Participant Information Sheet/Consent Form

Title	**Risk-guided Disease managEment plan to prevEnt heart failure in patients treated with previous cheMotherapy**
Short Title	REDEEM trial
HREC Reference	H0027424
Principal Investigator	Professor Tom Marwick
Co- Investigator	Dr Martin Schultz
Location	The Menzies Institute for Medical Research

Part 1 What does my participation involve?

1 Introduction

You are invited to participate in this study because you have had previous cancer treatment. In particular treatment with Anthracyclines, Trastuzumab (e.g Herceptin), Tyrosine kinase inhibitors (e.g. sunitinib) or had left chest radiotherapy.

The study aims to identify cardiac complications of cancer treatment (chemotherapy) and find exercise and medical treatment that will improve these complications. The study is coordinated by the Baker Heart and Diabetes Institute but will be conducted by the Menzies Institute for Medical Research.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section.

By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to the tests /treatment and research that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Some cancer treatments lead to a risk of heart muscle damage. If this process is left unchecked, it can sometimes cause heart failure, especially as patients grow older and develop other risks for heart failure.

Heart failure is a serious illness that is difficult to treat. Some new cardiac imaging methods have allowed the early detection of cardiac problems before the patient develops heart failure.

In this project an ultrasound of your heart (echocardiogram) will be taken in order to measure cardiac status. We are trying to establish whether information from simple tests of the heart could guide treatment to protect patients from developing heart failure.

If the test is abnormal, we could try to prevent the progression to heart failure by medications and lifestyle change, including exercise training.

The medications we will test for this purpose are Ramipril and Metoprolol. Both treatments are approved in Australia to treat high blood pressure and heart failure. They are also used to prevent heart failure, but although this is in the heart failure guidelines, they are not approved for this purpose by the Therapeutic Goods Administration (TGA). Accordingly, in order to study them in this trial, we have obtained a Clinical Trial Notification (CTN) to inform the TGA of this study.

3 What does participation in this research involve?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form at the end of this document.

This study is a randomised trial (see definition below) that will be conducted over one year.

<u>Randomisation</u>
Sometimes doctors don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different investigations, and the results are compared to see whether one approach is better.

To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the doctor nor you can decide which treatment you will receive.

First at screening test, cardiac measurements, obtained from a painless, ultrasound test of the heart, will be used to identify abnormal cardiac structure or function. If your test is normal you will not be able to participate further in the study.
In this study you will be allocated either to:

- Intervention group
  Or
- Non-intervention group (Usual care group)

You will have a 50% chance to be allocated to one of the study groups.

The aim is to identify whether the information provided by the test leads to better heart outcomes if your physician starts you on program of medication and lifestyle change to protect the heart. We will follow the benefit of this intervention by measuring exercise capacity, ultrasound measurements and blood samples.

If you agree to participate in this study, you will then be asked to undergo following procedures at entry to the study (baseline) and at 6 months and 12 months.

- Questionnaires to gather information about general health, wellbeing, your understanding on general heart health and sociodemographic data (to describe population characteristics, listed below):
  - Residence
  - Education
  - Employment and income
  - Drug use and/or smoking (alcohol, tobacco, e-cigarettes)
  - Language and ethnicity
  - Relationship status
  - Race/Ethnicity
  - Whether you receive any government pension or benefit

These questionnaires may be performed either in person / online via REDcap (Research Electronic Data Capture) which is a secure online database, used for managing online surveys.

- An exercise test, involving;
  - Maximum exercise using a bicycle or treadmill.
  - Monitoring of the blood pressure and electrocardiogram (ECG). An ECG measures the electrical activity of the heart. Up to 9 small electrodes are placed on the chest and limbs to measure this.
  - Measurement and analysis of expired gases.

- Ultrasound pictures of your heart
  - Ultrasound pictures are obtained by pressing an ultrasound probe against the skin; this transmits sound waves and collects the reflected waves to make a picture of the reflecting structures. Each ultrasound test takes approximately 45 minutes.
- Blood pressure and arterial stiffness
  - Blood pressure will be measured in the clinic at rest and also by 24-hour ambulatory monitor. This involves wearing a cuff and monitor that will take measures every 30 minutes for 24 hours.
  - Arterial stiffness will be estimated by pulse wave velocity, which involves inflation of a blood pressure cuff around your upper thigh and placement of a pen like device over your carotid artery. The test takes around 15 minutes.
- Blood tests are taken at baseline and one year
  - 10 mLs of blood is taken (two teaspoons).We will test for haemoglobin level, cholesterol level, insulin and glucose level along with tests for kidney function. These blood tests are the normal standard of care blood tests that your doctors would usually take. We will record the results of these tests for this study.

