**High-Intensity Interval Training (HIIT) for patients with cardiac disease: a randomised controlled trial.**

**Study Protocol**

Version Number: 2

Date of Protocol: November 2019

# SYNOPSIS

Protocol Title: HIIT RCT Study Protocol

Protocol Version: 2

# List of Investigators

## Chief Investigator:

Dr Andrew Keech

Department of Exercise Physiology, University of New South Wales, Kensington NSW 2052, [andrew.keech@unsw.edu.au](mailto:andrew.keech@unsw.edu.au)

## Principal Investigator:

Dr Jennifer Yu

Department of Cardiology, Prince of Wales Hospital, Barker St , Randwick NSW 2031 [Jennifer.Yu@ehc.com.au](mailto:Jennifer.Yu@ehc.com.au)

## Co-Investigators:

Katie Holgate

Jennifer Fildes

Dr Praveen Indraratna

Dr Clare Arnott

Lissa Spencer

Fiona Skarligos

Amanda Piggott

# SUMMARY

Study title: High-Intensity Interval Training (HIIT) for patients with cardiac disease: a randomized controlled trial.

Protocol version 2

Objectives To assess the comparative effectiveness, safety and enjoyment of high-intensity interval exercise training (HIIT) and ‘usual care’ (moderate-intensity exercise training) in patients with cardiac disease undergoing cardiac rehabilitation (CR).

Primary outcome Cardiac rehabilitation completion rate (defined as completed minimum 10 sessions of training intervention)

Secondary outcomes Blood pressure (resting systolic, diastolic, mean arterial pressure)

Cardiorespiratory fitness (six-minute walk test, 6MWT)

Body composition (total % body fat; weight; BMI; waist circumference)

Affective state (mood and quality-of-life questionnaires)

Safety (cardiovascular-related adverse events during or immediately after exercise)

Training enjoyment

Hospital re-admission rate 3-month follow-up

Physical activity levels 3-month follow-up

Study design: Randomised controlled trial

Planned sample size: 64 participants

Selection criteria: Inclusion criteria (12 step process) and exclusion criteria are detailed below.

Study procedure: Participants complete 6 weeks of HIIT or moderate-intensity continuous training (MICT) in cardiac rehabilitation. Pre- and post-training assessments will be performed across a range of cardiovascular health and fitness measures.

Statistical considerations Sample size calculated. Randomisation 3:1 HIIT vs MICT. Basic statistical design (2 groups × 2 time-points for most assessment measures) with ANOVA / t-tests as basis for analysis.

Duration of the Study 2 years

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# BACKGROUND

Cardiovascular disease is the primary cause of death worldwide [[1](#_ENREF_1)]. Cardiac rehabilitation (CR)isa key component in reducing morbidity and mortality for people with cardiac disease, with phase 2 outpatient programmes traditionally based around low- to moderate-intensity aerobic exercise training in addition to coordinated and individualised interventions around patient education, risk factor management and psychosocial care. The safety and efficacy profile of traditional low- to moderate-intensity exercise training within CR are well established, with reduced cardiovascular mortality and improved quality of life observed [[2-5](#_ENREF_2)]. However, the rate of CR service uptake and adherence are relatively poor, with only a minority of eligible patients participating in CR, and less patients again then completing a full exercise-training program within the CR setting [[6](#_ENREF_6), [7](#_ENREF_7)].

Determining the characteristics of exercise for patients within CR which optimally combine patient safety, efficacy and enjoyment is a key priority. There is increasing interest in the application of high-intensity interval training (HIIT) for this patient group. There is now robust evidence supporting HIIT as an efficacious training format in both healthy and chronic illness populations. HIIT appears more effective than moderate-intensity continuous training (MICT) for improving aerobic fitness [[8](#_ENREF_8)], a strong predictor of mortality and cardiovascular risk [[9-13](#_ENREF_9)]. In addition, HIIT is an effective exercise intervention for improving a range of cardiovascular health markers including body composition [[14](#_ENREF_14)], vascular function [[15](#_ENREF_15)] and diabetic profile [[16](#_ENREF_16)]. HIIT also shows a profile of positive affect and enjoyment at a level equal or greater than MICT [[17-19](#_ENREF_17)], factors which directly influence training adherence.

Based on the evidence of strong efficacy, recent proof-of-concept trials have been conducted applying HIIT on patients with coronary artery disease (CAD) and heart failure within CR. Findings from these studies so far have been generally positive. Multiple recent meta-analyses exploring the efficacy of HIIT within CR have reported greater magnitude of improvement in aerobic fitness compared to MICT, with estimates ranging from 1.15 to 1.78 mlO2/kg/minute [[20-24](#_ENREF_20)]. As a reference, an improvement in aerobic fitness by 3.5 mlO2/kg/minute equates to an ~8-17% reduction in all-cause and cardiovascular-related mortality [[9-13](#_ENREF_9)]. In addition, the safety profile of HIIT within CR, drawn from a review of 23 studies and including over 17,000 HIIT sessions equating to 11,333 training hours, has shown only 1 major cardiovascular-related adverse event during or immediately following HIIT sessions [[25](#_ENREF_25)].

