PROTOCOL

SMARTphone-Based Cardiovascular Risk Reduction Program in BREAST Cancer [SMART-BREAST]: A Randomized Controlled Trial

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Sponsor/s:
Austin Health

Statement of Compliance
This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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STUDY SYNOPSIS

Title:	SMARTphone-Based Cardiovascular Risk Reduction Program in BREAST Cancer [SMART-BREAST]: A Randomized Controlled Trial
Short Title:	The Smartphone Cardiovascular Risk Reduction in Breast Cancer Trial
Design:	Single-blinded, two-arm, parallel, randomized controlled trial
Study Centers:	The Olivia Newton John Cancer and Wellness Centre
Hospital:	The Austin Hospital
Study Question:	Does a smartphone-based cardiovascular risk reduction program improve exercise capacity in patients undergoing treatment for breast cancer?
Study Objectives:	To compare the effectiveness of a smartphone based cardiovascular risk reduction program to standard care in patients undergoing treatment for breast cancer.
Primary Objectives:	To assess change in exercise capacity (measured by six-minute walk test distance)
Secondary Objectives	To assess change in cardiovascular risk factors, major adverse cardiovascular events and quality of life
Inclusion Criteria:	Patients over the age of 18 with a diagnosis of breast cancer treated with any modality. The other major inclusion criteria will be personal ownership of a smartphone.
Exclusion Criteria:	Patients with metastatic disease and patients with a prognosis of less than 6 months as determined by their treating oncologist at the time of diagnosis. Patients who are unable to give informed consent, cannot communicate in written English will also be excluded
Number of Planned Subjects:	280
Investigational product:	Smartphone based secondary prevention program
Safety considerations:	Not applicable
Statistical Methods:	Baseline characteristics will be summarized using descriptive statistics. Continuous variables will be described as mean and standard deviation and be compared using Student's t test. Categorical variables will be described as frequencies and percentages and compared using Fisher's exact or chi-square tests as appropriate.

1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
ONJCWC	Olivia Newton John Cancer and Wellness Centre
App	Smartphone application
QoL	Quality of life

2. STUDY SITES

a. STUDY LOCATION/S

Site	Address	Contact Person	Phone	Email
Austin Hospital	145 Studley Rd Heidelberg 3084	Alexandra Murphy	03 9496 5000	acmurphy@rocketmail.com

3. INTRODUCTION/BACKGROUND INFORMATION

a. LAY SUMMARY

Heart disease and cancer are the two leading causes of death worldwide. There are a number of common risk factors and as such many patients will have both conditions. Treatments for cancer have improved significantly over recent decades and as a result less patients are dying from their cancer. These treatments however, have been associated with damage to the heart which can manifest in many different ways including heart failure, blockages in heart arteries, and a resultant increase in heart attacks, problems with the electrical system of the heart and even sudden cardiac death. As such it is important for cardiologists and oncologists alike to be familiar with the prevention, diagnosis and management of cardiovascular complications of cancer treatment.

Breast cancer is the most common cancer among women worldwide. Due to advancements in modern breast cancer therapy we are now seeing cure in many patients and the conversion of a terminal illness into a chronic disease. As a result, cardiovascular disease has become the leading cause of death in survivors of breast cancer. It is well established that lifestyle modifications which reduce traditional cardiovascular risk factors have an important effect on breast cancer and overall survival.

We aim to assess whether a smartphone based cardiovascular risk reduction program can improve exercise capacity and heart health in patients who are undergoing treatment for breast cancer. The smartphone program will enable patients to have access to education, real-time feedback and ongoing support at their fingertips.

Patients will be assessed and recruited after their diagnosis of breast cancer. The only extra time commitments will be an outpatient follow up at 12-months. At this time, we will be able to decide whether the smartphone program was beneficial.

b. INTRODUCTION

Breast cancer is the most common cancer among women worldwide and is treated with multiple modalities[1]. Due to advancements in modern breast cancer therapy we are now seeing cure in many patients and the conversion of a terminal illness into a chronic disease [2]. As a result, cardiovascular disease has become the leading cause of death in survivors of breast cancer[3]. Attention to reducing the risk of cardiovascular disease should thus be a priority in the long-term management of patients diagnosed and treated for breast cancer. The purpose of the present study is to establish the utility of a smartphone based cardiovascular risk reduction program in patients undergoing treatment for breast cancer. It has been well established that lifestyle modifications addressing cardiovascular risk reduction contribute importantly to both total mortality and breast cancer specific mortality, with physical exercise having the most robust effect on outcomes [4-8]. As such, the assessment and treatment of modifiable cardiovascular risk factors should be a priority in the long-term care of patients with breast cancer, both during their treatment and into survivorship. The utilization of a smartphone based cardiovascular risk reduction app will encourage patients to achieve the guideline recommended target of physical activity during treatment and into the future.

