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CARE CR - Cardiovascular and cardiorespiratory Adaptations to Routine Exercise-based Cardiac Rehabilitation; A study protocol for a community-based control study with criterion methods

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CARE CR - Cardiovascular and cardiorespiratory Adaptations to Routine Exercise-based Cardiac Rehabilitation; A study protocol for a community-based control study with criterion methods

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Author Contributions

Nichols, S - Is responsible for protocol design, study approval, data collection and analysis and, presentation of findings. He was also responsible for drafting this manuscript.

F. Nation - Is responsible for drafting this manuscript and is involved in data collection and analysis.

T. Goodman - Is responsible for protocol design and patient recruitment.

A.L. Clark - Is responsible for drafting this manuscript and facilitating patient testing.

S. Carroll - Is responsible for protocol design, study approval and drafting this manuscript.

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ABSTRACT

Introduction: Cardiac rehabilitation (CR) reduces all-cause and cardiovascular mortality in patients with coronary heart disease (CHD). Much of the improvement has been attributed to the beneficial effects of structured exercise training. However, UK-based studies have not confirmed this. Improvements in survival and cardiovascular health are associated with concurrent improvements in cardiorespiratory fitness (CRF). It is therefore concerning that estimated CRF improvements resulting from UK-based CR are approximately one third of those reported in international literature. Modest improvements in CRF suggest that UK CR exercise training programmes may require optimisation if long-term survival is to be improved. However, contemporary UK studies lack control data or, use estimates of CRF change. CARE-CR is a longitudinal, observational, controlled study designed to assess the short and longer-term effect of CR on CRF, as well cardiovascular and cardiometabolic health.

Methods and Analysis: Patients will be recruited following referral to their local CR programme and will either participate in a routine, low to moderate intensity, eight-week (16 sessions) exercise-based CR programme or freely abstain from supervised exercise. Initial assessment will be conducted prior to exercise training, or approximately two weeks after referral to CR if exercise training is declined. Reassessment will coincide with completion of exercise training, or 10 weeks after initial assessment for control participants. Participants will receive a final follow-up 12 months after recruitment. The primary outcome will be peak oxygen consumption determined using maximal cardiopulmonary exercise testing. Secondary outcomes will include changes in subclinical atherosclerosis (carotid intima-media thickness and plaque characteristics), body composition (dual X-ray absorptiometry) and cardiometabolic biomarkers.

Ethics and Dissemination: Ethical approval for this non-randomised controlled study has been obtained from the Humber Bridge NHS Research Ethics Committee - Yorkshire and the Humber on the 27th September 2013, (12/YH/0278). Results will be presented at national conferences and published in peer-reviewed journals.

Strengths

- **The use of 'gold-standard' maximal cardiopulmonary exercise testing will provide some of the most accurate and objective cardiorespiratory fitness outcomes derived from UK cardiac rehabilitation data**
- **Carotid intima-media thickness measurements will demonstrate the effect of cardiac rehabilitation on atherosclerotic disease progression**
- **The observational nature of this study within local CR ensures ecological validity of our findings**

Limitations

- **The non-randomised nature of this study may result in group allocation bias**
- **This is a single-centre study with participant referral/recruitment constraints that are characteristic of exercise training within UK-based cardiac rehabilitation.**

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INTRODUCTION

Coronary heart disease (CHD) affects 2.3 million people in the UK and is a leading cause of premature death[1]. Improvements in diagnosis and medical treatment have resulted in improved survival rates, however, the burden of CHD remains a major public health challenge. Cardiac rehabilitation (CR) is a comprehensive programme of secondary prevention measures that has been shown to have significant health benefits for patients with CHD.

The aim of CR is to increase survival, reduce cardiovascular disease (CVD)-related morbidity and hospital admissions, improve functional capacity, quality of life and facilitate early return to work[2 3]. This is achieved through structured exercise training and increasing physical activity, preventive medical therapies, education and behaviour change, counselling support and other cardiovascular risk factor reduction strategies[2 4]. Although variations in service provision exist across the UK[5], CR exercise training is usually offered in the early post-admission period following a cardiac event. The UK healthcare system no longer uses 'Phases' to describe CR, however, early post-admission supervised exercise training may be equated to Phase III CR.

Structured exercise training is one of the primary components of CR[2 6 7] and may make the largest contribution to increasing patient survival[8 9]. Exercise training alone is associated with a 28% all-cause mortality reduction[10]. Contemporary evidence suggests that all-cause and CVD mortality, recurrent cardiac events,[11] and, hospital admissions are reduced whilst quality of life is improved[9]. However, a recent Cochrane review questioned these findings and reported that CVD mortality (10.4 to 7.6%) but not all-cause mortality was reduced following CR[9 12].

