PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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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VERSION 1 – REVIEW

REVIEWER	Prof dr JWMG Widdershoven Elisabeth-TweeSteden Hospital Tilburg The Netherlands
REVIEW RETURNED	21-Aug-2019

GENERAL COMMENTS	Please give definition of non obstructive heart disease. In non obstructive patients, is it cardiac pain?

REVIEWER	Emma Motrico Universidad Loyola Andalucia, Seville- Spain.
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	Thank you for inviting me to review the paper "Development and Usability Testing of HEARTPA♀N: Protocol for An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain". Comments: 1) Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods. 2) As you said in the introduction section, "Women who present with persistent and recurrent cardiac pain/cardiac pain symptoms are frequent users of health care services and at risk for impaired function, depression, poor health-related quality of life (HRQoL), and death", how are you going to evaluate impaired function and depression in the study. 3) I suggest including a discussion section in the manuscript protocol.

REVIEWER	Horesh Dor-Haim O2 Hebrew University Israel
REVIEW RETURNED	23-Nov-2019

GENERAL COMMENTS	Development and Usability Testing of HEARTPA ♀N: Protocol for An Integrated Smartphone and Web-Based Intervention for Women with Cardiac Pain The study aim is to develop and systematically evaluate an integrated smartphone and web-based intention for self-management to reduce cardiac pain symptoms in women with CAD. The study including 3 phases (qualitive and quotative) is a pilot for a larger scale future trial (phase 4). The research agenda is important in order to understand cardiac patients' symptoms and to help clinicians and care givers to better interpret and treat woman with CAD. The study architecture uses sequential phased approach recommended by the Medical Research Council (MRC). Major reviewers concerns: 1. The authors state there are differences in the symptoms and the presentation of CAD in woman compared to man. Thus, it is difficult for health care providers to interpret and diagnose the pain and symptoms in general. Diagnosis of cardiac pain is somewhat very challenging even for an experienced cardiologist. Many of the symptoms reported by patients are not related to CAD. The authors do not state how do they define cardiac pain? Moreover, in post open heart surgery patient most of the symptoms would not be cardiac. This point should addressed in the introduction, in the inclusion criteria's and limitations. 2. The authors intend to use web-based mhealth technology including evidence informed symptom triage algorithms to help women recognize their cardiac pain. The authors do not provide information about the algorithm or the symptomizers. Was it validated? When will the patients report? If not validated it should be part of the research primary goals. 3. What kind of self-management tools do the authors intend to provide the patients? Only pain-management tools? Is it going to be part of a secondary preventive program? Cardiac prevention program? Pain management tools presented without CR would consider non ethical. Minor points: 1. Please address in the exclusion criteria's technological berries mainly age related 2. Considers excluding chronic peripheral pain patients 3. Provide information about safety and risk and patients 4. provide more information about data safety of patients such as HIPAA Privacy Rules

VERSION 1 – AUTHOR RESPONSE

Reviewer#1

1. Please give definition of non-obstructive heart disease.

Response: We thank the reviewer for the comment. We have defined non-obstructive CAD as less than a 50% epicardial coronary lesion on angiography. This definition is based on the American Heart Association's Scientific Statement published in *Circulation* in April 2019. The definition is located on page 6 of the manuscript.

2. In non-obstructive patients, is it cardiac pain?
Response: Thank-you for this comment. Yes, it is cardiac pain and or cardiac pain symptoms in non-obstructive CAD. We have included information on page 6 of the manuscript to indicate that non-obstructive CAD is cardiac pain without evidence of coronary artery obstruction, defined as less than a 50% epicardial coronary lesion on angiography. Coronary microvascular dysfunction/coronary spasm and coronary micro embolism also contribute to ischemia in non-obstructive CAD, as defined in the Fourth Universal Definition of Myocardial Infarction (2018). Recent evidence also suggests that up to 67% of women who present with cardiac pain and/or cardiac pain symptoms have ischemia related to non-obstructive CAD. 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. Many women describe typical obstructive and non-obstructive cardiac pain as tight, heavy and dull with additional symptoms that include nausea and palpitations, and/or dyspnea, weakness and unusual fatigue. Women also report that their cardiac pain is more likely to radiate to their left arm, back and/or jaw and neck.

Reviewer #2

1. Please revise the 'Strengths and Limitations' section of your manuscript (after the abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods.

