Participant Information Sheet/Consent Form

Menzies Institute for Medical Research

Title	**Persistent cardiovascular effects of COVID-19 viral infection trial (PERCEIVE-RCT substudy): A Randomised Controlled Trial of the Role of Optimal Cardioprotection Strategies to Prevent Heart Failure**
Short Title	PERCEIVE-RCT substudy
Project ID #	H0027543.
Co-ordinating Principal Investigator	Prof Tom Marwick
Co-Investigators	Dr Martin Schultz, Kristyn Whitmore RN
Location	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 a COVID-19 infection and have ongoing symptoms.

This study aims to identify people with impaired functional capacity and cardiac complications as a result of COVID-19, and find exercise and medical treatments that will improve these complications. The study is coordinated by the Baker Heart and Diabetes Institute. There are multiple study sites across Australia.

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 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?

This research has been initiated by the study doctor, Professor Tom Marwick and is based at the Baker Heart and Diabetes Institute, Melbourne. It will be conducted at the Menzies Institute of Medical Research (Hobart), the Baker Institute facilities (Prahran and Hoppers Crossing), Western Health, Northern Hospital in Melbourne, and Nepean and Westmead Hospitals in New South Wales.

There is some evidence that COVID-19 infection may result in impaired functional capacity and/or lead to a risk of heart muscle damage. If this process is left unchecked, it might deteriorate and lead development of other risks for heart disease.

We are trying to establish whether information from simple tests of the cardio-respiratory system could guide treatment to improve exercise capacity and protect patients from developing heart failure. If the tests are abnormal, we could try to prevent disease progression to heart failure by medications and lifestyle change, including exercise training.

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.

In this study, we will test your fitness (using online questionnaires and 6-minute walk distance) and do a blood test to see if there is any evidence of heart muscle damage. If so, an ultrasound of your heart (echocardiogram) and exercise test will be taken in order to measure cardiac status. Cardiac measurements, obtained from these painless tests will be used to identify abnormal cardiac structure or function. If the tests are abnormal, you will be randomly (description below) allocated into one of the groups:

Intervention group Or Usual care group

All participants in the intervention group will receive lifestyle coaching (for example information about the benefits of changing behaviours) and exercise training supervised by an exercise physiologist. The intervention is safe as it will be delivered by a qualified medical doctor and exercise physiologist. The lifestyle coaching and exercise training will be provided onsite and remotely and will be up to 3 sessions per week over 8-12 weeks. Participants in the intervention group who have identified changes in the heart - specifically left ventricular dysfunction will also receive medications to protect the heart by the supervising doctor. 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.

Participants in the usual care group will attend their baseline and scheduled reviews. All medical needs and risk factor modification will be provided at the discretion of their GP. No additional intervention will be delivered.

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

Randomisation

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.

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 lifestyle change and/or medication 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 be asked to undergo the following procedures (below) at entry to the study and at 6 monthly intervals for 2 years. (please see Table 1);

- Screening questionnaires to gather information about general health and wellbeing.
- An exercise test, involving;
  - Maximal intensity exercise using a bicycle
  - 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.
- We will seek your permission to access the previous investigations performed during treatment of your infection.
- Blood tests are taken at baseline and one year
  - 10 mLs of blood is taken (two tablespoons). 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.
- 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.

Involvement in the trial will take two years in total.
Participants recruited from the Tasmanian community will have their assessment done at the Menzies Institute. There will be no interstate travel involved.

Table 1. Study procedures

	Screening/Baseline	Month 6	Month 12	Month 18	Month 24	Early Discontinuation Visit
Informed Consent	X					
Review medical records	X					
Medical History and physical assessment	X	X	X	X	X	
12 Lead ECG	X		X		X	X
Resting Echocardiogram	X		X		X	
Maximal exercise test (VO_2)	X	X	X	X	X	X
Patient health questionnaires	X	X	X	X	X	
Vital Signs (BP*, heart rate , respiratory rate, PWV)	X	X	X	X	X	
Blood tests done as per standard care	X		X		X	
Current prescribed medications	X	X	X	X	X	
Adverse and serious event (AE/SAE) assessment	X	X	X	X	X	
Heart Failure Assessment	X	X	X	X	X	
Medication Compliance (pill counts)#	X	X	X	X	X	

*BP, blood pressure, will be measured via 24-hour ambulatory monitoring at baseline, 12 and 24 months. PWV, pulse wave velocity is a measure of arterial stiffness, also measured at baseline, 12 and 24 months.# if medication is prescribed.