Involvement in the trial will take one year in total. There will be four visits involved during the study trial at various time points (screening, baseline, 6 months, 12 months). We anticipate that each visit will last for under 2 hours. If for some reason you are not able to attend for a separate baseline appointment, the study staff will endeavour to administer the baseline testing on the day of your screening echo test, time and availability of equipment permitting. Details of each study visit including various tests undertaken at each of the visit is shown in Table 1.

Table1: Study procedures

	Pre screening*	Screening	Baseline	Month 6	Month 12	Early Discontinuation Visit
Eligibility criteria	X					
Informed Consent		X				
Medical History [a]			X			
Physical Exam			X			X
12 Lead ECG			X			X
Echocardiogram		X			X	
VO_2			X		X	X
Questionnaire			X	X	X	
Functional assessment (6MWD,DASI)			X		X	
Vital Signs[#] (BP, HR, RR, PWV)			X	X	X	
Pathology tests			X	X	X	
Concomitant Medications			X	X	X	

AE/SAE Assessment			X	X	X	
Provision of cardiac images to the intervention group			X			
Heart Failure Assessment (NYHA-HF)			X	X	X	
Chemotherapy Regimen & Review			X	X	X	
Medication Compliance (pill counts)				X	X	

*Pre screening test will be done via phone to test for eligibility. # BP, blood pressure, will be measured via 24-hour ambulatory monitoring at baseline and 12 months. PWV, pulse wave velocity is a measure of arterial stiffness, also measured at baseline and 12 months only.6MWD=6 minute walk distance; DASI= Duke Activity Status Index; NYHA-HF= New York Heart Association functional classification for Heart Failure

If medication is initiated, we will arrange follow-up every 2 weeks for up to 10 weeks, in addition to the study procedures listed above. This will allow the doctors (from the Baker Institute) to adjust the medication doses as required, and may be done by telehealth (either via phone or videoconference).

During the study period we will be sending monthly text messages and asking you to report your medication usage. We will request that you upload a photo of your pill blister pack and send it to our study email: redeem@utas.edu.au

None of these procedures are experimental, they are all tests used in routine patient care. However, the trial will investigate the process of screening heart function using ultrasound and exercise. We anticipate that the results from the study may be used to recommend exercise and lifestyle changes as well as medical therapy in the future to reduce the risk of heart failure in cancer survivors.

We wish to stay in touch with you (by phone or email) for at least 1 year after the completion of the study, and have permission to contact you again in the future and access your medical records for 5 years from the date you sign the consent form in order to obtain information relevant to the study.

4 Other relevant information about the research project

A total of 840 participants will be screened at the 6 Australian sites, and we expect that 400 will be randomized in the study.

Financial considerations:
You will not receive payment for taking part in this study.

All reasonable travel expenses ($50 voucher to cover cab or car parking) will be reimbursed. Please discuss this with the study staff.

If you are required to take the study medications (Ramipril and Metoprolol) during the study,

these medications will be given to you free of charge. Should you need to buy these medications, the cost of these medications will be reimbursed. Please discuss the process being used at this institution with the study staff.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Baker Heart and Diabetes Institute.

6 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this institution. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

7 What are the possible benefits of taking part?

This study aims to further medical knowledge and may improve treatment of future cancer patients by making cardiac and exercise testing part of routine care. At the moment we do not know if any of these steps are of benefit.

8 What are the possible risks and disadvantages of taking part?

There are few or no risks associated with involvement in this study.

Ultrasound risks

There are no proven long-term risks related to ultrasound scans as used in this research project. Discomfort may be associated with the ultrasound test – which involves pressure against the chest wall.

Risks of medication

Ramipril and metoprolol are commonly used medications used for blood pressure control and heart failure. The use of them can cause the blood pressure to fall excessively, leading to dizziness or blackouts. For this reason, the doses of these medications are increased gradually.

Both medications can cause stomach upset (nausea, vomiting, and diarrhoea), weakness or tiredness.

Asthma can be provoked by beta blockers (Metoprolol) but allergic responses (e.g. skin rash) are rare.

Ramipril may cause a dry cough. Ramipril can lead to impairment of kidney function – for this reason blood tests are checked after starting the drug.