The most commonly applied HIIT protocol is the so-called ‘Scandinavian’ model of HIIT, comprised of 4-minute intervals of high-intensity at 90-95% maximum heart rate (HRmax) interspersed with 3-min recovery intervals (4 × 4-min model). However, this model does not appear to be optimal within CR due to concerns around the safety profile [[26](#_ENREF_26)]. We have designed a HIIT protocol that attempts to balance the key CR priorities – patient safety, efficacy for lowering cardiovascular risk, and exercise training sustainability (adherence and enjoyment). The protocol involves short-duration (30-second) intervals and an intensity (approximating 85-90% HRmax) which is lower than the Scandinavian model. Feasibility data from a single-arm trial within the Prince of Wales Hospital cardiac rehabilitation service (N = 29 patients) showed that the novel HIIT protocol was effective (CRF +12%; blood pressure -6%; body fat -5% including visceral fat -12%; improved mood), safe (no cardiovascular-related adverse events associated with the exercise sessions) and enjoyable with high levels of patient adherence to the training [[27](#_ENREF_27)].

# STUDY OBJECTIVES

To assess the comparative effectiveness, safety and enjoyment/adherence of the HIIT protocol vs. ‘usual care’ MICT for patients with cardiac disease within outpatient (phase 2) cardiac rehabilitation.

# STUDY DESIGN

## Design

The study is a two-site prospective randomized controlled trial within tertiary-care outpatient CR services. Participants will complete 10 training sessions (5 weeks × 2 sessions per week) of their allocated training intervention. Interventions are work-matched. Assessments will be conducted pre- and post-intervention.

## Study Groups

Patients will be randomized in a 3:1 ratio to either a high-intensity interval training (HIIT) group or a ‘usual care’ group involving moderate-intensity continuous training (MICT).

## Number of participants

64 participants will be recruited across the 2 sites.

## Number of centers

The study represents a collaboration between 3 centers: Prince of Wales (PoW) Hospital (Cardiac Rehabilitation service), the Royal Prince Alfred (RPA) Hospital (Cardiac Rehabilitation service) and University of New South Wales Exercise Physiology (UNSW). Participants are patients with cardiovascular disease referred to CR at either RPA or PoW Hospital. All HIIT and MICT and pre- and post-training assessments will be conducted within the CR services. Stress testing prior to enrolment is to be performed in the outpatient setting. Some optional assessments will be performed at the Department of Exercise Physiology in the Wallace Wurth Building, UNSW, which is located adjacent to PoW.

## Duration

We anticipate that the study will start in first quarter 2020. Based on current CR enrolment rates and the speed of patient enrolment within the feasibility study, we estimate that we will recruit 64 study participants over approximately 2 years.

# PARTICIPANT SELECTION

## Inclusion Criteria

Inclusion criteria are:

1. Age between 18 and 75 years
2. Documented coronary artery disease (CAD), specifically recent acute myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), or, treated valvular heart disease, specifically following valve repair or replacement
3. Clinically stable for at least 4 weeks following AMI or PCI, or 6 weeks following CABG or other surgery requiring sternotomy
4. NYHA Class I
5. Sinus rhythm
6. First-time participant at the CR
7. Left ventricular ejection fraction > 40%
8. Receiving optimal medical treatment
9. Successful completion of a 2 session ‘run-in’ period of exercise training at the CR (‘usual care’ consisting of low to moderate-intensity continuous aerobic exercise and light-intensity resistance exercises).
10. Treating cardiologist’s clear approval for participation
11. Negative exercise stress test result

## Exclusion Criteria

Primary diagnosis of heart failure; having a pacemaker; haemodynamically significant valvular disease; severe chronic obstructive pulmonary disease; unstable symptomatology; post-surgical tachycardia; cognitive impairment; not fluent in English; unable to undertake cycling exercise; women lactating, pregnant or of childbearing potential who are not willing to avoid becoming pregnant during the study; or other co-morbidities precluding participation in a structured exercise programme.

# STUDY OUTLINE

The study flow chart is shown in **Figure 1**. Patients entering the CR service will be screened for their preliminary study eligibility at the initial assessment by the clinical nurse consultants (CNC) at each site. Patients who meet the preliminary inclusion (criteria 1-8) and exclusion criteria will be informed of the study and invited to participate at this consult. Potential participants will complete 2 sessions of low- to moderate-intensity exercise (‘usual care’) within the CR service to demonstrate stable physiological response to the exercise sessions (inclusion criterion 9). Clearance will then be obtained from the participant’s treating cardiologist to participate in this trial (inclusion criterion 10), and if a recent stress test has not been performed, a stress test will be performed either with the participant’s own treating cardiologist, or at the cardiology department of POWH or RPA.

