Comparison of telehealth and supervised phase III cardiac rehabilitation in regional Australia: protocol for a non-inferiority trial

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ABSTRACT

Introduction Exercise-based cardiac rehabilitation programmes (ExCRP) promote recovery and secondary prevention for individuals with cardiovascular disease (CVD). Despite this, enrolment and adherence to ExCRP in rural locations is low. Telehealth programmes provide a convenient, home-based intervention, but concerns remain about compliance to exercise prescription. This paper presents the rationale and protocol design to determine if telehealth delivered ExCRP is not inferior to supervised ExCRP for improving cardiovascular function and exercise fidelity.

Method and analysis A non-inferiority, parallel (1:1), single-blinded randomised clinical trial will be conducted. Fifty patients with CVD will be recruited from a rural phase II ExCRP. Participants will be randomly assigned to telehealth or supervised ExCRP and prescribed three weekly exercise sessions for 6 weeks. Exercise sessions will include a 10 min warm up, up to 30 min of continuous aerobic exercise at a workload equivalent to the ventilatory anaerobic threshold and a 10 min cool down. The primary outcome will be change in cardiorespiratory fitness as measured by cardiopulmonary exercise test. Secondary outcome measures will include change in blood lipid profile, heart rate variability, pulse wave velocity, actigraphy measured sleep quality and training fidelity. Non-inferiority will be confirmed if intention-to-treat and per-protocol analyses conclude the same outcome following independent samples t-test with p<0.025.

Ethics and dissemination Research ethics committees at La Trobe University, St John of God Health Care and Bendigo Health approved the study protocol and informed consent. Findings will be published in peer-reviewed journals and disseminated among stakeholders.

Trial registration number ACTRN12622000872730p; pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This non-inferiority clinical trial is low cost and scalable, ensuring external validity to address poor participant access in exercise-based cardiac rehabilitation programmes in regional areas.
⇒ The specific exercise prescription and provision of easily accessible training logs with objectively measured exercise intensity facilitates accurate calculation of training fidelity and dose-response adaptations to exercise interventions.
⇒ Randomisation with concealed allocation, analysis of primary outcomes conducted by blinded assessors and protocol registration will minimise potential bias.
⇒ A limitation will be participants and clinical staff administering the treatment will be aware of group allocation.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death and disability worldwide with an increase in prevalence expected due to an ageing and insufficiently active population.1–3 Improved treatment and management of acute cardiovascular events have increased survival rates with the residual population at risk of subsequent complications and increased total morbidity.4–6 Consequently, effective secondary prevention and post-event care are imperative to support disease management and reduce total health burden.7

Exercise-based cardiac rehabilitation programmes (ExCRP) are multiphase secondary prevention strategies incorporating education and behavioural change interventions to improve future health outcomes for people with CVD.8–9 Transitioning from in hospital to community-based programmes, ExCRP facilitates several physiological adaptations including increased mitochondrial biogenesis, cardiac remodelling, reversal of metabolic decoupling, reduced sympathetic tone and augmented cholesterol and triglyceride profiles.8 10 These adaptations translate to significant improvements in autonomic modulation, endothelial function, lipoprotein profile, glucose metabolism, cardiorespiratory fitness and an overall reduction in future health risks among patients with
coronary artery disease.\textsuperscript{8, 10} Outpatient ExCRP (phase II) is sufficient to elicit improvements in the aforementioned measures of cardiac function,\textsuperscript{11} however, long-term exercise participation is necessary for disease management.\textsuperscript{12}

Community-based ExCRP (phase III) promotes exercise participation with reduced levels of supervision to support long-term physical activity and associated health benefits.\textsuperscript{13, 14} However, enrolment in phase III ExCRP and subsequent participation rates are often less than prescribed\textsuperscript{15–18} with a lack of perceived benefit, low levels of motivation\textsuperscript{19–21} and poor access in regional areas identified as primary barriers.\textsuperscript{22, 23} Telehealth programmes that use home-based training with online support have been hypothesised to improve exercise participation.\textsuperscript{24, 25} Despite additional cost in the provision of exercise sensors and access to web-based applications, telehealth has comparable or decreased individual and societal health-related expenditure.\textsuperscript{26} Demonstrated accessibility and cost-effectiveness, without elevating adverse events despite less supervision,\textsuperscript{24, 27} telehealth programmes were extensively adopted during the COVID-19 pandemic.\textsuperscript{28} However, the perceived improvements in programme accessibility associated with telehealth programmes are commonly measured by sessional attendance.\textsuperscript{25} An approach that fails to quantify participants’ compliance with the training intensity and duration.\textsuperscript{29, 30} Given the specific association of exercise dose (frequency, intensity and type of exercise) with physiological adaptation, valid measures of exercise compliance are essential when evaluating the efficacy of ExCRP. By failing to consider all elements of exercise prescription (compliance and adherence) the fidelity of ExCRP has not been systematically demonstrated. Therefore, further work is needed to consider exercise fidelity when comparing cardiovascular adaptation including cardiorespiratory fitness, lipid profile, autonomic modulation and arterial compliance to supervised ExCRP.

**Aim**

The primary aim of this non-inferiority trial is to determine if telehealth delivered ExCRP is non-inferior to supervised ExCRP to elicit changes in peak oxygen consumption ($\text{VO}_2\text{peak}$ (primary outcome)) with additional comparisons conducted for lipid profile, autonomic modulation, arterial compliance and quality of life. The secondary aim is to compare the fidelity of prescribed exercise in each intervention.

**Hypotheses**

The primary hypothesis is that telehealth delivered ExCRP is not inferior to supervised delivered ExCRP for inducing improvements in cardiorespiratory fitness as assessed by $\text{VO}_2\text{peak}$. Comparisons for improvements in lipid profile, autonomic modulation, arterial compliance and quality of life will also demonstrate non-inferiority of telehealth ExCRP. A second hypothesis is that objectively monitored telehealth delivered ExCRP will result in comparable exercise prescription fidelity to supervised delivered ExCRP.