Contradictory to consecutive meta–analyses[9 11 13], UK-derived data suggest that CR may not improve CVD or all-cause mortality[14-16]. The most recent UK randomised control study reported no survival benefit[16], though did not consider cardiorespiratory fitness (CRF) changes. Peak oxygen uptake [VO_{2peak}](determined during maximal cardiopulmonary exercise testing (CPET) [17] is used to quantify CRF. VO_{2peak} is inversely associated with all-cause and cardiovascular mortality in patients with CHD[18 19]. A 1% improvement in VO_{2peak} following 3 months exercise training confers a 2% improvement in cardiovascular mortality[20] with the least fit patients showing the greatest survival advantage from any improvements[21 22]. However, a dose-response relationship between the amount of exercise training undertaken and increase in VO_{2peak} may exist[20].

UK clinical trial data [23] in patients who sustained a myocardial infarction (MI), reported increases in VO_{2peak} following 12 months supervised exercise training compared to controls.

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However, a recent multicentre study of routine UK-based CR (current clinical practice) indicates that the "exercise dose" within outpatient CR may be insufficient to meaningfully improve CRF[24 25] (~0.5 METs; or VO_2 1.75 $ml \cdot kg^{-1} \cdot min^{-1}$) when compared to international programmes [~1.5 METs; or VO_2 1.75 $ml \cdot kg^{-1} \cdot min^{-1}$][26]. Fewer than 50% of patients completing a 'typical' UK CR programme may achieve minimal clinically important improvements to CRF, (70 metres) derived from incremental shuttle walk testing[27]. These findings may explain why UK CR programmes do not appear to improve patient survival[14-16]. However, UK studies typically estimate CRF changes from submaximal exercise testing protocols. This may lead to inaccurate reporting of VO_{2peak} changes following CR in patients with CHD[28]. There is a need to investigate the exercise-based CR findings of Sandercock, et al. [29] using 'gold-standard' CPET testing methods.

Numerous mechanisms may be responsible for improving survival associated with exercise-based CR and improved CRF, including cardiovascular risk factor modification (smoking, lipids, blood pressure, glucose metabolism). Within one meta-analysis, approximately half of the 28% reduction in cardiac mortality achieved with exercise-based CR was attributed to reductions in major cardiovascular risk factors, particularly reduced smoking[9]. Anti-ischaemic/thrombotic effects, cardiac remodelling, and anti-atherosclerotic and vascular conditioning have also been documented[30 31]. Larger volumes of exercise training (associated with higher energy expenditures) have been shown to underline regression of atherosclerosis[32]. Carotid intima-media thickness (C-IMT) is a practical, valid and reliable non-invasive surrogate marker of sub-clinical atherosclerosis[33-35]. Carotid ultrasound has been used to non-invasively characterise dynamic changes in atherosclerotic plaque characteristics. Whilst some data suggest that exercise training may reduce C-IMT in patients at elevated CV risk[36 37], the evidence is still unclear[38]. Furthermore, no UK study has investigated the effects of a short-term, routine CR exercise training programme on longer-term atherosclerotic disease progression. The modest improvements in CRF reported within UK CR patients[39 40], and the reported absence of improved survival outcomes, may indicate that the exercise dose prescribed to patients is too low to meaningfully influence CRF, cardiometabolic risk factors and atherosclerotic plaque progression. Therefore, the objectives of this controlled trial are:

To determine, when compared to CR without exercise training, the short (eight-week) and longer-term (12-month) effects of a routine, eight week, low to moderate intensity UK CR exercise training programme on:

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1. Changes in VO_{2peak} assessed using 'gold-standard' cardiopulmonary exercise testing (CPET)

2. Subclinical and clinical atherosclerosis progression using C-IMT measurements

3. Standard risk factors including lipid profiles, blood pressure and blood glucose, measurement, and cardiometabolic markers including NT-Pro BNP and hs-CRP)
4.
5. Estimated all-cause 5-year mortality risk using the comprehensive CALIBER score[41])

METHODS

Ethical Approval

Ethical approval has been obtained from the Humber Bridge NHS Research Ethics Committee - Yorkshire and the Humber (12/YH/0278). Any protocol amendments will be submitted to the committee prior to implementation.