Smartphone technology can revolutionize the landscape of cardiovascular risk reduction as it can provide a platform for a patient-centered program with the capacity to incorporate education, real-time feedback, motivation, reminders and support. Furthermore, it can monitor diet, physical activity, medications and cardiovascular risk factor parameters. Lastly and most importantly, a smartphone-based program can be delivered from anywhere at any time and for extended periods of time.

The evidence for smartphone based cardiovascular risk reduction programs in this population is limited. Thus, we aim to conduct a randomized controlled trial using smartphone technology assessing exercise capacity as the primary endpoint.

c. BACKGROUND INFORMATION

Heart disease and cancer are the two leading causes of death in the developed world. There are numerous common risk factors and as such many patients are afflicted by both conditions[9]. Cytotoxic agents and targeted therapies used to treat cancer can affect the cardiovascular system. Furthermore, combination therapy is often adopted to improve cancer-specific survival which further amplifies cardiotoxicity [10].

Breast cancer is the most common cancer among women and accounts for almost a quarter of all cancer diagnoses worldwide[1]. Due to advancements in modern breast cancer therapy we are now seeing higher rates of cure and the conversion of a terminal

illness into a chronic disease [2]. As a result, cardiovascular disease has become the leading cause of death in survivors of breast cancer[3].

It has been well established that comorbid conditions which correspond with increased cardiovascular risk contribute importantly to both total mortality and breast cancer-specific mortality among breast cancer survivors[3]. Of all lifestyle factors which contribute to cardiovascular risk, physical activity has the most robust effect on breast cancer outcomes[4]. A systematic review and meta-analysis investigating the association between physical activity and breast cancer recurrence and death has demonstrated an inverse relationship between exercise and all-cause death, breast cancer-related death and breast cancer events[5]. Despite this, most cancer survivors experience a significant decline in exercise levels after diagnosis and particularly when undergoing treatment[6]. There are multiple explanations for this, including fatigue and other symptoms associated with cancer and the cancer treatment, time constraints, lack of confidence and confusion regarding the safety of exercise and the lack of access to individual recommendations or cancer-specific exercise programs [7, 8].

Telehealth is defined as the delivery of healthcare through the use of portable devices and has been widely adopted across multiple medical domains[11]. Smartphone technology is an advance on previous telehealth technologies and has been demonstrated to effectively deliver cardiac rehabilitative and secondary preventative services in multiple previous studies [12-16]. The use of smartphone technology has the potential to revolutionize the landscape of cardiovascular risk reduction in the breast cancer population. A survey performed by Bravo et al analyzing the acceptability and usability of Telehealth tools for breast cancer patients demonstrated a preference for a smartphone app over paper brochure[17]. In a randomized controlled study by Valance et al those equipped with a pedometer had a greater increase in physical activity compared with the control group[11]. Furthermore, patients in the pedometer group were still engaged in substantially more physical activity at follow up.

Over time, as women survive their breast cancer, they become less likely to die as a result of their cancer diagnosis and more likely to die of cardiovascular disease. As such, attention to reducing the risk of cardiovascular disease should be a priority in the long-term management of patients diagnosed and treated for breast cancer.

4. STUDY OBJECTIVES

a. HYPOTHESIS

We hypothesize that a smartphone based cardiovascular risk reduction program will improve exercise capacity. Secondary hypotheses include improvements in cardiovascular risk factors (lipid profile, blood pressure, HbA1C, anthropometry), major adverse cardiovascular events (composite of death, myocardial infarction, stroke, unplanned revascularization) and quality of life scores.

b. STUDY AIMS

The aim of this study is to establish the efficacy of a smartphone based cardiovascular risk reduction program in patients undergoing treatment for breast cancer.

c. OUTCOME MEASURES

Primary outcome: The primary outcome is a change in exercise capacity (measured by six-minute walk test distance).