**METHODS**

**Study design**

Telehealth delivery is unlikely to elicit substantially greater improvements in cardiovascular function when compared with the established effect of supervised ExCRP. Therefore, a 6-week, two-arm parallel, randomised non-inferiority trial with blinding of the outcome assessor and data analyst will be conducted. Standardised assessment of primary and secondary outcomes will be conducted at baseline prior to randomisation and after completion of the exercise intervention. Mean and SD of testing follow-up time will be reported in the final report. An overview of the study design is provided in figure 1 (Consolidated Standards of Reporting Trials diagram).

The trial has been prospectively registered with the Australian New Zealand Clinical Trial Registry with approval provided by the relevant institutional Human Research Ethics Committees. This protocol has been guided by The Standard Protocol Items: Recommendations for Interventional Trials reporting checklist (online supplemental file A).\textsuperscript{31}

**Participant eligibility and recruitment**

We will recruit 50 participants, aged 18 years or older with a recent diagnosis of CVD following completion of an outpatient (phase II) comprehensive cardiac rehabilitation programme.

Participants will be excluded if they have any condition for which exercise or exercise testing is contraindicated or have musculoskeletal or neurological conditions that prevent them from completing the exercise testing. Those diagnosed with CVD risk factors in the absence of CVD, congenital heart disease, diagnosis of heart failure (defined as previously documented left ventricular ejection fraction $\leq 45\%$), hypertrophic cardiomyopathy, or have received a heart transplant will be excluded. In addition, participants will be excluded if they do not have access to a phone for telehealth delivery or have limitations in English language production or comprehension skills that precluded them from understanding the consent form.

To facilitate participants from a wide range of socio-economic background, recruitment will be conducted from two publicly funded and private hospitals in regional Victoria, Australia. Both hospitals service regional and rural communities and offer phase II comprehensive cardiac rehabilitation programmes.

The local cardiac rehabilitation coordinators will provide all eligible attendees with recruitment flyers on entering and exiting the programme beginning on 22 August 2022. Attendees will be encouraged to contact the research team via email, phone call or by completing a Research Electronic Data Capture (REDCap) survey, a web-based application developed to capture data
for clinical research (Vanderbilt University, Nashville, Tennessee, USA). Following initial screening, eligible individuals will be provided with a participant information statement (online supplemental file B) and written informed consent will be sought before data collection.

**Randomisation and blinding**

After baseline assessment, participants will be randomly allocated to either the telehealth delivered or supervised delivered ExCRP group, using permuted block (blocks of 8), by a computer programme (www.randomizer.org). To prevent selection bias, the allocation sequence will be generated by an independent member of the research team (MK) and concealed from the investigator enrolling and assessing participants, in sequentially numbered, opaque, sealed envelopes. Assessments will be collected by researcher’s blind to group allocation (LCH and JH). Researchers blinded to group allocation will analyse the data. It is not possible to blind participants or therapists to group allocation.

**Intervention description**

**Exercise intervention**

Participants will be prescribed three exercise training sessions per week for 6 weeks. Training will be individually prescribed at a workload equivalent to the ventilatory anaerobic threshold (VAT) identified during baseline cardiopulmonary exercise testing (CPET). Specifically, the heart rate (HR) and workload in watts (W) at the time point where VAT is identified will be used in exercise prescription. Training sessions will consist of three phases:

**Warm up**

In accordance with general exercise guidelines and frameworks for cardiac rehabilitation, participants will complete a dynamic warm up to progressively increase HR. The warm up will be a duration of 10 min consisting of light callisthenics (marching on the spot, body weight squats and lunges) and aerobic activity (stationary cycling or walking at 80% VAT).
Aerobic training

Participants will be prescribed continuous aerobic exercise at individual VAT. The absolute mechanical workload corresponding with VAT during the exercise test will be the initial starting intensity of exercise and guided by HR measured and Rating of Perceived Exertion (RPE; 6–20 scale) reported at the same workload. If aerobic exercise is completed using an exercise mode other than cycling, the intended exercise intensity will be converted to relative energy expenditure in metabolic equivalents (METs) using metabolic equations and an equivalent mechanical workload will be calculated for the preferred exercise modality using the relevant metabolic equations. Exercise will initially be prescribed for up to 30 min per session with exercise terminated if participants’ HR exceeds 15 beats above the prescribed rate (corresponding to that at VAT) or an RPE greater than two points above the rating corresponding to VAT. If average sessional HR is 10 beats less than HR observed at VAT during CPET despite achieving the prescribed exercise workload, workload will be increased by 10% for the same exercise duration. If sessional RPE is two points or more less than RPE corresponding to that at VAT in three consecutive sessions despite achieving the recommended workload, total duration will be extended by 5 min. If both occur during the same session, intensity will be increased by 10% and RPE reassessed before a change in duration.

Cool down

Given the recent diagnosis of a cardiac event and likelihood of deconditioned state, an extended cool down is recommended. Participants will complete 5 min of light aerobic activity (<80% VAT) and 5 min stretching of major muscles to complete each session.

Supervised delivered ExCRP

The supervised delivered ExCRP will be conducted on-site at the university and serve as the standard intervention. Participants will complete the continuous aerobic exercise on a stationary cycle ergometer (mode used during CPET) or treadmill with workload converted to an equivalent treadmill speed and grade. A training schedule will be provided and supervised by an accredited/registered exercise or healthcare professional with participants offered the opportunity to nominate preferred training times. Participants will exercise at the same time as other individuals completing the trial with a maximum participant to supervisor ratio for the group of 8:1. Intensity of the training sessions will be monitored and recorded in 5 min intervals using an HR monitor (Polar Electro Oy, Kempele, Finland) and RPE to measure compliance to the prescribed workload. During one session per week a member of the research team who has been trained in the delivery of integrated motivational interviewing and cognitive behavioural therapy (MI-CBT) techniques will employ open-ended questions, affirmations, reflections and summaries to encourage motivation and self-efficacy to be physically active and achieve the recommended exercise dose during the intervention. Examples of the MI-CBT approach include discussing the participants’ goals and expectations from the exercise intervention, past experiences with physical activity programmes, how to identify potential barriers to long-term physical activity and strategies to overcome the identified barriers.