Study Design

This study will be a pragmatic, single-centre longitudinal controlled study of a routine NHS outpatient CR programme. Patients recruited to the study will have the option to attend a routine low to moderate intensity, eight-week circuit-based CR exercise training programme (routine CR), or voluntarily abstain (control group) from the structured exercise training component of the CR programme. Study measures will be made before starting exercise training, or approximately two weeks after recruitment for patients who decline the exercise programme (visit 1). Follow-up assessment will be conducted after completion of a patients CR programme (visit 2) or approximately 10 weeks after recruitment for controls. The difference in planned reassessment times accounts for a typical two week waiting time to receive NHS treatment (exercise training) and will allow both groups to be reassessed within a similar timeframe. Patients will also be invited for assessment 12-months after visit 1 (visit 3).

Routine CR will be delivered by clinical (not research) staff within existing NHS secondary prevention care pathways. The study will be conducted in collaboration with Hull's CR team (City Health Care Partnership CIC) who follow the Department of Health [42] 'best care

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pathway' for referral and delivery of CR. Adherence to national guidelines on exercise prescription will allow broad generalisability of the findings to UK-based CR programmes. The trial protocol adheres to the Standard Protocol Items: Recommendations for Clinical Trials (SPIRIT) guidelines.

Setting

Patients can attend CR at three sites across Hull; The University of Hull (West Hull), Hull Royal Infirmary (Hull Centre) and the Freedom Centre (Community Centre, East Hull). Testing will be conducted at the Academic Cardiology Research Laboratory at Castle Hill Hospital, Hull.

Participants

Patients who have had a recent hospital admission for stable angina, MI (STEMI and Non-STEMI), coronary artery bypass graft (CABG) surgery, and elective percutaneous coronary intervention (PCI) will be recruited recruitment by a specialist CR, typically within two-week of sustaining a cardiac event. Patients will be offered all CR secondary prevention components recommended by the BACPR [2], including exercise training. Those opting to take part in structured, supervised exercise training will be referred to as the treatment group (TG). Those who decline exercise training will be known as the control group (CG). Group randomisation was not performed as this was deemed unethical given the current evidence for the benefits of exercise-based CR[9]. Patients in both groups will be advised to increase unsupervised physical activity levels.

General inclusion criteria

1. Primary diagnosis of CHD including recent MI, coronary artery bypass graft CABG surgery, elective percutaneous coronary intervention (PCI) or exertional angina.
2. Clinically stable patients.
3. Aged 30-85 years.
4. Absence of contraindications to exercise testing and exercise training.
5. Capable and mentally able to understand and follow the instructions of the health professional team.

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General exclusion criteria

1. Clinically unstable patients.
2. Clinically significant valvular heart disease.
3. Patients with a non-ischaemic diagnosis
4. Patients with co-existing congenital heart conditions, significant co-morbidities including severe CHF (left ventricular ejection fraction <30%), advanced cancer and conditions preventing the patient from providing informed consent.
5. Current drug abusers and excessive alcohol drinkers.
6. Patients not freely living in the community, such as those currently serving a sentence with HM prison.
7. Patients unwilling or unable to participate in key aspects of the study.
8. Patients with ongoing clinical complications, open wounds or systemic infections.
9. Women who are pregnant or breastfeeding.

A study flow diagram is presented in Figure 1. Patients will be referred to CR via the local tertiary hospital (Castle Hill Hospital, Hull) where they will receive a one-to-one assessment with a CR specialist nurse. Nursing staff will provide patients with information on cardiac medications, diet, smoking cessation, physical activity, structured exercise training and other secondary prevention measures. Eligible patients' will be offered the opportunity to participate in this study. Group specific patient information sheets will be provided.

Written informed consent will be obtained by a medical doctor at the Academic Cardiology Research Laboratory, Castle Hill Hospital, Hull. Patients will be asked to attend in a euhydrated state and having not conducted strenuous exercise within the previous 24 hours. Patients will not fast prior to any visit due to the need to conduct maximal CPET at the end of the four-hour visit. Patients will be advised to eat a light meal prior to each visit.

A resting ECG, echocardiogram, venepuncture, carotid ultrasound (C-IMT) and dual X-ray absorptiometry [DXA] at each visit. A CPET to volitional exhaustion or clinically-relevant symptoms[43] will be conducted after all other investigations have been completed. Patients will then follow their chosen treatment plan (treatment or control). All measurements taken at visit 1 will be repeated at visit 2 and 3. At visit 2 and 3, all patients will be asked to verbally report the typical number of structured exercise sessions they engaged in during the previous week, as well as how many minutes each of those session lasted. This will allow a comparison of exercise dose between both groups. Adverse events will be reported in accordance with NHS good clinical practice guidelines.