Patients with both cardiology clearance and negative exercise stress test will be considered enrolled in the study and undergo randomisation. Their treating doctors (including the cardiologist and GP) will be notified of study enrolment and random assignment.

## Figure 1. Study flow chart

## Randomisation and blinding

Participants will be randomly assigned to HIIT or MICT on a 3:1 basis. Block randomisation will be applied for site, gender and diagnosis (stable CAD, acute coronary syndrome, valvular heart disease). A random number sequence generated by an independent statistician will be used to determine the 3:1 block randomised allocation sequence. Participants will be informed of their randomised group allocation upon arrival to the first training session, after enrolment into the study and after completion of all pre-training assessments. The lead cardiopulmonary physiotherapist conducting the training sessions will receive the allocation sequence from the lead investigator (who is ‘off-site’) and will then inform the patient of their randomised group allocation, and will not be involved in any subsequent participant outcome assessments or data analysis. Participants cannot be blinded to their training group allocation but will be blinded to the hypotheses of the study and to their baseline assessment data. Researchers performing all outcome assessments will be unblinded to the participant’s training group allocation.

## Interventions

Prior to enrolment, all participants will undergo at least 2 training sessions of ‘usual care’ (low-moderate intensity continuous aerobic exercise). For new patients within the service this typically involves 30-40 minutes aerobic exercise at RPE ~11, performed on either a treadmill (walking), cycling or cross-trainer machine. Potential study participants will be monitored for RPE responses during these initial sessions, and BP is monitored before and after the sessions.

Once enrolled, training will involve completing 10 sessions (5 weeks × 2 sessions per week) of either HIIT or MICT. **Table 1** details training characteristics for HIIT and MICT participants. Individual training progression will be based on HR and RPE targets during sessions. The training interventions (HIIT and MICT) are nominally matched for total work performed based on the approximated workloads. Based on feasibility study data (mean pre-training maximal workload = 177 watts) and anticipated training workloads, we estimate mean total work of ~1.25 × 105 Nm expended in the initial training session for both HIIT and MICT groups, building up to ~1.72 × 105 Nm expended for the final training session – a ~37% increase in total work performed across the 6-weeks of training for both groups. All session workloads will be recorded and used post-study to determine matching for total work performed.

Training will be conducted on electronically-braked cycle ergometers (Ergo-Fit 457Med, Germany). The bikes allow for pre-programming of the HIIT session workloads and timing of the work intervals. All training sessions will be performed under supervision by a cardiopulmonary physiotherapist and/or an exercise physiologist. During each session, heart rate will be continuously monitored using a standard monitor (Polar H10, USA) and RPE monitored using the modified Borg scale (6-20) [[28](#_ENREF_28)].

### HIIT protocol

The HIIT programme consists of 15-20 repetitions × 30-second intervals at 85-90% HRmax (RPE ~14-17), interspersed with 30-second active recovery. Each session will begin with a 10-minute moderate-intensity warm-up at ~65% HRmax and ended with a 5-minute active recovery cool-down. Training progression characteristics for HIIT participants are detailed in **Table 1**. For the first 3-weeks of training, all patients will complete 15 repetitions per session (including 2 passive rests for BP measurement – after the 5th and 10th repetition); in the final 3-weeks of training, patients will complete 20 repetitions per session (including 1 passive rest – after the 10th repetition). The passive rest periods will be ~30-seconds or until BP measurement has been accurately recorded. Workloads are determined by the clinical staff to maintain the target HR (and/or RPE) range for the 5- or 10-repetition block (before a passive rest for BP measurement). HR and RPE will be recorded in the last 5 seconds of every 5th work interval. HR and BP will be monitored during the cool-down period to ensure patient safety. The total time commitment for each HIIT session is 30 minutes (for 15 total repetitions) to 35 minutes (for 20 total repetitions), equating to mean across all sessions 32.5 minutes.

### MICT protocol

The MICT programme consists of 35-43 minutes continuous cycling at 65-70% HRmax (RPE ~11-13). Training progression characteristics for MICT participants are detailed in **Table 1**. Workloads will be adjusted the clinical staff based on HR response over the duration of the training session to maintain the HR range, as such, workloads will likely change within individual training sessions. HR, RPE and workload will be recorded every 5 minutes. No warm-up or cool-down is required due to the moderate-intensity of the training. The total time commitment for each MICT session is 35 to 43 minutes, equating to mean across all sessions 39 minutes.

**Table 1.** Exercise training programming characteristics for HIIT and MICT interventions.

|  |  |  |
| --- | --- | --- |
| **Sessions** | **HIIT** | **MICT** |
| **Target HR: 85-90% HRmax**  **Target RPE: 14-17** | **Target HR: 65-70% HRmax**  **Target RPE: 11-13** |
| 1 - 5 | 15 × 30-sec @ 85-90% HRmax | 35-min @ 65-70% HRmax |
| 6 - 10 | 20 × 30-sec @ 85-90% HRmax | 43-min @ 65-70% HRmax |

**Physical activity and dietary behaviours**

Resistance exercise will be offered to patients after some training sessions as part of the usual care provided by the CR services. These group-based, whole-body low-intensity resistance exercise sessions are 15-30 minutes in duration and are conducted immediately following the training sessions. The number of resistance exercise sessions performed by each participant will be recorded.