Telehealth delivered ExCRP

Participants randomly allocated to the telehealth delivered ExCRP will attend on-site training for the first three sessions (week 1) before continuing the exercise programme away from the university (weeks 2–6) and serve as the experimental intervention. Participants will choose their preferred mode of aerobic exercise (walking, jogging or cycling) based on exercise preference and access to equipment. To ensure standardised exercise intensity between intervention arms, participants will be provided with a target HR as well as the exercise intensity that correlates to the workload at individual VAT. Each participant will be provided with a Polar Unite fitness watch (Polar Electro Oy, Kempele, Finland) to objectively measure HR response. Participants will be required to log their training data and sessional RPE online using the Polar Flow software (Polar Electro Oy, Kempele, Finland) secured by login and password, allowing the research team to monitor adherence and training intensity weekly. Finally, participants will be required to attend a weekly audio or audio-visual meeting to discuss training adherence and compliance. MI-CBT will be incorporated into the weekly audio/audio-visual meeting for participants in the telehealth delivered ExCRP with a trained member of the research team implementing the same MI-CBT strategies as the supervised group.

Outcome measures and data collection

Outcome measures will be collected by experienced members of the research team with familiarity of all testing measures. Participants will be asked not to discuss any aspect of the intervention with the assessor to protect assessor blinding.

Cardiovascular fitness

The primary outcome of interest is training induced changes in $V_O^{\text{peak}}$. A symptom-limited CPET, widely considered the gold standard for assessing cardiopulmonary capacity and risk stratification among ExCRP participants, will be conducted at the baseline and follow-up assessments. Participants will complete the CPET on a cycle ergometer (Excalibur Sport; Lode B.V., Groningen, Netherlands) using a ramp protocol. The test will consist of stationary cycling at a cadence of 60–70 revolutions per minute, with starting resistance of 10–30 W, increasing by 10–15 W per minute depending on current activity levels until symptom-limited or volitional exhaustion is reached. HR (Polar Electro Oy, Kempele, Finland) and RPE will be monitored throughout the test and peak values will be recorded at cessation of the test. Oxygen
consumption will be measured by indirect calorimetry (TrueOne 2400; ParvoMedics Sandy, Utah, USA). $\dot{V}O_{2\text{peak}}$ will be determined as the highest period of oxygen consumption achieved by each participant averaged over 30 s, with post analysis conducted to assess maximum HR, RPE response and VAT via the ventilatory equivalents and V-slope method.42

Cardiovascular function and sleep quality
Central arterial pressure waveform and pulse wave velocity will be determined using pulse wave analysis as a non-invasive assessment of arterial stiffness.46 Participants will arrive in a fasted state and rest supine for 5 min before analysis is carried out using applanation tonometry according to the manufacturer’s instructions (Sphygmocor XCEL PWA & PWV; AtCor Medical Holdings, Australia). Heart rate variability (HRV) will be used to assess autonomic function with abnormal HRV, including hyperactive sympathetic influence, an independent risk factor for cardiovascular mortality.47 Holter monitoring will be conducted continuously for 24 hours using a 5-lead Holter (ARmedilog; Schiller, Switzerland). Beat-to-beat interval data will be exported and analysed for HRV and arrhythmia assessment post-intervention. Finally, participants will be required to wear a wrist-mounted sleep watch (ActiGraph GTX3; ActiGraph, Florida, USA) on the non-dominant wrist and complete a sleep diary for 7 days. Previous research has established a link between poor sleep quality (duration and continuity) with increased risk of developing adverse cardiac conditions including ischaemic heart disease.48 Actigraphy provides a validated and non-invasive assessment of sleep quality without the necessity of specialised equipment and expertise required for polysomnography.43

Blood analyses
A venous blood sample will be collected following an overnight fast and analysed for serum triglycerides (mmol/mol), total cholesterol (mmol/mol), high-density lipoprotein cholesterol mmol/mol, glycated haemoglobin (mmol/mol) and low-density lipoprotein cholesterol (mmol/mol) calculated using the Friedewald equation.44 Blood samples will be drawn from an antecubital vein using a 19-gauge needle into two EDTA containing tubes and two serum-separator tubes (SST). One SST and EDTA tube will be transported as a whole blood sample to a commercial laboratory for immediate analysis, while one SST and EDTA will be centrifuged, and serum/plasma will be aliquoted in-to cryotube and stored at −80°C to enable future analysis.

Training fidelity
To facilitate a direct comparison between delivery modes, the fidelity of telehealth and supervised ExCRP will be assessed. Fidelity will be assessed via the product of exercise performed at the prescribed intensity for the prescribed duration, and training adherence, defined by the percentage of weekly sessions of exercise attended by each participant. Polar Flow will be used to monitor individual sessions for telehealth delivered ExCRP, with Polar HR monitors used for supervised delivered ExCRP.

Subjective health assessment
During the baseline assessment process and at follow-up, participants will be required to complete a general health and information questionnaire developed by the research team to collect demographic information, current diagnosis, medication and Likert scale ratings and opinions on their rehabilitation experience during and following completion of the phase II cardiac rehabilitation programme and a global rating of change in health during this time. Additional standardised questionnaires will be completed including the Medical Outcomes Study 36-item Short Form (MOS SF-36), The International Physical Activity Questionnaire (IPAQ), the Duke Activity Status Index (DASI) and 21-item Depression Anxiety Stress Scale (DASS). All questionnaires will be completed prior to exercise testing online via REDCap or where necessary using a hard copy paper version.