Very rarely, Ramipril causes swelling around the lips and mouth – in which case you should stop the medication and advise your doctor as soon as possible.

Other risks
Other known risks of this study are possibly:

- Inconvenience associated with regular visits to the study site
- Exercise tests can cause fatigue or joint pains
- ECG's may occasionally cause some minor chest discomfort from the removal of the ECG electrodes but are not associated with any adverse reactions
- Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated
- Having your blood pressure measured (and arterial stiffness) may cause some discomfort associated with inflation of a cuff around your upper arm and leg.

There may also be risks associated with this trial that are presently unknown or unforeseeable.

9 What will happen to my results?

The ultrasound images and exercise test results will be stored on a secure computer for 15 years. They will not be used for other research projects, except with your written consent or, under some circumstances, with the approval of a Human Research Ethics Committee at that time.

Blood test samples will be destroyed after one week as per the routine Hobart Pathology services protocol. Results will be accessed from Hobart Pathology for this study.

10 What if I withdraw from this research project?

New information about managing heart disease in cancer survivors may become available during the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

11 What happens when the research project ends?

You may be able to continue with treatments following completion of this study if your doctor considers them to be of benefit to you. This decision will be made in consultation between you and your treating doctor about the most appropriate treatment for you at that time.

Part 2 How is the research project being conducted?

12 What will happen to information about me?

The data collected will be re-identifiable using a participant-specific study code (coded data).

Any information obtained for research project that can identify you, will be treated as confidential and securely stored in Menzies Institute for Medical Research offices. All offices and/or rooms are locked unless a member of staff is present. Data stored on computer will be password protected. Access to data will only be by the investigators. It will be disclosed only with your permission, or in compliance with the law.

Coded data will be transferred to the Baker Heart and Diabetes Institute for further analysis.

By signing the consent form, you agree to use of the data for extended research into cardiovascular disease. Any future research would need to be approved by a Human Research Ethics Committee.

Information about you will be obtained from your health records held at this, and other, health services for the purposes of this research.

Your health records and any information obtained during the study are subject to inspection (for verifying the procedures and the data) by the relevant authorities, the Therapeutic Goods Administration, the treating institution, the Human Research Ethics Committee that approved this research or as required by law. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Information about your participation in this research project may be recorded in your health records.

At the end of this study, medical records and clinical study notes will be archived at an approved archive facility by the Menzies Institute for Medical Research as per the institution policy.

It is possible that the information collected for all participants, including you, may be presented at a local or international scientific conference or published in a scientific journal. All information will be presented in such a way that neither you nor any other participant may be identified. By signing the consent form you give permission for your coded data to be used in this way.

13 Who is organising and funding the research?

This research project is being conducted at the lead site of the Baker Heart and Diabetes Institute by Cardiologist Professor Tom Marwick.

None of the investigators have any conflict of interest. Sites are being paid for the work involved in doing this study, however no money is paid directly to individual researchers.

14 What if I get injured in the research?

If you suffer any injuries or complications because of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. As you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

15 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Tasmanian Health and Human Research Ethics Committee, as well as the governance committee of the University of Tasmania.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the site study co-ordinator Kristyn Whitmore on 6226-4235. or email Kristyn.whitmore@utas.edu.au.

17. University of Tasmania Human Research Ethics Committee

This study has been approved by the University of Tasmania Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, you can contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote H0027424.

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Consent Form

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Short Title	REDEEM trial
HREC Reference	H0027424
Principal Investigator	Professor Tom Marwick
Co-Investigator	Dr Martin Schultz
Location	The Menzies Institute for Medical Research

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to the Menzies Institute for Medical Research concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

Name of Participant (please print) _____

Signature _____ Date _____

☐ Optional: By ticking this box, I consent to the storage of my data from this study and contact details in a database for future research into diabetes and heart disease.

☐ Optional: By ticking this box, I consent to the storage of my contact details in a database for use in relation to other studies.

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Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project
Note: All parties signing the consent form must date their own signature

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Form for Withdrawal of Participation

Title	**Risk-guided Disease managEment plan to prevEnt heart failure in patients treated with previous cheMotherapy**
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Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with the Menzies Institute for Medical Research.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, please provide a description of the circumstances below.

☐ Optional: By ticking this box, I consent to the storage of my data from this study and contact details in a database for future research into diabetes and heart disease.

☐ Optional: By ticking this box, I consent to the storage of my contact details in a database for use in relation to other studies.

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Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project. Note: All parties signing the consent section must date their own signature.