Standard lifestyle education services will be offered as part of the usual care provided by the CR services, including modules covering nutrition, physical activity and other topics relevant for managing cardiovascular disease. Individualized advice on diet and exercise will not be provided to study participants.

Patients on β-blocker medication will be asked to take the medication in the morning before each assessment and training session so as to maintain consistent HR response throughout the study. Self-reported physical activity patterns outside of scheduled training sessions will be monitored using the International Physical Activity Questionnaire (IPAQ). Dietary patterns will be monitored by via food diary in the first and last weeks of training. Participants will be asked not to consume excessive alcohol or perform strenuous exercise 24 hours prior to each assessment and training session.

## Outcome measures

## *Training session adherence, enjoyment and affect*

The number of training sessions completed will be recorded for each patient (training session adherence). The primary outcome measure is completion of the study, defined as 10 sessions of CR following randomization. Training session characteristics will be calculated including mean HR (as % of HRmax), RPE and workload.

Patients will rate their enjoyment of each training session using the Exercise Enjoyment Scale (EES) [[29](#_ENREF_29)]. The EES applies a one-item Likert scale from 1 (not at all) to 7 (extremely) that asks: “Use the following scale to indicate how much you enjoyed the exercise session” (**Appendix 1**).

The Feeling scale (FS) will be applied to assess any exercise-induced change in mood [[30](#_ENREF_30)]. The FS is a one-item validated measure of generalised affective valence (–5 very bad to +5 very good) (**Appendix 2**). Patients will be asked their session enjoyment and current mood at the conclusion of the session, with the mood score compared to the value reported immediately before starting the training session.

***Health outcomes***

Assessments of health outcomes will be conducted at the CR service before and after the training intervention. Assessments will be conducted in a standardized order (affective state, body composition, blood pressure, functional capacity). For body composition assessment reasons, participants will attend the assessment session fasted, having been asked to not consume food (or caffeine, tobacco or alcohol) within 4 hours. The post-training assessment will be conducted between 1-4 days following the final training session. All assessments will be conducted by a trained practitioner unblinded to the participant’s training group allocation.

### *Affective state*

The Depression Anxiety Stress scale (DASS21), the Positive and Negative Affect Schedule (PANAS) and the MacNew Heart Disease Health-related Quality of Life questionnaire (MacNew) will be applied. DASS is a 21-item questionnaire using a 4-point Likert scale (0 = not at all; 3 = very often or very much) to analyse negative emotional states in the previous week (**Appendix 3**). PANAS is a 20-item questionnaire using a 5-point Likert scale (1 = not at all or only slightly; 5 = extremely) to analyse both positive and negative feelings and emotions in the previous week (**Appendix 4**). The MacNew questionnaire consists of 27 items covering physical limitations, emotional function and social function [[31](#_ENREF_31)] (**Appendix 5**).

### *Body composition*

Body composition will be assessed via measures of total percent body fat using bioelectrical impedance analysis (BIA) scales; body mass index (BMI, calculated from height measured using a stadiometer and weight measured using calibrated scales); and waist circumference (measured via tape measure in the horizontal at the point of the umbilicus).

### *Blood pressure*

Blood pressure (resting) will be assessed using an automated, upper-arm cuff-oscillometric sphygmomanometer (Omron HEM-907, Kyoto, Japan). This will provide measures of brachial systolic pressure, diastolic pressure, mean arterial pressure and resting heart rate. The measure will be conducted after 5 minutes seated rest.

### *Aerobic fitness*

Aerobic fitness will be assessed by the 6-minute walk test (6MWT) and rate of heart rate recovery (HRR) following the 6MWT. 6MWT will be conducted using standard procedures. Patients are instructed to walk as far as possible along a 30-meter corridor for 6 minutes, to achieve their maximum possible walking distance. Standardized instructions are provided during tests, and HR and RPE will be measured. HRR will be assessed by the change in HR at 1-minute post-test (seated rest immediately upon test termination) compared to HR reached during the test (recorded in last 5 seconds of the test).

## *Safety*

Exercise-related adverse events (AE), defined as occurring during or up to 4 hours following a HIIT or MICT session, will be recorded. All other AEs are also recorded. All exercise-related AEs will be reviewed by the data safety monitoring board comprised of three clinicians, including two cardiologists. AEs will be categorised according to origin (cardiovascular or non-cardiovascular) and severity (minor – stable, symptoms relieved without requiring intervention by the CR CNC; or major – unstable and requiring immediate emergency intervention, or persistent signs or symptoms requiring CR CNC review).