Secondary outcome: The secondary outcomes are:

1. Cardiovascular risk factor profile
    a. Change in blood pressure (mmHg)
    b. Change in lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides)
    c. Change in fasting glucose levels and HbA1C
    d. Smoking status assessed by self-reporting
    e. Change in weight and body mass index (BMI)
2. Major adverse cardiovascular events (composite of death, myocardial infarction, stroke, unplanned revascularization)
3. Change in quality of life assessed by SF-36 questionnaire.

5. STUDY DESIGN

a. STUDY TYPE & DESIGN & SCHEDULE

Study Design:

This study is a single-blinded, two-arm, parallel randomized controlled trial recruiting consecutive patients with newly diagnosed breast cancer. The protocol is in accord with the SPIRIT 2013 statement and the intervention is described in accordance with the CONSORT-EHEALTH checklist. Patients over the age of 18 with a new diagnosis of breast cancer will be eligible for inclusion. The other major inclusion criteria will be personal ownership of a smartphone. Exclusion criteria includes patients with metastatic disease and patients with a prognosis of less than 6 months as determined by their treating oncologist.

Intervention:

All patients will receive standard of care treatment for their breast cancer. This includes inpatient and outpatient oncology review as required, planning and prescription of chemotherapy, radiotherapy, targeted therapy or hormone therapy as appropriate and promotion of self-care with access to the Breast Cancer Network Australia resources during cancer treatment.

Eligible patients will be randomized in a 1:1 fashion to a smartphone-based cardiovascular risk reduction program or usual care alone. Assessors of the primary outcomes are blind to treatment allocation; however, participants are not blinded.

The smartphone-based cardiovascular risk reduction program will be delivered over 12 months, starting at the beginning of cancer treatment through a smartphone app. Participants in the smartphone intervention cohort will download the intervention app into their smartphone. They will then receive education on how to use the app. The program is a multi-faceted intervention with particular emphasis on physical activity. The app provides a platform for comprehensive assessment of cardiovascular risk factors and utilizes a 'traffic light' system to represent target achievement. 'High Risk' parameters are displayed in red, 'Suboptimal' parameters are displayed in yellow and 'On Target' parameters are displayed in green. Participants will receive a notification if a risk factor parameter is not on target. Non-pharmacological and pharmacological treatment of risk factors will be prescribed according to the National Heart Foundation Secondary Prevention Guidelines[18] with up titration of medications until target parameters have been achieved.

The different components are discussed in detail below:

Dynamic tracking of cardiovascular risk factors - Patients will have an interactive personal dashboard highlighting the status of their cardiovascular risk factors. They will be graded depending whether they are at recommended target levels.

Exercise Prescription - Patients will have access to real-time feedback of their activity levels through the app's activity tracker which links to the iphone's accelerometer feature. Patients will be able to monitor the number of steps taken and the distance walked. Feedback will be provided through messaging services.

Dietary Habits - Dietary habits will be tracked through the app via access to the phone's inbuilt camera. Participants will be encouraged to take photos of the food they are eating to keep record of their diet. They will have capabilities to rate and comment on the food.

Interactive and Personalized Feedback - Patients will receive personalized messages via the app messaging service providing feedback on risk factor control and physical activity.

Support - The messaging service also allows the patient to initiate contact if they have any questions regarding their cardiac condition. Replies will be made within one working day.

Outcome Assessment:

Participants will be evaluated at baseline and at 12 months. Baseline assessment will include the following measurements: height, weight, waist circumference, resting heart rate and blood pressure, smoking status, fasting cholesterol and glucose levels.

Data Collection and Storage:

Participants will be evaluated at the commencement of treatment and at 12 months. Baseline demographics will be collected. Assessments will include the following measurements: height, weight, waist circumference, resting heart rate and blood pressure, smoking status, fasting cholesterol and glucose levels. Exercise capacity will be measured by a six-minute walk test. Patient information will be identifiable to enable matching of 12-month assessment to original assessment. At this point, all data will be de-identified. Non-identifiable data will be used for analysis and publication of study results.

Blood samples will be collected at The ONJ by a registered oncology nurse and analyzed by the Austin Pathology service. Blood samples will not be stored following analysis.

Abnormalities detected on routine blood tests will be initially evaluated by the principal investigator with further referral to a specialist depending on the nature of the abnormality.