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Anthropometry and resting haemodynamic measurements

Patients will be instructed to remove footwear, jackets and items from their pockets prior to standing in the centre of the scales. Body mass (Kg) will be measured using a Tanita Body Composition Analyser MC – 180MA (Tanita, Amsterdam, The Netherlands) and recorded to one decimal place. Stature (cm) will be measured (Leicester Height Measure, SECA, Birmingham, United Kingdom) with patients positioned in the Frankfort plane with their heels and head positioned to the back of the stadiometer. The highest measurement recorded during a single full in-breath will be taken as the individual's height. Body mass index (BMI) will reported as $kg{\cdot}m^2$, where kg is a patients' body mass and m^2 is height squared.

A single waist and hip circumference measurements will be taken 1 cm above the iliac crest, and from the widest aspect of the buttocks using an inflexible tape. Both measurements will be recorded in cm and the waist-to-hip circumference ratio (waist/hip) will be reported[44].

Patients will rest for 15 minutes in a semi-supine position on an examination bed. A 12-lead ECG (GE Healthcare, Buckinghamshire, UK) and left arm brachial blood pressure recorded using an ECG-gated automated BP cuff (Tango, SunTech Medical, Eynsham, United Kingdom). Resting HR and BP will be recorded following the 15-minute rest period.

Cardiopulmonary Exercise Testing

Respiratory gas exchange data will be collected using an Oxycon Pro (Jaeger, Hoechburg, Germany) breath-by-breath metabolic cart. Calibration to ambient temperature, humidity, altitude and barometric pressure will be performed. Gas flow-volume will be calibrated using a 3L syringe and will be repeated on at least two occasions. Offset values are automatically calculated for accurate measurement of ventilatory volumes. Two-point calibration, using known gas concentrations, will be performed to allow accurate quantification of inspired O_2 and expired CO_2 concentrations (control gases: O_2 16.4%; CO_2 4.5%). The 12-lead ECG will be measured continuously throughout the CPET. An ECG-gated automated BP will be monitored from the start of CPET and at the second minute of each exercise test stage until the end of the test.

CPET will be conducted according to international recommendations [4345-47]. A description of the CPET protocol, RPE scale, potential adverse symptoms and CPET stop procedures will be given to participants. The Modified Bruce Protocol[48] will be used for all CPETs (Table 1).

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Exercise tests will be preceded by a three-minute seated rest period to record pre-test gas exchange, BP, and HR values. Patients will undertake CPET on a treadmill (General Electric [GR]) driven by a GE Case system (GE Healthcare, Buckinghamshire, UK). Ventilatory expired gases will be collected continuously during the rest period, exercise and a six-minute recovery period. Talking during CPET will be discouraged with the exception of reporting symptoms, asking to stop exercise, and to provide serial RPE scores.

Table 1 - The modified Bruce protocol

Stage	Speed (mph)	Gradient (%)
0	1.7	0
1	1.7	5
2	1.7	10
3	2.5	12
4	3.4	14
5	4.2	16
6	5.0	18

HR, RPE and estimated arterial oxygen saturation (SpO_2) will be obtained after two and a half minutes of each test stage, at peak exercise and during the recovery period. Criteria for termination for CPET are displayed in Table 2[41].

Data will be saved and exported for offline analysis. Data will be exported in 30 second, 15 second and middle 5 of 7, breath-by-breath averages. Table 3 provides a list of traditional and novel CPET variables.

The primary outcome measure will be the change in VO_{2peak} (mean VO_2 over final 30 seconds of a CPET). Secondary CRF outcome measures including the ventilatory anaerobic threshold (VAT), VE/VCO_2 slope, peak O_2 pulse (VO_2/HR) and O_2 uptake efficiency slope and plateaus (OUES and OUEP) will be assessed.

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Table 2 – Exercise test termination criteria

Indications for exercise test termination
Chest pain suggestive ischemia
Ischemic ECG Changes (>2mm ST segment depression)
Complex Ventricular Ectopy
Second or third degree heart block
Fall in systolic pressure 20 mmHg from highest value during the test
Hypertension (250mmHg systolic; 120mmHg diastolic)
Severe oxygen desaturation: SpO_2 less than 80% when accompanied by symptoms and signs of severe hypoxemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory distress

ECG = Electrocardiogram; mmHg = Millimetres of Mercury; SpO_2 = Peripheral Capillary O_2 saturation

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Table 3 – Cardiopulmonary Exercise Test Variables