### *Optional sub-study measures*

Patients will also be offered the choice of assessment of whole-body composition measured using dual energy x-ray absorptiometry (DXA) and central blood pressure and aortic stiffness using applanation tonometry. These participants will be tested using standard procedures, including following an overnight fast and after removing all metals and jewellery. Participants are positioned in the centre of the DXA platform (Lunar iDXA, GE Medical Systems, Wisconsin), supine, with arms by their side, and are instructed to remain still for the duration of the scan. Data will be recorded using standard DXA software (enCORE version15). The DXA machine will be calibrated prior to each day of testing. Outcome measures are levels of body fat and lean body mass (in kg and as % of body weight) for both total body and regional-specific sites (trunk, android, gynoid, visceral, legs, arms). Applanation tonometry (SphygmoCor XCel, AtCor Medical, Sydney, Australia) will be conducted using techniques as stipulated in the expert consensus guidelines regarding testing of arterial function [[32](#_ENREF_32)]. Participants are tested in supine position after at least 10 minutes supine rest. For pulse-wave analysis, a cuff will be placed around the participant’s upper arm, with the cuff inflated and then deflated to assess central (aortic) and peripheral (brachial) measures of blood pressure (BP), and central index of pulse wave augmentation (AIx). For pulse-wave velocity, a tonometer will be pushed against the participant’s carotid artery to detect carotid pulse, while a thigh cuff will be applied to detect femoral pulse. The carotid-femoral pulse wave velocity (PWVcf) will be calculated from these values and used to assess changes in aortic stiffness.

## Health outcomes at 3-month follow-up

At 3 months following participation in the training intervention, patients will be contacted via phone. Incidence of hospital re-admission will be recorded. Physical activity patterns during the 3 months following study involvement will be discussed using a semi-formal interview style, and incidence of sedentary behaviours (no formal exercise training post-study) or maintenance of regular HIIT or MICT will be recorded.

## Table 1. Schedule of events

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Initial Consult with CNC | ‘Usual care’ exercise training (MICT)  (2 sessions) | Stress Test | Pre-training assessments (compulsory & optional) | Exercise training  (10 sessions) | Post-training assessments (compulsory & optional) |
| Inclusion (steps 1-8) / exclusion criteria | ✓ |  |  |  |  |  |
| Informed consent | ✓ |  |  |  |  |  |
| ‘Run-in’ period of usual care (step 9) |  | ✓ |  |  |  |  |
| Approval of treating cardiologist (step 10) |  | ✓ |  |  |  |  |
| Negative ECG (step 11) |  |  | ✓ |  |  |  |
| Assessments @ CR service (BP, body composition, fitness, mood & QoL questionnaires) |  |  |  | ✓ |  | ✓ |
| Optional assessments @ UNSW (DEXA, applanation tonometry) |  |  |  | ✓ |  | ✓ |
| HIIT or ‘usual care’ MICT |  |  |  |  | ✓ |  |
| Exercise enjoyment assessment |  |  |  |  | ✓ |  |
| Adverse event reporting |  | ✓ | ✓ | ✓ | ✓ | ✓ |

# STUDY PROCEDURE RISKS

## Risk of cardiovascular event during training sessions

In the event of a medical emergency during the HIIT sessions, a Code Blue will be initiated by any of the staff present. As the HIIT sessions occur on hospital grounds, urgent medical assistance will be provided from the Code Blue team (generally intensive care doctors and nurses, as well as a cardiology registrar). During the HIIT sessions, the supervising CNC, the lead physiotherapist and all Exercise Physiology students assisting with conducting the sessions will be First Aid certified and competent at administering first-aid if necessary. A flow-chart for treatment of medical problems in the cardiac rehabilitation department is presented in **Appendix A**. Both cardiac rehabilitation departments have a fully stocked emergency resuscitation trolley as medical emergencies may occur during day-to-day running of these departments.

## Risk of musculoskeletal injury during training sessions or assessments

A brief warm-up (stretching + moderate-intensity aerobic stage) will be conducted at the start of the training sessions and the stress tests to minimise risk of a muscle strain during cycling exercise.

## General risks during optional assessments at UNSW

The optional assessment tasks completed at the UNSW lab (body composition; vascular function) are very low risk of injury and essentially are conducted during supine rest. All assessments will be conducted by an exercise physiology academic (AK). The Research Lab (UNSW Exercise Physiology LG44 Wallace Wurth) contains a defibrillator and an emergency phone with security on-call. The researcher conducting the assessments is First Aid accredited and trained in use of the defibrillator. The test of aortic stiffness requires application of light pressure (tonometer) to the carotid artery, therefore patients will be advised to remain lying still for ~30 seconds after the tonometer application to minimize risk of carotid-massage induced lightheadedness.

## Risk of radiation from DEXA testing (optional assessment at UNSW)

Dual energy X-ray absorptiometry (DXA) is a non-invasive medical imaging technique which is the gold standard instrument to assess three compartment body composition. Our DXA machine is high resolution, fan beam, and research-grade (GE Lunar iDXA). DXA involves the utilisation of ionising radiation through low energy X-rays.