The MOS SF-36 provides an estimate of eight domains of health-related quality of life including physical functioning, role-physical, role-emotional, bodily pain, general health, vitality and social functioning, used to monitor changes in generic functional health and wellbeing.45 The IPAQ will be used to assess the average amount of physical activity completed by the participants in the previous week.46 The DASI will be used to assess daily activities such as personal care, ambulation, household tasks and recreation activities to assess functionality and independence.47 Finally, the DASS questionnaire will be used to assess participants’ self-reported measures of depression, anxiety and stress.48

Adverse events
To determine the safety of the intervention all exercise-related adverse events will be documented. Serious adverse events will be defined as death, cardiac arrest and syncope, with minor adverse events including muscle-skeletal injuries, angina and palpitations. The supervised group will be monitored in all sessions, while the telehealth group will be instructed to immediately inform the research coordinator of any adverse events, with progress reviews conducted during the weekly telehealth call. An independent health professional will be responsible for reviewing any adverse events with recruitment ceasing if multiple serious adverse events are attributable to the study.

Management and monitoring
Study data will be collected in a combination of hard copy (data collection sheets and questionnaires) and electronic data, captured via Polar Flow and REDCap which is hosted by the primary research institution. Hard copy information will be transferred to an electronic format and stored using a unique participant number assigned to each participant.
by the research team. The primary investigator (BC) will oversee all general processes for the study including securing and managing ethical and regulatory approvals, document and questionnaire preparation, auditing measurement standardisation and data entry procedures, while recruitment will occur at the hospitals that deliver phase II cardiac rehabilitation by a local coordinator. The primary investigator, with documented training in Good Clinical Practice will monitor the conduct of the trial, verifying the protection of the rights and well-being of participants, ensure obtained data is accurate, complete and checked against source documents, and that the study is being conducted consistently with the approved protocol in accordance with the Good Clinical Practice guidelines and ethical requirements. This will be completed through annual reports submitted to the approving Human Research Ethics Committees, with any alterations or amendments communicated to all parties.

**Patient and public involvement**

The research project was developed to assess the effectiveness of current ExCRP in regional areas with outcomes used to inform future practices. To achieve this members of the in-hospital ExCRP team were engaged during the study design phase to ensure protocols are reflective of current clinical requirements. Additionally, members of the community were involved in the respective institutional ethics committees that assessed the study design. Patients were not provided an opportunity to assess study conduct or burden but are provided individual results via post project feedback sheets.

**Sample size calculation**

If there is truly no difference between the standard and experimental interventions, then 20 participants are required in each arm (40 participants in total) to be 80% sure that the lower limit of a one-sided 95.7% CI (or equivalently a 95% two-sided CI) will be above the non-inferiority limit of $-3.5\, \text{mL.kg}^{-1}.\text{min}^{-1}$. One MET ($3.5\, \text{mL.kg}^{-1}.\text{min}^{-1}$) was considered the minimum clinical difference (non-inferiority limit) due to its association with reduced cardiovascular mortality. An SD of the primary outcome measure (oxygen uptake) in a regional cardiac rehabilitation population of $3.9\, \text{mL.kg}^{-1}.\text{min}^{-1}$ was used from preliminary data collected by our research group. To allow for up to 20% participant dropout rate, similar to that reported by Price et al., the initial target is to recruit 50 participants.

**Statistical analysis**

Statistical analyses will be performed using SPSS software (V.26.0 SPSS, Chicago, Illinois, USA). Baseline characteristics will be summarised using descriptive statistics, with data reported as mean±SD or mean and 95% CIs. Non-inferiority will be confirmed if intention-to-treat (ITT) and per-protocol analyses conclude the same outcome. To allow ITT, missing data will be filled by bringing the last known data forward. Per-protocol analysis will include only those participants who complete at least 80% of training sessions (80% adherence). If non-inferiority is confirmed, then superiority will be evaluated by considering if the lower bound of the 95% CI for the mean difference in changes between telehealth delivered ExCRP and supervised delivered ExCRP at the conclusion of the intervention is above zero. The comparison between intervention groups in terms of change from pre-intervention to post-intervention will be assessed using independent sample Student’s t-tests. Analysis of covariance regression model will be used to evaluate the treatment effect on the primary outcome between the two-treatment groups, adjusting for baseline measure and age.

**DISCUSSION**

This non-inferiority trial is designed to determine if telehealth ExCRP is not less effective than supervised ExCRP in eliciting changes in $\text{VO}_2^{\text{peak}}$ (primary outcome) and other key markers of cardiovascular health among patients with CVD. Telehealth interventions present an opportunity to overcome pre-existing barriers to exercise adherence by increasing accessibility to ExCRP. However, a robust evidence base is needed for telehealth interventions to be adopted in-to ExCRP practice. A non-inferiority trial design enables researchers to develop this evidence base.

Telehealth interventions are usually completed at-home which raises unique concerns regarding compliance to appropriate exercise intensity and overall dose. The proposed telehealth intervention is designed to support adherence and compliance through addressing previously identified barriers to exercise participation among patients during ExCRP. The anticipated lack of perceived benefit and motivation to maintain post-event exercise, which has potential to negatively impact training fidelity through reduced exercise compliance, is primarily addressed in these interventions through the provision of integrated MI-CBT support. MI-CBT techniques facilitate motivation and self-efficacy among participants, translating to increased amounts of physical activity. To further enhance training fidelity by supporting training compliance, participants will be provided with real-time objective feedback on exercise intensity (HR monitor), while the online training log allows the research group to monitor and quantify duration, frequency and intensity of exercise. Therefore, a telehealth delivered ExCRP programme providing MI-CBT supported home-based individualised exercise training has potential to have similar fidelity as supervised delivered ExCRP while addressing the well-documented lack of access to phase III ExCRP that exists in regional areas.

**ETHICS, DISSEMINATION AND IMPACT**

The study protocol and the informed consent form were approved by the Human Research Ethics Committees...
at La Trobe University, St John of God Health Care and Bendigo Health. In the design of this proposal, the fulfillment of ethical principles has been considered: the value of the research question, methodological rigour, that investigators are scientifically qualified and the protocol has been independently evaluated. The results will be reported in accordance with the Consolidated Standards of Reporting Trials, with the intention of publishing in a peer-reviewed journal in a punctual and accurate way. Research findings and corresponding ExCRP service implications will additionally be disseminated among stakeholders. De-identified data will be published on the sponsoring institutions open access repository (OPA[AL]). We anticipate that if the telehealth delivered ExCRP is demonstrated, a feasible model of ExCRP will be established, increasing participant access, saving resources and improving cardiovascular health outcomes with the potential of influencing clinical practice guidelines.