Variable	Definition	Significance
Peak Oxygen Uptake (VO_{2peak})	Mean VO_2 over the last 30 seconds of CPET Reported in raw units (ml), adjusted for body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) and lean body mass determined using DXA ($ml \cdot kg^{-1} \cdot min^{-1}$)	Traditional definition of peak aerobic fitness and limit of cardiovascular function Indicative of cardiovascular disease severity, universal prognosticator Abnormal when below 85% of the predicted value
Ventilatory Anaerobic Threshold (VAT)	Determined using the V-slope method method using the middle 5 of 7 breath data averaging. Reported in raw units (ml), adjusted for body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) and lean body mass determined using DXA ($ml \cdot kg^{-1} \cdot min^{-1}$).	Represents the point above which, further increments in work rate are increasingly sustained through anaerobic metabolism. Objective marker of submaximal aerobic fitness/endurance. A VO_2 at VAT between 40 and 60% VO_{2peak} is considered normal
Peak Respiratory Exchange Ratio (RER)	The ratio of ventilated CO_2 to O_2 averaged over the last 30 seconds of CPET Reported in arbitrary units	In conjunction with the attainment of one other marker of peak performance, RER of > 1.10 is indicative of a 'peak' effort during CPET
VE/VCO_2 slope	The slope relationship between VCO_2 (x-axis) and VE (y-axis) throughout the entire CPET Reported in arbitrary units	Index of ventilatory efficiency representing the matching of ventilation and perfusion of the lungs and heart respectively, as well as peripheral chemoreceptor sensitivity Slope> 34 suggest poor prognosis
Oxygen uptake efficiency slope (OUES)	The slope relationship between the logarithmically transformed minute ventilation (x-axis) and VO_2 (y-axis) throughout the entire CPET Reported in arbitrary units	Index of ventilatory efficiency with strong correlation to VO_{2peak} Slope <1.4 considered suggest poor prognosis High accuracy even when exercise tests are not maximal
Oxygen uptake efficiency plateau (OUEP)	The highest plateau in VO_2 in relation to VE. Reported as the highest consecutive values of VO_2/VE over 90 seconds.	Indicates the efficiency of oxygen uptake and global cardiovascular function Can be used to profile severity of CHD and CHF with mean plateau values of 20-30 (VO_2/VE mL/L) for CHF phenotypes Low OUEP (<65% predicted) prognostic
Oxygen Pulse (O_2/HR)	The ratio of VO_2 to HR (O_2/HR) Values can be reported at a single point in time e.g. peak O_2/HR averaged over 15 seconds or, plotted to demonstrate a response across an entire CPET	Indirect measure of stroke volume response to exercise O_2/HR plateau or reduction despite increases work rates, especially a lower to moderate work rates may indicate falling stroke volume and possible myocardial ischaemia/myocardial wall motion abnormality. Low O_2 pulse (< 85% predicted) and early plateau/reduction in O_2 pulse indicate poorer prognosis

VO_{2peak} = Peak Oxygen Uptake; VO_2 = Oxygen Uptake; CPET = Cardiopulmonary Exercise Test; DXA = Dual X-ray Absorptiometry; VE = Minute Ventilation; RER = Respiratory Exchange Ratio; VAT = Ventilatory Anaerobic Threshold; VCO_2 = Carbon Dioxide Elimination; VE/VCO_2 = Ventilatory Efficiency with Respect to CO_2 elimination; OUES; Oxygen Uptake Efficiency Slope; OUEP = Oxygen Uptake Efficiency Plateau; O_2/HR Oxygen Pulse; CHD = Coronary Heart Disease; CHF = Chronic Heart Failure

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Spirometry

Resting spirometry will be conducted using an Oxycon Pro. Patients will breathe into a mouth piece connected to the respiratory flow turbine of the metabolic cart. Patients will be instructed to and breathe normally during resting tidal volume measurements (litres). Ten full breathing cycles will be observed to allow normalisation of the breathing pattern. Flow volume loops will be conducted to obtain forced spirometry measurements. Demonstration and instruction will be given prior to patients attempting the manoeuvre. Up to eight flow-volume loops will be conducted to obtain three high quality manoeuvres. Acceptable reproducibility will be defined as ≤0.150 L difference between the largest and second largest forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements[49]. FEV_1, FVC and peak expiratory flow (PEF) will be recorded. Maximum voluntary ventilation will be estimated (eMVV) using the calculation $FEV_1 \times 40$[50-52].

Dual X-Ray Absorptiometry (DXA) Scan

Body composition will be analysed using DXA (Lunar iDXA, GE Healthcare, Buckinghamshire, UK). Body composition analysis will be performed by the Lunar iDXA's integrated software. Total body mass, total body fat, compartmental body fat, lean body mass and compartmental lean body mass will be recorded for this study. Total body mass will be used for the calculation of BMI.