Response: We thank the reviewer for this recommendation and have amended the 'Strengths and 'Limitations' section to include the following five short bullet points:

- 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

2. As you said in the introduction section, "Women who present with persistent and recurrent cardiac pain/cardiac pain symptoms are frequent users of health care services and are at risk for impaired function, depression, and poor health-related quality of life (HRQoL) and death". How are you going to evaluate impaired function and depression in the study?

Response: Thank-you for this valuable comment. Function and depression are important outcomes for women with persistent and recurrent cardiac pain/cardiac pain symptoms. We are undertaking a process and preliminary effect evaluation of the HEARTPA♀N intervention for women with cardiac pain, as guided by the MRC framework. Our primary objective in Phase 3 is to determine the feasibility of implementing an RCT of the HEARTPA♀N intervention. We will conduct a process evaluation to examine: 1) the feasibility of randomization, recruitment and retention, 2) acceptability and barriers to implementing the intervention (including the symptom triage algorithms), and 3) the extent of engagement with the intervention. We will also undertake a preliminary efficacy evaluation of our primary outcomes. Based on our theorized mechanism of change, we hypothesize that the HEARTPA♀N intervention will reduce pain and improve health-related quality of life (HRQoL) (primary outcomes). We will assess the variability and sensitivity to change for both outcomes. We will not use separate measure for function or depression in this pilot trial. However, we have chosen the use the SF36v2™ to measure HRQoL. Sensitivity to change will be assessed by determining the number of participants who had a clinically meaningful increase in HRQOL scores over time, which has been defined for the SF-36v2™ among patients with chronic heart disease, as the following: ≥15 points in physical functioning, general health and mental health; ≥16.7 in role emotional functioning; ≥18.5

points in role physical functioning and vitality; ≥20 points in bodily pain; and ≥25 points in social functioning. 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), adjusting for baseline scores and providing us with some information on the physical and mental function of participants. This will help determine the magnitude and direction of effect and provide a signal of the intervention's effectiveness, which can be evaluated in Phase 4. In addition, cost (direct [out-of-pocket] and indirect [time] costs related to medications/supplies and physician, clinic and hospital visits) will be measured using the Ambulatory and Home Care Record in our larger multi-site RCT (Phase 4, future work).

3. I suggest including a discussion section in the manuscript protocol.
Response: Thank-you for this comment. We have followed BMJ Open guidelines for protocol manuscripts and have reported the planned phases for the development and usability Testing of HEARTPA♀N. Results and conclusions are not available. Moreover, we have used the guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial

Protocols (SPIRIT-PRO) to report the protocol for the pilot RCT (Phase 3). These guidelines do not include a discussion section. We therefore have not included a discussion section in this protocol manuscript.

Reviewer #3
1. The authors state there are differences in the symptoms and the presentation of CAD in women compared to men. Thus, it is difficult for health care providers to interpret and diagnose the pain and symptoms in general. Diagnosis of cardiac pain is somewhat very challenging even for an experienced cardiologist. Many of the symptoms reported by patients are not related to CAD. The authors do not state how they define cardiac pain? Moreover, in post open heart surgery patients most of the symptoms would not be cardiac. This point should be addressed in the introduction, in the inclusion criteria and limitations.

Response: We thank the reviewer for this comment. We have more clearly defined cardiac pain on pages 6 and 7 of the manuscript and included the following information:

"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 nonobstructive (microvascular) CAD."

"Compared to men, women with obstructive CAD who undergo a percutaneous coronary intervention (PCI) and/or cardiac surgery have more persistent pain of moderate to severe intensity. 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. Women describe persistent post-sternotomy pain as aching, tender and exhausting."

"Many women describe typical obstructive and non-obstructive cardiac pain as tight, heavy and dull with additional symptoms that include nausea and palpitations, and/or dyspnea, weakness and unusual fatigue. Women also report that their cardiac pain is more likely to radiate to their left arm, back and/or jaw and neck".

2. The authors intend to use web-based mHealth technology including evidence informed symptom triage algorithms to help women recognize their cardiac pain. The authors do not provide information about the algorithm or the symptomizers. Was it validated? When will the patients report? If not validated it should be part of the research primary goals.