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REFERENCES


28 O’Doherty AF, Humphreys H, Dawkes S, et al. How has technology been used to deliver cardiac rehabilitation during the COVID-19 pandemic? an international cross-sectional survey of Healthcare professionals conducted by the BACPR. *BMJ Open* 2021;11:e046051.


Participant Information Sheet/Consent Form

Adult providing own consent

Title
Cardiac rehabilitation in regional areas: developing a predictive model for ventilatory thresholds and assessing telehealth in phase III cardiac rehabilitation

Short title
Improving exercise prescription in regional cardiac rehabilitation programs

Principal Investigator
Dr Blake Collins

Associate investigator(s)
A/Prof Brett Gordon, Prof Michael Kingsley, Dr Daniel Wundersitz, Dr Lisa Hans, Ms Jacquelyn Dunstan, Dr Simon Nichols and Mr Alasdair O’Doherty

1. Am I eligible to participate?
Thank you for showing interest in participating in the research project titled “Cardiac rehabilitation in regional areas: developing a predictive model for ventilatory thresholds and assessing telehealth in phase III cardiac rehabilitation”. To participate you must meet the following criteria:

- Able to understand and respond to spoken English
- Aged 18 years and older
- Diagnosed with cardiovascular disease and exiting out-patient cardiac rehabilitation program
- Available to meet the time commitments and physically able to complete testing

If you have any difficulty in understanding the requirements of participation, please contact a member of the research team.

2. What is the study about?
Cardiac rehabilitation is important following a heart attack. However, prescribing the exercise correctly within rehabilitation relies on specialised equipment that may not be available in regional areas. Further, implementing exercise using telehealth may be more appropriate for some people facing barriers to participation. This project involves two experimental phases to understand these issues. The first phase aims to develop a model for prescribing exercise using exercise tests that can easily be conducted in a doctor’s clinic. The second phase aims to assess the benefit of cardiac rehabilitation programs delivered using telehealth compared to in person. The first phase will require you to attend three (3) times within a week:

- Three (3) laboratory sessions at La Trobe University involve six (6) maximum effort exercise tests through walking, cycling, standing, and stepping. During these sessions we will be collecting information on your general health (via questionnaires) and fitness levels.

Participants who complete the first phase will be invited to complete additional testing (measure of sleep quality, heart function, and blood testing) and a 6-week exercise program conducted either onsite at La Trobe University or at-home via telehealth

This Participant Information Sheet/Consent Form tells you about the research project, including explaining the tests, activities and your rights as a participant to help you decide if you want to take part in the project. Please read this information carefully. Ask questions about anything that you do not fully understand or if...
you want to find out more information. You may also want to talk about the project with a relative, friend or medical professional before you decide to take part.

Participation in this research is voluntary, if you do not wish to take part you do not have to. If you decide you want to take part, 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
• Understand that if eligible you will be invited to participate in the training intervention and additional testing described below

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

3. What is the purpose of this research?

The purpose of this research project is to determine an accurate way of assessing fitness and prescribing exercise for cardiac rehabilitation and to identify if exercise as part of cardiac rehabilitation is beneficial when provided by telehealth.

4. What does participation in the research involve?

If you wish to participate in this research project, and meet the eligibility criteria, you are required to give consent by signing the participant consent form attached to the bottom of this Information Sheet before you participate. There are no costs associated with participating in this research project, nor will you be paid. The project involves:

• Attending La Trobe University Bendigo Campus on three separate occasions to complete baseline testing
• At or prior to the first session, you will complete questionnaires about your current sleep, mental and physical health
• At the first session you will complete two exercise tests
• At the second session you will complete a different two exercise tests
• If you complete the exercise tests in the first two sessions without complication you will complete a final maximum effort exercise test measuring your breathing response
• If you wish to participate in the 6-week exercise program you will have measures of heart function and sleep conducted and undergo a blood test before being randomly allocated the on-site or at-home exercise training study
• If you participant in the 6-week exercise program you will be required to return to the laboratory one final time at the completion of the intervention to repeat exercise and health testing

Volunteering for the initial phase of the research project does not mean you need to participate in the exercise program and are free to withdraw consent and cease participation at any time.
Details of the testing session are explained below:

First Laboratory Testing Session (La Trobe University Bendigo, Exercise Physiology Laboratory)

In the first session you will undertake three (3) activities for a total duration of 45-50 minutes

1. Activity One – you will be asked to complete seven (7) questionnaires:
   a) General health questionnaire
   b) ESSA Adult Pre-exercise Screening System
   c) Duke Activity Status Index
   d) New York Heart Association Questionnaire
   e) Short Form 36 Questionnaire
   f) International Physical Activity Questionnaire
   g) Depression Anxiety Stress Scale

   You will then be randomly allocated two (2) of four (4) submaximal functional exercise tests. Listed below are examples of the potential order testing may occur.

2. Activity Two – Six Minute Walk Test (6MWT), a safe well-tolerated method to assess functional exercise capacity. You will be asked to cover as much distance as possible on an indoor walking track in 6 minutes.

3. Activity Three – Incremental Shuttle Walk Test (ISWT), after a recovery period you will be asked to complete the ISWT. Another commonly used functional exercise test where you will be instructed to complete laps (of a 10m track) in time with an external pace (beeps) that progressively gets faster until you can no longer keep up with the pace. Because of the external pacing, this test is considered a maximal test of fitness

Second Laboratory Testing Session (La Trobe University Bendigo, Exercise Physiology Laboratory)

In the second session you will undertake two (2) activities for a total duration of 35 minutes

1. Activity One – Astrand-Ryhming submaximal cycle test will require you to cycle on a stationary bike at a predetermined resistance while maintaining a consistent pedal rate, for 6 minutes. Exercise heart rate and rating of perceived exertion is collected in the final two minutes and used to predict maximal capacity.