Echocardiogram

S trained echocardiograph technician will conduct each echocardiogram. Standard echocardiogram techniques will be used including 2D, M-mode, pulse wave Doppler to assess cardiac structure and function (systolic and diastolic). Left ventricular function will be determined from 2D echocardiography. Left ventricular function will be assessed by estimation on a scale of normal, mild, mild-to-moderate, moderate, moderate-to-severe, and severe. Left ventricular ejection fraction (LVEF) will be calculated using the Simpson's formula from measurements of end-diastolic and end-systolic volumes on apical 4-chamber and 2-chamber views 2D views, following the guidelines of Schiller and colleagues[53]. LVSD will be diagnosed if LVEF is ≤45%. When LVEF cannot be calculated, LVSD will be diagnosed were LVEF ≤45 or there was at least "mild-to-moderate" impairment.

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Carotid-Intima-Media Thickness

C-IMT will be measured using an automated ultrasound system (Panasonic CardioHealth Station, Panasonic Biomedical Sales Europe BV, Leicestershire, UK). This system has low measurement variability in healthy and cardiac populations when investigations are conducted by experienced and inexperienced operator's alike[34 54]. C-IMT will be assessed using previously outlined methods[34]. Briefly, the CHS is equipped with a broadband probe (5-13 MHz) with a centre frequency optimised for carotid imaging. When correctly positioned over the CCA, automated integrated software locates the vessel's far wall using a region of interest tool. The CHS automatically captures a sequence of images at end-diastole by monitoring vessel distension characteristics and 'freezes' when pre-defined C-IMT boundary quality criteria are met. Multiple measurements taken from a 1cm segment of the CCA located 1cm proximally from the carotid bifurcation will be obtained. C-IMT will be measured at the right anterior (150°), lateral (120°) and posterior (90°) aspects and on the left anterior (210°), lateral (230°) and posterior (270°) aspects. Mean and maximum (max) IMT will be recorded to three decimal places. Image quality will be manually inspected and trace lines modified where required. To enhance measurement reproducibility, the probe is equipped with an accelerometer and gyroscope that tracks the angle (˚) of insonation relative to ground. Each C-IMT measurement is recorded with the angle that the image was taken.

Blood Samples

Blood samples will be drawn and placed in a refrigerated (4°C) centrifuge at 3000 revolutions per minute, for 15 minutes. Routine testing will include full blood cell count, total cholesterol, estimated LDL cholesterol, HDL cholesterol, Triglycerides), kidney (eGFR) and liver function tests, non-fasting glucose and, NT-proBNP. Additional blood serum and plasma samples will be stored in a -80°C freezer for future analysis of current and emerging biochemical markers of cardiovascular and metabolic health.

Estimated All-cause Mortality

A 5-year risk of all-cause mortality will be calculated for each patient using the CALIBER 5-year prognostic risk score for stable CHD phenotypes (https://www.ucl.ac.uk/health-informatics/caliber)[41]. The CALIBER risk assessment model includes socio-demographics, CVD diagnosis and severity, CVD and non-CVD co-morbidities, primary risk factors, psychosocial risk factors and plasma biomarkers.

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Cardiac Rehabilitation Exercise Intervention

Patients in the TG will undergo a routine eight week (twice weekly, 16 sessions) CR exercise programme. A physiotherapist will conduct a one-to-one assessment before each patient commences exercise training. A personal exercise prescription will be developed for each individual. Patients will be asked to self-monitor exercise intensity and encouraged to maintain a HR corresponding to 40-70% of their predicted heart rate reserve (HHR) or, an exercise 'effort' between "light" and "somewhat hard" (11-14) on Borg's ratings of perceived exertion[55]. Estimated training zones will be calculated using the Karvonan formula:

((206 - (0.7 x age)) – resting heart rate (- 30 if taking beta-blockers)

Heart rate will be monitored with a Polar heart rate monitor. HR and RPE will be recorded at the end of each CV exercise station. This conforms to the recommendations of the Association of Chartered Physiotherapists in Cardiac Rehabilitation[56] and the British Association of Cardiac Prevention and Rehabilitation[57 58] (i.e., >20 min aerobic exercise at 40–70% heart rate reserve). An example list of CV and active recovery (AR) exercises are displayed in Table 4.

Table 4 – Example cardiovascular and active recovery exercises

Cardiovascular circuit Exercises	Active Recovery Exercises
Box stepping	Arm curls
Static cycling	Sit to stand
Treadmill walking	Wall press-up
Concept II rower	Leg curls
Marching on the spot	Lateral arm raises
Knee raises	Trunk rotation
Half stars	

Each exercise circuit will consist of a structured eight or nine station programme incorporating CV and AR exercises. CV exercises will initially be prescribed for approximately 1-2 min duration and up-titrated for each session- depending on HR and RPE responses. The target CV exercise duration for each session will be 20 minutes although CV exercise duration may be less than this in the first instance.