Response: We thank the reviewer for this very thoughtful comment. The overall goal of this program of research is to develop and evaluate an integrated smartphone and webbased intervention (HEARTPA♀N) to help women recognize and self-manage persistent cardiac pain. It is not our intent to develop decision tools for health care providers, but we do want to ensure that women using the HEARTPA♀N intervention are not having acute cardiac pain/cardiac symptoms. Triage algorithms will be incorporated into the HEARTPA♀N intervention and these will be based on women completing an 'event' profile when they first log-in. Goldman and Kirtane (2003) suggest patients often describe their pain as similar to previous episodes of cardiac ischemia. Moreover, Ferry et al. (2019) suggest typical symptoms are more common and have greater predictive value in women compared to men; the presence of $\geq$ 3 typical features is associated with a positive likelihood ratio for the diagnosis of myocardial infarction in women (1.18; 95% CI, 1.03-1.31). Our triage algorithms are intended to assist women to assess their pain, including seeking further assessment with either their primary care provider or in the emergency department based on their symptom presentation. Phase 2A in intended to develop the algorithms, which will be validated with cardiologists, family physicians and emergency department physicians prior to usability testing (Phase 2B) and the pilot RCT (Phase 3).

3. What kind of self-management tools do the authors intend to provide the patients? Only pain-management tools? Is it going to be part of a secondary prevention program? Cardiac prevention program? Pain management tools presented without CR would be considered non ethical.

Response: The HEARTPA♀N intervention will be developed and informed by women who have cardiac pain (Phase 2A). This 3-year CIHR-funded study builds on our Phase 1 systematic review of self-management programs in women with cardiac pain. We used methods described by the Evidence for Policy and Practice Information (EPPI) and the Coordinating Centre at the Institute of Education to complete this Phase 1 2-step review. The first step in the EPPI review process involved a broad mapping and quality screening exercise to answer the overarching review question: *What is known about the selfmanagement of cardiac pain in women*? This is published in BMJ Open

(doi:10.1136/bmjopen-2017-018549). We searched several article and research databases and grey literature sources using a combination of keywords and medical subject headings. Non-pharmacologic interventions women used to self-manage cardiac pain included physical exercise and relaxation, cognitive-behavioral therapy, music, and peer support. Important aspects of pain in women focused on the accuracy and interpretation of signs and symptoms, delays in seeking care, pain interference, chronic pain, treatment compliance, and outcomes. The second step was to present results of the broad mapping and screening exercise to our Patient partner Advisory Committee (PAC) to re-confirm search terms for a more in-depth review of the literature. These results were published in the Canadian Journal of Cardiology (https://doi.org/10.1016/j.cjca.2017.12.011). Our systematic review and meta-analysis indicated that self-management interventions for cardiac pain/cardiac pain symptoms were more effective if they included a greater proportion of women, goal setting, and collaboration/support from health care providers. Two of our co-investigators (Price, Harvey) are from Women's College Hospital in Toronto, ON and are involved in the women's-only cardiac rehabilitation program. We plan on incorporating physical exercise strategies into the HEARTPA♀N intervention. These strategies are utilized by the women's-only cardiac rehabilitation program and are based on the Canadian Physical Activity Guidelines and the living well with heart disease guidelines published by the Heart and Stroke Foundation of Canada. Safety tips will be incorporated as per the guidelines and all content is being developed and reviewed by experts at the women's-only cardiac rehabilitation program at Women's College Hospital.

4. Please address in the exclusion criteria's technological barriers mainly age-related. Response: We thank the reviewer for this comment. We do not envision age to be a barrier to using the HEARTPA♀N intervention. The intervention will be an integrated smartphone and web-based intervention; accessible to women on computers, tablets or smartphones. Smartphone penetration in Canada in 2016 was s 76%. This has increased to 90% in in those 15 to 44 years of age. In fact, Statistics Canada (2017) indicated the older Canadians were the fastest-growing segment of internet users nationally. Online activity in those aged 65 to 74 increased 16% between 2013 and 2016 and 15% in those over 75 years of age. Women with cardiac pain (n=5) participated in preliminary HEARTPA♀N user design sessions; women liked the daily check-ins to track pain and mood, SMART goal setting, library, and community features. They wanted a website that offered content that could be more personalized for women, with larger screen fonts and variations in color. Women wanted self-management strategies related to breathing techniques and meditation, information presented in text and in audio, and videos of patient stories/testimonials. These women also suggested information related to cardiac pain, surgery and risk factors was needed, with links to key websites. In fact, all women who participated in our preliminary HEARTPA♀N user design sessions said they would use an integrated smartphone and web-based intervention to manage their cardiac pain. We are building on these preliminary sessions to obtain more feedback from women with cardiac pain in Phase 2A, to ensure content and accessibility meets the needs of women across all ages. We have also budgeted to provide women with smartphones for use during the pilot trial (and pay for a 3-month data plan) if they do not have a smartphone. Interested participants for our Phase 3 pilot trial will have an appointment for an initial study visit and during this visit, core functionalities of the HEARTPA♀N intervention will be reviewed.