2. Activity Two – Chester Step Test will require you to step onto and off a step according to an external pace in the form of a metronome recording. The test includes five (5) 2-minute stages but can be stopped early.

Third Laboratory Testing Session (La Trobe University Bendigo, Exercise Physiology Laboratory)

1. The time frame and activities for the third session you will depend on your participation in the exercise program. **If you consent to participate in the 6-week exercise program, you will complete activities three to six below (30 minutes combined time).** Activity One – you will be asked to complete a 30
second sit-to-stand (STS) test which involves you rising from a seated position before sitting back down as quickly and safely as possible in 30 seconds.

2. Activity Two - Maximum effort exercise test will involve a riding on a stationary bike with resistance regularly increasing until you feel that you can no longer continue. You will be required to wear a heart rate monitor and facemask (similar in size and shape to an oxygen mask) that will record how much air you breathe during exercise (20 minutes).

3. Activity Three – A blood test collected from a needle inserted into a vein in your arm (usual blood test procedure). Two small tubes of blood (approximately 15 ml in total) will be collected to determine your cholesterol profile

4. Activity Four – you will wear a 5-lead Holter monitor (portable ECG) to record and measure heart function

5. Activity Five – You will be required to lay on your back while a blood pressure cuff is placed around your upper arm and thigh. The time between heart beats will be measured by a device touching the skin over a vein on your neck.

6. Activity Six – you will wear a watch-like device for seven (7) days and record sleep quality in a sleep diary.

Exercise Program

If you volunteer to participate in the exercise program, you will be randomly allocated an onsite intervention (conducted at La Trobe University Bendigo) or at-home intervention conducted via a telehealth program. Telehealth component will involve patients remotely monitoring and logging training sessions (training diary) and attending a weekly virtual appointment with a member of the research team to discuss the training progress. The exercise program will involve three weekly sessions of aerobic exercise (i.e. walking) for up to 60 minutes per session. Following the 6-week exercise program you will be required to return for one final laboratory testing session.

Final Laboratory Testing Session (La Trobe University Bendigo, Exercise Physiology Laboratory)

In the final session you will repeat the testing activities in Session Three, with the addition of questionnaires from the first laboratory session a total duration of 60 minutes

1. Activity One – you will be asked to complete seven (7) questionnaires:
   a) General health questionnaire
   b) ESSA Adult Pre-exercise Screening System
   c) Duke Activity Status Index
   d) New York Heart Association Questionnaire
   e) Short Form 36 Questionnaire
   f) International Physical Activity Questionnaire
   g) Depression Anxiety Stress Scale

2. Blood testing

3. 5-lead ECG
4. Wearing a watch for seven (7) days

5. What will I be asked to do?

To fully participate in this study, you need to agree to the following restrictions:

- Time commitment of initial testing is three (3) laboratory sessions totalling approximately 2-3 hours
- Time commitment of the exercise program is sixty (60) minutes three times a week for six (6) weeks plus an additional sixty (60) minute post testing session. Training will be conducted onsite at La Trobe University or at-home via telehealth (requiring you to keep a log of training sessions and attend a weekly, online visit)
- A watch and recording sleep in a diary is recorded for a total fourteen (14) days, seven (7) days each pre and post exercise

6. What are the benefits?

The proposed research project has potential benefits to both you as an individual and the wider community. Firstly, exercise-based cardiac rehabilitation has been demonstrated to improve individual functioning, quality of life and reduce risk of future heart problems. While these results cannot be guaranteed, enrolment in initial testing and exercise program has the potential to improve important health measures. During the project you will also have access to additional testing, resources and support you may not otherwise receive. These include assessment by an Accredited Exercise Physiologist, measure of cardiac fitness and supervised exercise programs (onsite or at-home). Finally, your participation will benefit the wider community as results from this project will inform future research projects and cardiac rehabilitation programs.

7. What are the risks?

With any study there are (1) risks we know about, (2) risks we don’t know about and (3) risks we don’t expect. If you experience something that you aren’t sure about, please contact us immediately so we can discuss the best way to manage your concerns.

Potential risk for participants involved in the proposed research project include sustaining musculoskeletal injury during fitness testing or the subsequent exercise program. To complete exercise testing and the exercise program participants will be required to exert a level of physical effort that be considered uncomfortable and has a risk of muscular pain and/or injury. To minimise the risk of musculoskeletal injury volunteers will be recruited following referral to and discharge from Phase II cardiac rehabilitation programs and prescribed exercise training by their health care professional. Further assessment of disease severity and risk of exercise participation will be conducted by an Accredited Exercise Physiologist and the project is designed in such a way that submaximal exercise testing is conducted first to inspect participant functionality and response to increasing exercise loads.

Participants are exposed to an additional risk of physical injury during blood collection. Blood collection will involve a blood sample being taken from a vein in your arm using a needle, which is associated with a level of discomfort and potential risk of infection. Physical injury during the collection of blood is addressed by having the collection procedure conducted by trained and experienced researchers. Researchers will use appropriate personal protective equipment including gloves, alcohol wipes to disinfect the collection site and sterilised, sealed single-use material which is disposed of in puncture resistance biohazard containers. Finally, the smallest size needle that allows for adequate flow will be used to minimise discomfort during the collection procedure.
Finally, disclosing sensitive personal information may cause distress for participants undergoing rehabilitation programs for clinically significant cardiovascular conditions. Distress may be related to acknowledging risks associated with current conditions including the risk of future morbidity/mortality and anxiety about how the information may be used. To address the issue of potentially distressing information you will be encouraged to discuss involvement in the research project with the research team and your health care provider before commencing the project. During this time the treatment/storage/presentation of collected data will be explained to potential volunteers with an opportunity to ask questions or voice their concerns. Further, we will be checking in with you toward the end of the study to see if you would like your own customised report on your results.

**What if you become upset or distressed as part of this research?**
We do not anticipate any risks arising as a result of your participation in the study. However, if you become upset or distressed as a result of your participation in the research, and wish to talk to someone, we encourage you to contact your local GP, Lifeline (call 13 11 14 or visit [https://www.lifeline.org.au/](https://www.lifeline.org.au/)), Beyond Blue (call 1300 22 4636 or visit [https://www.beyondblue.org.au/](https://www.beyondblue.org.au/)) or another support service (see [https://www.healthdirect.gov.au/mental-health-helplines](https://www.healthdirect.gov.au/mental-health-helplines)).