None of these procedures are experimental – they are all tests used in routine patient care. However, the trial will investigate the process of screening for long-COVID and 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 improve heart function and minimise the progression of heart damage.

4 Other relevant information about the research project

A total of 820 participants will be screened at the study sites and we expect that 654 will be randomized in the study.
Up to 100 participants will be involved in the study at the Menzies Institute for Medical Research.

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

All reasonable travel expenses (i.e., car parking) will be reimbursed to a maximum of $100. Please discuss this with the study staff.
If you are required to take the study medications (Ramipril and Metoprolol) during the study, The cost of these medications will be reimbursed. Please discuss this 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 Menzies Institute for Medical Research.

6 What are the possible benefits of taking part?

This study aims to further medical knowledge and may improve treatment of future COVID patients, by making cardiac and exercise testing part of routine care, and by defining whether exercise and medical treatment are of value in people with abnormal tests. At the moment, we do not know if any of these steps are of benefit.

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

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

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

Exercise tests can cause fatigue or joint pains. The risk of a significant cardiac complication (heart attack, serious heart rhythm problem) is about 1:10,000 in this setting. In some people, the exercise testing procedure may induce severe fatigue or post exercise malaise (PEM). If you have a history of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), it is recommended that you seek professional medical advice before participating in this study. For participants indicated to have PEM in the days following their CPET, exercise participation will be discontinued, and a member of the study team will discuss ongoing care options as part of the study. The efficacy of exercise in long-Covid sufferers is unknown at present. It is possible that the intervention in this study may be ineffective, or even exacerbate symptoms.

Cardio-protective medications (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 known risks of this study are possibly:

- Inconvenience associated with regular visits to the study site
- 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.

8 What will happen to my results?

The ultrasound images and exercise test 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.

9 What if I withdraw from this research project?

New information about managing heart disease from COVID 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 by contacting Kristyn Whitmore, study co-ordinator (contact details are at the end of this form), without having to give a reason. You will be asked if you wish your data to be deleted, and if so, the records will be removed electronically from the database.

10 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?

11 What will happen to information about me?

The data collected will be re-identifiable using a patient specific study code. Any information obtained for research project that can identify you, will be treated as confidential and securely stored in the Menzies Institute 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 Institute for further analysis.
Your information in the Menzies Institute for Medical Research. Medical record will be retained by the Menzies Institute for Medical Research, under their data management arrangements, unrelated to this study.
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 Menzies Institute for Medical Research, or to comply with 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 and the Baker Heart and Diabetes Institute as per the institution policy. It is possible that the information collected for all patients, 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 patient may be identified. By signing the consent form you give permission for your coded data to be used in this way.

In accordance with relevant Australian and Tasmanian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

12 Who is organising and funding the research?

This research project has been initiated by the Baker Heart and Diabetes Institute by Professor Tom Marwick. They have obtained funding from the National Heart Foundation and medical research foundation fund. None of the investigators have any conflict of interest. Sites like the Menzies Institute are being paid for the work involved in doing this study, however no money is paid directly to individual researchers.

13 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.

14 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 University of Tasmania 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.

15 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 coordinator.

Site study coordinator

Name	Kristyn Whitmore
Position	Research Nurse
Telephone	03 6226 4235
Email	Kristyn.whitmore@utas.edu.au

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 H0027543.

Consent Form

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Co-ordinating Principal Investigator	Prof Tom Marwick
Co-investigators	Dr Martin Schultz, Kristyn Whitmore.
Location	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 Menzies Institute for Medical Research to release information to the Baker Heart and Diabetes Institute 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.

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

Form for Withdrawal of Participation

Title	**Persistent cardiovascular effects of COVID-19 viral infection trial (PERCEIVE-RCT substudy): A Randomised Controlled Trial of the Role of Optimal Cardioprotection Strategies to Prevent Heart Failure**
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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 Menzies Institute for Medical Research or my relationship with the Baker Heart and Diabetes Institute.

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.

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.