5. Consider excluding chronic peripheral pain patients.
Response: We thank the reviewer for this comment. We will include all interested

English-speaking women greater than 18 years of age with obstructive/non-obstructive CAD pain or post PCI/cardiac surgery pain lasting greater than 3 months. Women will be excluded if they have severe cognitive impairment assessed using the Six-Item Screener administered by telephone or in face-to-face interview, or major comorbid medical or psychiatric illness that could preclude their ability to participate in an interview. Additional exclusion criteria for our Phase 3 pilot trial will also include women who participated in Phase 2A or 2B studies. As noted, non-pharmacologic self-management strategies to assist women to self-manage cardiac pain will physical exercise and relaxation, cognitive-behavioral therapy, music, and peer support (as some examples). The HEARTPA♀N intervention is personalized so that any user can choose strategies that will best help them manage cardiac-related pain, including women with chronic peripheral pain. Phase 3 is a pilot RCT designed 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 nonparticipation, whether or not they completed follow-up assessments and reasons for dropout. We will also track any issues or difficulties encountered during trial implementation, such as problems using the app. Adverse events will be recorded on the *Adverse Event Form*. Engagement will be assessed using *Google Analytics*, which will track patterns of app and website usage. We will also assess acceptability and satisfaction at the end of the 3-month period. The results of the Phase 3 trial will help us determine if the HEARTPA♀N intervention is appropriate for women with chronic peripheral pain, which is why we are conducting a larger pilot trial focused on feasibility to inform the design of a future full-scale RCT.

6. Provide information about safety and risk and patients.
Response: We thank the reviewer for this question. As previously noted, we are designing a triage algorithm to help ensure women with acute cardiac pain are triaged appropriately to either their primary care provider or the emergency department. We know that women minimize their cardiac symptoms, prefer to consult with family and friends, have caring responsibilities and have concerns for their family. As a result, women delay seeking appropriate care for their cardiac pain; the time from

symptom onset to emergency department arrival for women is 85 to 320 minutes, and this has not changed in the last decade. We are hoping that our event profile and triage algorithm will help women recognize their event pain and push them to seek appropriate care. Our triage algorithms will be validated in Phase 2A. The physical exercise strategies that will be incorporated into the HEARTPA♀N intervention are already utilized by the women'sonly cardiac rehabilitation program. These are based on the Canadian Physical Activity Guidelines and the living well with heart disease guidelines published by the Heart and Stroke Foundation of Canada. Safety tips will be incorporated as per the guidelines and all content is being developed and all of our physical exercise content will be reviewed by experts at the women's-only cardiac rehabilitation program at Women's College Hospital.

7. Provide more information about data safety of patients such as HIPAA Privacy Rules. Response: We thank the reviewer for this comment. This information was requested and approved by our Research Ethics Board at the University of Toronto. All identifiers will be removed, and a code number assigned at the beginning of data collection. Only that code will be used to identify the data. The contact form that links participant names with code numbers will be kept separate from all other study materials and stored in a locked filing cabinet by the PI. All information obtained during the course of the study will be kept strictly confidential and anonymity will be protected at all times. Participants will not be identified in any publications, reports or presentations. During the focus group sessions, participants will also be asked to use only their first names. Consent form(s) will alert those participants who will be part of a focus that they will have anonymity through the use of their first name and ask that they 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.

All study related hard copy materials, including copies of consent and demographic forms will be stored in a locked filing cabinet in a locked secure office of the PI at the Lawrence S. Bloomberg Faculty of Nursing, University of Toronto. All study-related electronic data files (focus group recordings and transcripts) will be stored on a password-protected, encrypted secure network at the Faculty of Nursing, University of Toronto. Access to the electronic data files will be password protected and only available to the PI and Project Coordinator. 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/check-in (via automated alerts) every 1 to 2 days over the 3-month period and develop and track their goals related to their pain, activities, sleep, and emotions. Participants will be directed to the Project Coordinator for technical problems. To ensure privacy, 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. The HEARTPA♀N website, including the information layout and organization, editing text content, and design will be based on a WordPress back-end, with password projection during the study period. We have budgeted for secure self-directed hosting with a SSL certificate registration.

VERSION 2 – REVIEW

REVIEWER	Emma Motrico Universidad Loyola Andalucia
REVIEW RETURNED	03-Jan-2020

GENERAL COMMENTS	Thank you for inviting me to review a revision of the manuscript "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". This manuscript presents the protocol of the study. The authors have responded to editor/reviewer comments appropriately.