**What happens if a medical emergency occurs?**
If something unexpected happens during experimental procedures, trained first aiders will be on hand to immediately assist and notify emergency services. The member(s) of the research team will not leave your side and will provide support to the best of their abilities.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>How often is it likely to occur?</th>
<th>How severe might it be?</th>
<th>How long might it last?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side effects related to exercise testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discomfort (sitting on bike for 6h)</td>
<td>Unlikely to occur</td>
<td>Mild</td>
<td>Several minutes</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Unlikely to occur</td>
<td>Mild</td>
<td>Several minutes</td>
</tr>
<tr>
<td>Muscle soreness</td>
<td>Somewhat likely</td>
<td>Mild</td>
<td>Several days</td>
</tr>
<tr>
<td>Heart palpations</td>
<td>Very unlikely</td>
<td>Mild</td>
<td>Several minutes</td>
</tr>
<tr>
<td>Muscle injury</td>
<td>Very unlikely</td>
<td>Moderate-severe</td>
<td>1-4 weeks</td>
</tr>
<tr>
<td>Heart attack</td>
<td>Very unlikely</td>
<td>Severe</td>
<td>Lifelong</td>
</tr>
<tr>
<td><strong>Side effects related to taking blood samples</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor infection</td>
<td>Unlikely to occur</td>
<td>Moderate</td>
<td>1 – 7 days</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Unlikely to occur</td>
<td>Moderate</td>
<td>Several minutes</td>
</tr>
<tr>
<td>Bruising</td>
<td>Somewhat likely</td>
<td>Moderate</td>
<td>1 - 7 days</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Unlikely to occur</td>
<td>Mild</td>
<td>Several minutes</td>
</tr>
<tr>
<td><strong>Side effects related to wearing the 5-lead Holter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Somewhat likely</td>
<td>Mild</td>
<td>1 – 14 days</td>
</tr>
</tbody>
</table>
8. What will happen to information about me?

Electronic and (where necessary) hard copy information is being collected as part of this research project. Where hard copy information is collected, the information will be transferred to an electronic format. The hard copies will be destroyed with electronic copies stored on password protected computers and destroyed fifteen years after publication.

All information will be stored in a re-identifiable format (name and personal identifying information removed) using a unique participant number assigned by the Chief Investigator. Only one File (participant identification code sheet) will be kept that can link you to your stored samples. Upon completion of the research project, the participant identification code sheet will be securely destroyed, resulting in the previously re-identifiable data now de-identifiable. Electronic files with re-identifiable data will be stored on the University P drive requiring permission to access, of which only investigators and medical professionals at Bendigo Health and St John of God will have access to the information. Re-identifiable data collected during the research projects will be stored using Cloudstor online with the University research data management policy. All files will be on password protected computers. Summary data (group averages and standard deviation of datasets) will be uploaded to an online institutional repository (OPAL) in the interest of collaboration and shared data.

Blood samples are being collected to analyse for markers of future cardiac risk and are stored in the same coded manner to protect your individual privacy for fifteen years in accordance with the University Research Data Management Policy. Any samples of written information linking you to the coded samples will not be released and the lead researcher will do everything possible to ensure privacy and confidentiality is maintained.

The results from the research project are expected to be published in peer reviewed journals and presented at research conferences. The format the data is presented in is non-identifiable group average ± standard deviation with no personal details reported anywhere in the documents. This project does not involve the collection, storage, or analysis of genetic testing that would result in information about an identifiable future health risk to themselves or relevant health information for their family members who are not part of the project.

It is also our responsibility to inform you that any issues requiring mandatory reporting will be acted upon by the lead researcher who will report it to the necessary authority as required by law. The personal information you provide will be handled in accordance with applicable privacy laws, any health information collected will be handled in accordance with the Health Records Act 2001 (Vic). Subject to any exceptions in relevant laws, you have the right to access and correct your personal information by contacting the research team.

9. Will I hear about the results of the study?

At the end of the study, you will be asked if you wish to receive your personal result collected during the research project including individual aerobic capacity (fitness), sleep quality and heart function data. If you express interest in receiving a copy, you will be emailed a de-identified and summated report at the conclusion of the research project with confidentiality and anonymity maintained at all times. If interested in the overall results, you will be given access to the published data following peer review and publication process. In the event any data is collected with possible prognostic outcomes, the research team will contact you with the relevant information and encourage you to discuss the results with your medical professional, as interpreting such results are outside the research team’s expertise.
10. What if I change my mind?
You can choose to no longer be part of the study at any time until four weeks following the collection of your data. You can let us know by:
   1. Completing the 'Withdrawal of Consent Form' (provided at the end of this document);
   2. Calling us; or
   3. Emailing us

Your decision to withdraw from the project will not affect your routine treatment, your relationship with those treating them, or your relationship with Bendigo Health, St John of God Health Care or La Trobe University. If you decide to withdraw, you will be informed if there are any special requirements linked to withdrawing and arrangements will be made to collect any experimental devices they may have. If you choose to withdraw during the project, we will stop collecting information from you, however any information collected up until that point will form part of the research project. If you withdraw after data analysis has commenced, we can only remove your name and contact details.