The radiation hazard to the patient is often expressed in terms of the effective dose (ED). This is defined as the sum of the absorbed doses to each irradiated organ weighted for the radiation type and the radio-sensitivity of that organ (ICRP, 1991). The ED is equivalent to the uniform whole-body dose that will put the patient at equivalent risk from the carcinogenic and genetic effects of radiation (ICRP, 1991). For low doses, as encountered in DXA, the principal risks to patients are the stochastic process of carcinogenesis and genetic effects. The level of risk for stochastic effects can be estimated from the effective dose. The risk refers to the total detriment from the radiation exposure: namely the sum of the probability of fatal cancers, the weighted probability of non-fatal cancers and the probability over all succeeding generations of serious hereditary disease resulting from the dose. This risk estimate to the general population is averaged over the full age distribution.

Utilising NRPB 4 methodology, the maximum exposure from a scan of the manner being used for this research is 0.035 mSv per scan. The total excess effective dose for this research trial (0.035 mSv x 2 assessments = 0.07 mSv) is less than 0.2 mSv which is the dose delivered by natural background radiation over a few weeks. The ED also does not exceed the dose constraints of the ARPANSA Code of Practice RPS8 (annual dose constraint of 5 mSv and not to exceed 10 mSv over 5 years).

Using the categorisation recommended in RPS8, the radiation risk from this research trial is: Category I – Minimal low risk (less than 1 in 100,000). The numerical risk of developing solid tumour associated with exposure to 0.035 mSv is about 1 in 574,000.

We have attached a statement confirming that the site of the DXA is involved in a quality assurance program. Additionally, a statement of radiation related risk will be provided to the participants in the Participant Information Sheet.

## Recruitment and Screening

New patients referred to cardiac rehabilitation will be screened for study eligibility by the Cardiac Rehabilitation Clinical Nurse Consultant (CNC) at the initial consult.

## **Informed Consent**

The study will be discussed verbally with the patient at the end of the initial consult with the CNC and the written PIS&CF will be provided to the patient if they show interest in participating. As part of the PIS&CF, patients will be informed that their participation is free and voluntary and that their decision not to participate will not impact on their future medical care / cardiac rehabilitation. Irrespective of the patient's participation in the study, the cardiac rehabilitation staff will continue to treat that patient per current standard of care and protocol.

## Ethics

All procedures are in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

# SAFETY

## Adverse event reporting

An adverse event is any untoward medical occurrence in a participant which may or may not have a causal relationship with the study procedure. It can be any unfavourable or unintended symptom, sign or condition. A serious adverse event results in death or is life-threatening, in hospitalisation or prolongation of existing hospital admission, persistent or significant disability/incapacity or congenital/birth defect, or in a condition requiring medical or surgical intervention,

Participants will be asked to immediately report any adverse events or symptoms during CR sessions to the CR CNC. Events will also be categorised as: minor (stable, symptoms relieved without requiring intervention by the CR CNC) or major (unstable and requiring immediate emergency intervention, or persistent signs or symptoms requiring CR CNC review). The PoW CR Adverse Events flowchart is provided as an Appendix for this Ethics application. Participants will also be asked to report any adverse events which occur outside CR sessions to Dr Jennifer Yu, the POWH Principal Investigator, or Dr Arnott, the RPA Principal investigator.

## Data Safety and Monitoring Board

The DSMB will review all adverse events and notify the study PIs of any safety or compliance issues as well as make recommendations of study termination if necessary. The DSMB will function in accordance with regulatory guidelines. DSMB members include 3 clinicians who are independent from the study.

# STATISTICAL CONSIDERATIONS

The sample size calculation is based on a significant difference between the two groups for the completion rates. Therefore, with power of 0.8 and a 0.05 significance level, and anticipating a 5% drop-out rate (loss to follow-up) for the HIIT intervention (based on feasibility study findings of 95.8% completion) and 35% drop-out rate for the MICT intervention (based on historical CR site completion rates for usual care for the analogous study population in terms of age and CAD indication for CR referral) in addition to accounting for the 3:1 allocation, we calculate a minimum of 64 participants will be required (HIIT N = 48, MICT N = 16).

Analyses will be performed using standard statistical software (IBM Statistical Package for Social Sciences; SPSS version 25, Chicago, IL, USA). Shapiro-Wilk tests will be applied to assess normality of the continuous variables. Unadjusted tests of group differences at follow-up will be examined using independent samples t-test for continuous, normally-distributed variables. Assuming no missing data, paired-samples t-tests will be applied for within group comparisons (pre vs post). If there are missing data, mixed models will be used to obtain test change over time. Mixed models will also be used to obtain adjusted tests between and within groups differences. If data violate normality assumptions, then appropriate transformations or non-parametric tests will be used. Pearson’s Chi-square test will be applied to assess associations among categorical variables. Effect sizes will be calculated using Cohen’s *d* for normally-distributed outcomes or Cliff’s *D* for non-normally distributed outcomes. Variables will be presented as mean ± standard deviation or median (inter-quartile range) (for continuous variables) or frequencies (percentages) (for categorical variables). Significance is set at p < 0.05.