Electronic records will be kept with the principal investigator. Any paper records will be kept in the Cardiology Department at the Austin Hospital. At the completion of the study, the physical records will be kept with the principal investigator for a total of 7 years.

Timeline:

Assessment	Screening	12-Months
Informed Consent	X	
Demographic Information	X	
Cancer diagnosis details	X	
History and Cardiovascular risk factors	X	X
Weight and Waist Circumference Measurement	X	X
Resting blood pressure and heart rate measurement	X	X
Fasting lipid profile, fasting glucose, HbA1c	X	X
Quality of life assessment (EQ-5)	X	X
Six-Minute Walk Test	X	X
Major adverse cardiovascular event		X
Health care utilization		X

b. Standard Care and Additional to Standard Care Procedures

Standard Care Procedures		Additional to Standard Care	
Assessment	**Time of Assessment**	**Assessment**	**Time of Assessment**
Fasting lipid profile and HbA1c	Prior to commencing chemotherapy	Six-minute walk test	At baseline and 12-month follow up
Cardiovascular risk factor review	Prior to commencing chemotherapy	Fasting lipid profile and HbA1C	Prior to radiotherapy an at 12-month follow up
QoL Questionnaire (SF-36)	At time of diagnosis	QoL Questionnaire	Prior to radiotherapy

c. Randomization

Eligible patients will be randomized in a 1:1 fashion to smartphone based cardiovascular risk reduction program or usual care. Assessors of the primary outcomes are blind to treatment allocation; however participants are not blind.

6. STUDY POPULATION

a. RECRUITMENT PROCEDURE

The recruitment procedure has been detailed in section 5a. Screening will occur at the time of breast cancer diagnosis at ONJCWC. Potential participants will receive study information and informed consent will be obtained. Recruitment will be open for 12 months or until recruitment target is met. Bias will be avoided as all patients diagnosed with breast cancer undergoing treatment at ONJCWC will be screened.

b. INCLUSION CRITERIA

Patients over the age of 18 with a diagnosis of breast cancer treated with any modality. The other major inclusion criteria will be personal ownership of a smartphone.

c. EXCLUSION CRITERIA

Patients with metastatic disease and patients with a prognosis of less than 6 months as determined by their treating oncologist at the time of diagnosis. Patients who are unable to give informed consent, cannot communicate in written English will also be excluded.

d. CONSENT

Potential participants will receive study information and informed consent will be obtained.

7. PARTICIPANT SAFETY AND WITHDRAWAL

a. RISK MANAGEMENT AND SAFETY

The smartphone based cardiovascular risk reduction program is a safe intervention. If at any time the patient is uncomfortable with the intervention, they can delete the app. Furthermore, the participant can contact the principal investigator directly if they have any concerns.

b. HANDLING OF WITHDRAWALS

If a patient withdraws from the study, their data will be de-identified and will not be used for final analysis. All patients receive standard of care for management of their breast cancer regardless of whether they participate in the study. This ensures patients continue to receive optimal oncological care even if they withdraw from this study.

8. Statistical Methods

a. Sample Size Estimation & Justification

We calculate a sample size of 224 (112 per group) will be required to detect a minimal clinically important difference of 25 meters for the six-minute walk test in patients with breast cancer with 80% power at 5% level of significance. Accounting for a 20% loss to follow-up rate, we will aim to recruit 140 patients in each arm.

b. Statistical Methods To Be Undertaken

Statistical analyses will be performed using SPSS (IBM, USA). Baseline characteristics will be summarized using descriptive statistics. Continuous variables will be described as mean and standard deviation and be compared using Student's t test. Categorical variables will be described as frequencies and percentages and compared using Fisher's exact or chi-square tests as appropriate.

9. Storage of Blood and Tissue Samples

a. Details of where samples will be stored, and the type of consent for future use of samples

This is not applicable to this study.

10. Data Security & Handling

a. Details of where records will be kept & How long will they be stored

Electronic records will be kept with the principal investigator. Any paper records will be kept in the Cardiology Department at The Austin Hospital. At the completion of the study, the physical records will be kept with the principal investigator for a total of 7 years.

b. Confidentiality and Security

Electronic records will be password encrypted. Any paper records associated with the study will be stored in a locked cabinet in the Cardiology Department at The Austin Hospital.

c. Ancillary data

Ancillary data requiring storage will not be collected in our study.

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