11. Who can I contact for questions or want more information?
If you would like to speak to us, please use the contact details below:

<table>
<thead>
<tr>
<th>Name/Organisation</th>
<th>Position</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Blake Collins</td>
<td>Holsworth Research Initiative – Research Officer</td>
<td>0409598135</td>
<td><a href="mailto:b.collins@latrobe.edu.au">b.collins@latrobe.edu.au</a></td>
</tr>
</tbody>
</table>

12. What if I have a complaint?
If you have a complaint about any part of this study, please contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Research Ethics Advisor</td>
<td>Senior Research Ethics Advisor</td>
<td>(03) 9479 1443</td>
<td><a href="mailto:humanethics@latrobe.edu.au">humanethics@latrobe.edu.au</a></td>
</tr>
<tr>
<td>Research Governance Manager</td>
<td>Bendigo Health Human Research Ethics Committee</td>
<td>(03) 5454 6412</td>
<td><a href="mailto:researchofficer@bendigohealth.org.au">researchofficer@bendigohealth.org.au</a></td>
</tr>
</tbody>
</table>
Consent Form – Adult providing own consent

Title
Cardiac rehabilitation in regional areas: developing a predictive model for ventilatory thresholds and assessing telehealth in phase III cardiac rehabilitation

Short title
Improving exercise prescription in regional cardiac rehabilitation programs

Principal Investigator
Dr Blake Collins

Associate investigator(s)
A/Prof Brett Gordon, Prof Michael Kingsley, Dr Daniel Wundersitz, Dr Lisa Hanson, Ms Jacquelyn Dunstan, Dr Simon Nichols and Mr Alasdair O’Doherty

Consent Agreement
I have read the Participant Information Sheet, or someone has read it to me in a way 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 participation in Phase Three will be offered to eligible participants.

I understand I am free to withdraw at any time during the project without effecting my future health care.

I understand that I will be given a copy of this document to keep and will be offered the opportunity to access a customised report of test results at the conclusion of the project.

I am aware that if I decide to withdraw in future that data collected by the researchers up to the time of withdrawal will form part of the research project results.

I agree to have blood samples collected and understand the risks involved (please tick one); Yes ☐ or No ☐

I understand that my data collected during this project including blood samples will be stored for 15 years post publication before being disposed of.

Declaration by Participant – for participants who have read the information

Name of Participant (please print) ______________________________________________________

Signature __________________________________________________________________________ Date _____________________________

Declaration by 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 Senior Researcher (please print) __________________________________________________

Signature __________________________________________________________________________ Date _____________________________
Form for Withdrawal of Participation – Adult providing own consent

Title
Cardiac rehabilitation in regional areas: developing a predictive model for ventilatory thresholds and assessing telehealth in phase III cardiac rehabilitation

Short title
Improving exercise prescription in regional cardiac rehabilitation programs

Principal Investigator
Dr Blake Collins

Associate investigator(s)
A/Prof Brett Gordon, Prof Michael Kingsley, Dr Daniel Wundersitz, Dr Lisa Hanson, Ms Jacquelyn Dunstan, Dr Simon Nichols and Mr Alasdair O'Doherty

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 Bendigo Health, St John of God Health Care or La Trobe University.
I understand that the data collected up until this stage will form part of the research project results

Name of Participant (please print) _____________________________________________________________
Signature __________________________________________________ Date ____________________________

Declaration by 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 Senior Researcher (please print) __________________________________________________________
Signature __________________________________________________ Date ____________________________
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative information</td>
<td></td>
<td>Title 1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2a</td>
<td>Trial registration 2a Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>2, 6</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Protocol version 3 Date and version identifier</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Funding 4 Sources and types of financial, material, and other support</td>
<td>16, 17</td>
</tr>
<tr>
<td></td>
<td>5a</td>
<td>Roles and responsibilities 5a Names, affiliations, and roles of protocol contributors</td>
<td>1, 17</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>7, 13, 14</td>
</tr>
<tr>
<td>Introduction</td>
<td>6a</td>
<td>Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>4, 5</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Objectives 7 Specific objectives or hypotheses</td>
<td>5</td>
</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
<td>6</td>
</tr>
<tr>
<td>---------------</td>
<td>---</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td><strong>Methods: Participants, interventions, and outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study setting</td>
<td>9</td>
<td>Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained</td>
<td>7</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>10</td>
<td>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</td>
<td>7</td>
</tr>
<tr>
<td>Interventions</td>
<td>11a</td>
<td>Interventions for each group with sufficient detail to allow replication, including how and when they will be administered</td>
<td>8, 9, 10, 11</td>
</tr>
<tr>
<td></td>
<td>11b</td>
<td>Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>11c</td>
<td>Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)</td>
<td>9, 10</td>
</tr>
<tr>
<td></td>
<td>11d</td>
<td>Relevant concomitant care and interventions that are permitted or prohibited during the trial</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcomes</td>
<td>12</td>
<td>Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended</td>
<td>10, 11, 12</td>
</tr>
<tr>
<td>Participant timeline</td>
<td>13</td>
<td>Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)</td>
<td>Supplementary attachment</td>
</tr>
<tr>
<td>Sample size</td>
<td>14</td>
<td>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</td>
<td>13</td>
</tr>
</tbody>
</table>
## Recruitment

15. Strategies for achieving adequate participant enrolment to reach target sample size

<table>
<thead>
<tr>
<th>Methods: Assignment of interventions (for controlled trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation:</td>
</tr>
<tr>
<td>Sequence generation</td>
</tr>
<tr>
<td>16a. Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions</td>
</tr>
<tr>
<td>Allocation concealment mechanism</td>
</tr>
<tr>
<td>16b. Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
</tr>
<tr>
<td>Implementation</td>
</tr>
<tr>
<td>16c. Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</td>
</tr>
<tr>
<td>Blinding (masking)</td>
</tr>
<tr>
<td>17a. Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how</td>
</tr>
<tr>
<td>17b. If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
</tr>
<tr>
<td>Methods: Data collection, management, and analysis</td>
</tr>
<tr>
<td>Data collection methods</td>
</tr>
<tr>
<td>18a. Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol</td>
</tr>
<tr>
<td>18b. Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols</td>
</tr>
<tr>
<td>Data management</td>
</tr>
<tr>
<td>Statistical methods</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>20c</td>
</tr>
</tbody>
</table>

**Methods: Monitoring**

| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |

**Harms**

| 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |

**Auditing**

| 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |

**Ethics and dissemination**

| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 7, 16 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7 |
| 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 7 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13, 16 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 13 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 16 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 16 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 16 |

**Appendices**

| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons *Attribution-NonCommercial-NoDerivs 3.0 Unported* license.