.

Confidentiality
I understand that information about specific individuals in this study will be kept strictly confidential and will not be available to anyone except the Principal Investigator (PI) and members of the investigative team. Only an identification number will appear on the demographic questionnaires, and therefore my responses will remain anonymous. One copy of my name and my study identification number will be kept in a locked drawer in the researcher's office. No one but Dr. Parry and the Project Coordinator will have access to the file. All information obtained in this study will be used for research purposes only. I will be able to access the results of the study from the PI when it is complete.

The research study with which you are participating may be reviewed for quality assurance to ensure that required laws and guidelines are followed. If chosen, representatives of the Human Research Ethics Program (HREP), may access study related data and/or consent materials as part of their review. All information accessed by the HREP will be upheld to the same standard of confidentiality that has been stated by the research team.

Right to Refuse or Withdraw
I understand that my participation in this study is entirely voluntary and I am free to withdraw at any time without penalty. I also understand that I can choose not to answer any given question without penalty. I understand if I withdraw from the study that my data will only be withdrawn if I explicitly

request this to be done. I also understand that after I receive my group assignment, it will not be possible for me to withdraw my data from the study.

Contact

I understand that if I have any questions about the study, I can contact Dr. Monica Parry at 416-946-3561 (Principal Investigator). I understand that if I have question about my rights as a research participant, I can contact the University of Toronto, Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273. I may keep this copy of the information and consent letter for my own reference.

SUBJECT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given enough time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form.

_____ _____

(Signature of participant) (Date)

STATEMENT OF INVESTIGATOR AND SIGNATURE SECTION

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to subjects in this study.

_____ _____

(Signature of study personnel) (Date)

SPIRIT and SPIRIT-PRO reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2, 4, 12-16, 18
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors. **SPIRIT-PRO Elaboration/Extension**: Specify individual(s) responsible for the PRO content of the trial protocol	18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2, 18
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15, 18
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention. **SPIRIT-PRO Elaboration/Extension:** Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies	6-8, 11-12
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	13
Objectives	#7	Specific objectives or hypotheses. **SPIRIT-PRO Elaboration/Extension:** State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	14
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	12
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists). **SPIRIT-PRO Elaboration/Extension:** Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample	9, 12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13, 14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. **SPIRIT-PRO Elaboration/Extension:** Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final	14, 15

		value, time to event) and the principal time point or period of interest	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended. **SPIRIT-PRO Elaboration/Extension:** Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized	12-14 Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. **SPIRIT-PRO Elaboration/Extension:** When a PRO is the primary endpoint, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample is not established based on the PRO endpoint, then discuss the power of the principal PRO analyses	14-15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who	12, 13

		enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol. **SPIRIT-PRO Elaboration/Extension:** Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the	12-15

		population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned. Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other). Specify if more than one language version will be used and state whether translated versions have been developed using currently recommended methods. When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols. **SPIRIT-PRO Elaboration/Extension:** Specify PRO data collection and management strategies for minimizing avoidable missing data. Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	12-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. **SPIRIT-PRO Elaboration/Extension:** State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error	15-16

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation). **SPIRIT-PRO Elaboration/Extension:** State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses)	15-16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct. **SPIRIT-PRO Elaboration/Extension:** State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form	13-14

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16-17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12-13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplementary Material
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	16-17

		the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

Calvert M, Kyle D, Mercieca-Bebber R, Slade A, Chan AW, King MT, and the SPIRIT-PRO Group. Guidelines for the Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols, The SPIRIT-PRO Extension. JAMA. 2018; 319(5):483-494.