# STORAGE AND ARCHIVING OF STUDY DOCUMENTS

The Informed Consent forms and assessment data forms will be stored in a secure filing cabinet in a secure room at each CR site. Paper and electronic data will be stored only in a coded fashion utilising the unique subject identifiers (Study ID e.g. HIIT1; 2 x 2 code). The password-protected datasets will be stored on the UNSW SOMS server (Z:\EPR\clinical projects\Project-HIIT-CAD). Only the lead researchers will have the passwords to access the datasets. Dissemination of findings will not include any identifying details for any of the participants. All identifiable data related to the study will be destroyed 7 years after publication of the results of the studies. Paper files will be shredded, electronic data will be erased.

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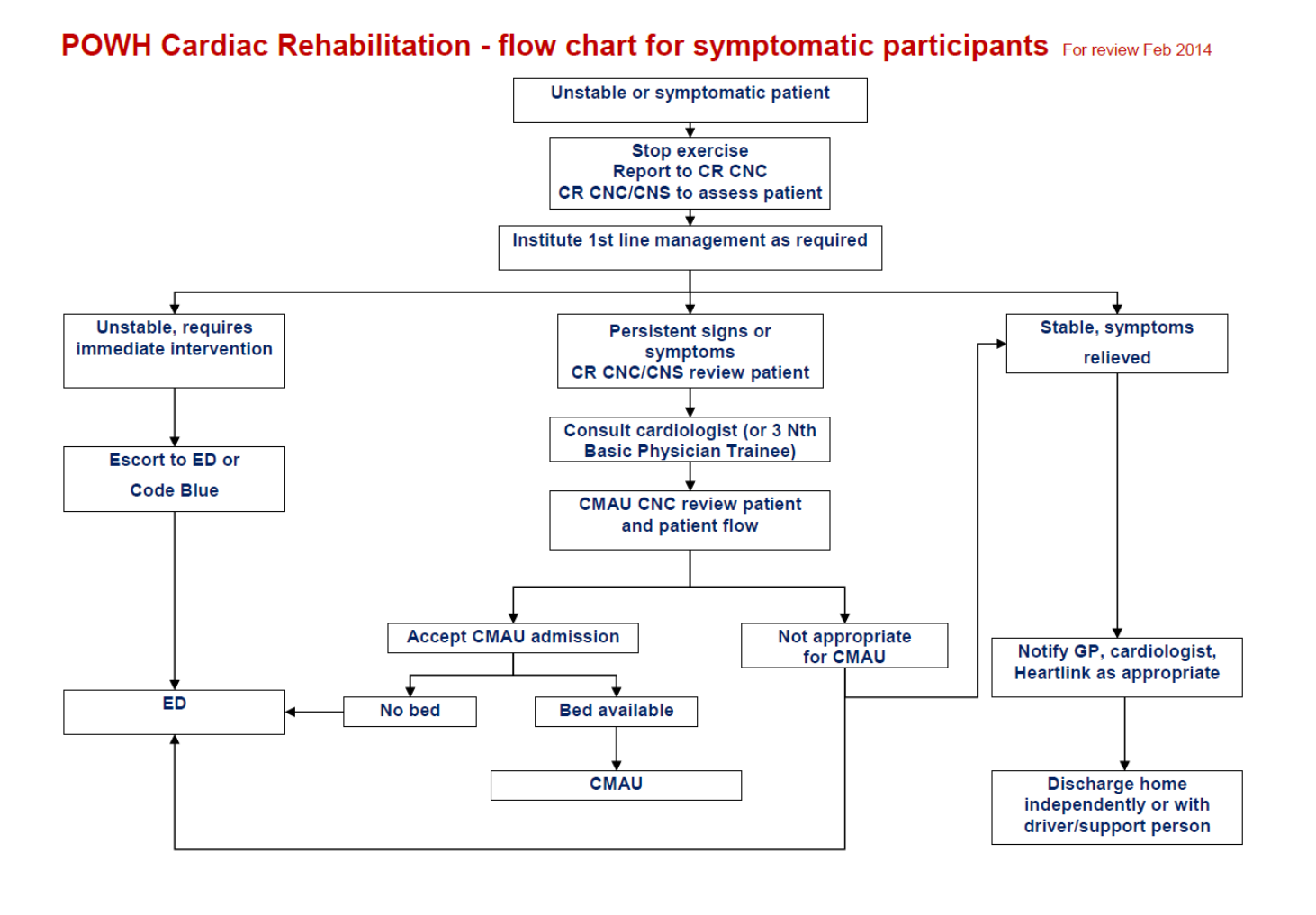
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# APPENDICES