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Statistical analysis

The primary end point for statistical analysis is the mean change in $VO_{2\ peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) from visit 1 to visit 2. For statistical purposes, visit 3 will be treated as a follow-up. This will establish the initial effect of the eight-week exercise intervention and any effects that it may have on CRF and cardiometabolic health over the 12-month study period. A main effect and an interaction effect for VO_{2peak} will be investigated using a general linear model (parametric approach). The number of patients achieving a VO_{2peak} improvement greater than 0.5 and 1.5 METs will also be reported[24 26]. These values correspond to improvements in CRF resulting from UK and international CR respectively. Changes in other CRF variables will be discussed within the context of clinically meaningful thresholds (Table 3). Baseline $VO_{2\ peak,}$ age, and the categorical covariate, gender will be entered as covariates in exploratory analysis. Significant differences in group characteristics identified at baseline will also be treated as covariates. Secondary outcome measures, including C-IMT, and both maximal and submaximal CRF fitness measures will be evaluated using the same approaches and covariates as the primary outcome analysis. Continuous measures of exercise dose will be used to predict changes to peak VO_2peak and other CPET variables.

Data will be entered into SPSS by a single investigator who will maintain overall responsibility for data quality. The primary and secondary outcome analyses will be conducted at the conventional (two-sided) 5% alpha level. Where parametric data distribution allows, partial eta squared values will also be reported. To reduce the risk of false-positive claims, secondary analyses will be considered exploratory if non-significant results are obtained from the primary analysis. All analyses will be performed on an intention-to-treat basis. Analysis carrying the last observed values forward (baseline or 3-month outcomes) will be performed for patients lost to follow-up. A *per protocol* analysis, will also be conducted. Patients completing at least 14 (out of 16) exercise sessions will be classed as having completed CR. No timeframe for completion will be imposed, as cardiac rehabilitation is typically extended to incorporate any missed exercise sessions. All data will be summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline[49].

Power analysis, performed in G-Power[59] showed that 203 patients (total) would be needed to attain statistical significance between the two groups. This was based on an estimated post intervention between group (TG compared to CG) VO_{2peak} difference of 2 $ml \cdot kg^{-1} \cdot min^{-1}$ with a pooled standard deviation of 4 $ml \cdot kg^{-1} \cdot min^{-1}$. 2 $ml \cdot kg^{-1} \cdot min^{-1}$ was selected based on a predicted 0.52 MET ($ml \cdot kg^{-1} \cdot min^{-1}$) CRF increase recently reported in UK CR programmes[24].

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A power of 90% and a group allocation ratio of 70% TG (123 participants) to 30% CG (80 participants) and a predicted study attrition rate of 15% were applied. The assumption of uneven group sizes was made based on a local audit reporting that more patients participate in structured exercise than decline (TG 57%; CG 43%).

Approximately 440 patients attend the local nurse led CR clinic each year. With a recruitment rate of 10%, (44 patients per year) the study duration is estimated to be 5 years. The first patient was recruited in March 2014 and recruitment is ongoing. The study is expected to complete in March 2019. A formal interim analysis[60] on the primary and secondary outcomes will be conducted when 70 patients have completed the study (one third of the cohort required on the a priori determined sample size). A decision on trial progression will be collectively made by the research team (estimated to be January 2018). A data monitoring committee will not be used owing to the observational nature of the study.

Cardiac Rehabilitation Exercise Prescription Analysis

Recent evidence[11] suggests that no single exercise component within CR is predictive of mortality outcomes. However, reductions in both total and cardiovascular mortality were reported in trials which reported high levels of participant exercise adherence compared to those recording lower levels[11]. Patients' exercise doses have also been related to long-term survival outcomes [61]. Accordingly, all exercise training characteristics including adherence to the programme, will be recorded. CV exercise duration achieved by each patient at each of their 16 CR sessions will be calculated and summed to report a total exercise training duration. To characterise exercise intensity during each exercise session, the mean of patients' HR following completion of all CV exercises for each session will be calculated. Patients' 'mean peak HR' for each exercise session willbe pooled for analysis. A 'median of the mean' HR will be reported. 'Median peak HR' will expressed as a percentage of the VAT determined from visit 1 CPET and relative to HRR obtained from visit 1 CPET. A simple composite score of intensity and CV exercise duration for each training session will be calculated and summed to provide an overall "exercise dose" for each participant. The composite score will be:

$$\frac{\text{Mean peak HR}}{\text{Patients' CPET HRR}} \times \text{CV exercise duration}$$

As an additional marker of exercise intensity the mean of a patient's RPE following completion of an exercise session will be calculated (mean RPE). As with HR, patient's RPE scores for each exercise session will be pooled for analysis.