## Appendix A: Adverse events flow chart



## Appendix B: Rating of perceived exertion (RPE) [[28](#_ENREF_28)]



|  |  |
| --- | --- |
| Rating | Perceived Exertion |
| 6 | No exertion |
| 7 | Extremely light |
| 8 |  |
| 9 | Very light |
| 10 |  |
| 11 | Light |
| 12 |  |
| 13 | Somewhat hard |
| 14 |  |
| 15 | Hard |
| 16 |  |
| 17 | Very hard |
| 18 |  |
| 19 | Extremely hard |
| 20 | Maximal exertion |

## Appendix C: Data Collection

***Patient characteristics***

* Age
* Gender
* Body mass index (BMI)
* CAD History
  + ACS
  + NSTEMI
  + STEMI
  + Stable angina
  + Asymptomatic
* Treatment
  + PCI
  + CABG
  + Medical
* Cardiovascular risk factors
  + Family history of CVD
  + Hypertension
  + Smoker
  + Sedentary (no formal exercise)
  + Diabetes (type II)
  + Arrhythmia
* Medications
  + Statins
  + Dual antiplatelet therapy
  + ACE inhibitors or ARB or other antihypertensive medication
  + B-blockers
  + Nitrates
  + Anticoagulants
  + Antidepressants
  + Antiarrhythmics

***Outcome Measures***

**Primary:**

* Number (%) patients who completed the training (minimum 10 sessions of intervention)

**Secondary:**

Training adherence

* Number of sessions completed
* Number of drop-outs (% of total participants enrolled)

Body composition

* % body fat (BIA analysis)
* Body weight
* BMI
* Waist circumference

Blood pressure (resting)

* Systolic, diastolic, mean arterial

Aerobic fitness

* 6-minute walk test (6MWT)
* Rate of heart rate recovery (HRR) following the 6MWT

Affective state and Quality of Life

* Emotional state and mood (PANAS / DASS21)
* Quality of life (MacNew)
* Acute change in mood following an exercise session (Feeling Scale, FS)

Training Enjoyment

* Exercise enjoyment scale (EES)

Safety

* Number of adverse events
  + Minor or Major
  + Cardiovascular-related or Other (e.g. musculoskeletal)

Hospital re-admissions at 3-month follow-up

* Number (%) of participants reporting hospital re-admission for i) cardiac symptoms directly related to the initial CVD diagnosis, ii) other cardiovascular-related disorders and iii) all-causes.

Physical activity patterns at 3-month follow-up

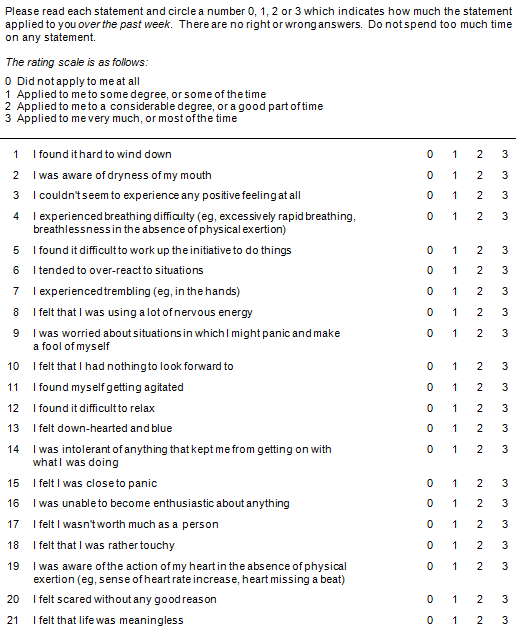
* Number (%) of participants reporting i) maintaining regular HIIT or MICT over the 3-month period post-study, or ii) returning to predominantly sedentary behaviours (no formal regular exercise training) over the 3-month period post-study

## Appendix D: Questionnaires

**PANAS** [[33](#_ENREF_33)]

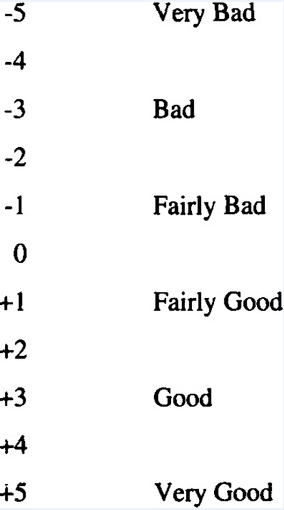


**DASS21** [[34](#_ENREF_34)]



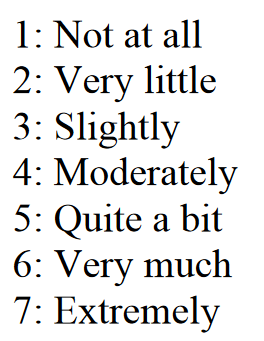
**Feeling Scale** [[35](#_ENREF_35)]

**How are you currently feeling?**



**Exercise Enjoyment Scale** [[36](#_ENREF_36)]

How much are you enjoying this exercise session?



## Appendix E: Data recording sheets

### Training session data