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DISSEMINATION AND IMPACT

It is anticipated that throughout the trial, the experiences gained will be presented at national conferences and non-academic outlets such as national governing body publications. On completion, the study results will be published in peer-reviewed journals and presented at scientific meetings.

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Figures

Figure 1 – Study flow diagram

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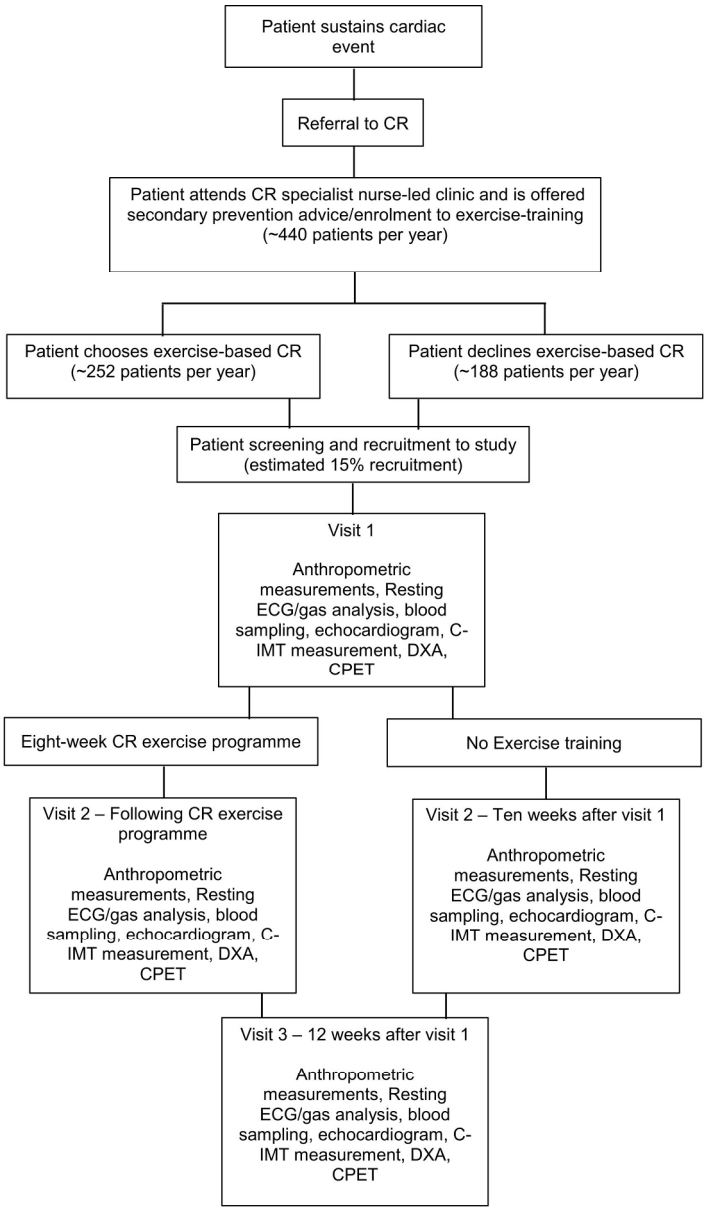

Figure 1 - Study flow diagram

152x242mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Observational Study - Not Required
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	All Pages - Footer
Funding	4	Sources and types of financial, material, and other support	Not Funded
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 2
	5b	Name and contact information for the trial sponsor	1
	5c	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	No role

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	5d	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)	N/A
Introduction			
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	4 to 6
	6b	Explanation for choice of comparators	6 to 7
Objectives	7	Specific objectives or hypotheses	5 to 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6 to 8
Methods: Participants, interventions, and outcomes			
Study setting	9	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	6 (also Figure 1 and page 8)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7 (echocardiogram on 11)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Figure 1, Table 1,2,3 and 4. Page 8 to 14
	11b	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)	Page 13 - Interim power analysis
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A - Assessment of routine care

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	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	Page 5 - relevance on page 4 and 5 as well as Table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6 to 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	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	N/A
Allocation concealment mechanism	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	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6 to 7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	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	7 to 14
	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	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13 to 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

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Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1 and 6
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)	6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
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
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	N/A
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	3 and 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			

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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
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	11 to 12

*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.

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