

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

NICHOLS, Simon <<http://orcid.org/0000-0003-0377-6982>>, NATION, Fiona,  
GOODMAN, Tony, CLARK, Andrew, CARROLL, Sean and INGLE, Lee

Available from Sheffield Hallam University Research Archive (SHURA) at:

<http://shura.shu.ac.uk/17457/>

---

This document is the author deposited version. You are advised to consult the  
publisher's version if you wish to cite from it.

**Published version**

NICHOLS, Simon, NATION, Fiona, GOODMAN, Tony, CLARK, Andrew, CARROLL,  
Sean and INGLE, Lee (2018). CARE CR - Cardiovascular and cardiorespiratory  
Adaptations to Routine Exercise-based Cardiac Rehabilitation; A study protocol for a  
community-based control study with criterion methods. *BMJ Open*, 8 (1), e019216.

---

**Copyright and re-use policy**

See <http://shura.shu.ac.uk/information.html>

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019216.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Oct-2017
Complete List of Authors:	Nichols, Simon; Sheffield Hallam University - Collegiate Crescent Campus, Centre for Sport and Exercise Science Nation, Fiona; University of Hull, Sport, Health and Exercise Science Goodman, Toni; City Health Care Partnership CIC, Integrated Community Services Clark, Andrew; University of Hull, Carroll, Sean; University of Hull, Sport, Health and Exercise Science Ingle, Lee; University of Hull, Sport, Health and Exercise Science
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Exercise Training, VO2peak, Cardiac Rehabilitation, Cardiopulmonary Exercise Testing, Carotid intima-media thickness

SCHOLARONE™  
Manuscripts

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

**\*Nichols, S<sup>1</sup>., Nation, F<sup>2</sup>., Goodman, T<sup>3</sup>., Clark<sup>4</sup>, A.L., Carroll, S<sup>2</sup>., Ingle, L<sup>2</sup>..**

\*Corresponding author

Dr Simon Nichols

<sup>1</sup>Centre for Sport Health and Exercise Science  
Sheffield Hallam University  
Collegiate Hall  
Collegiate Crescent  
Sheffield  
S10 2BP

[s.j.nichols@shu.ac.uk](mailto:s.j.nichols@shu.ac.uk)

<sup>2</sup>Sport Health and Exercise Science  
Don Building  
University of Hull  
Cottingham Road  
Hull  
HU6 7RX

<sup>3</sup>City Health Care Partnership CIC  
East Riding Community Hospital  
Swinemoore Lane  
Beverley  
HU17 0FA

<sup>4</sup>Academic Cardiology  
Castle Hill Hospital  
Castle Road  
Cottingham  
HU16 5JQ

Trial Sponsor - University of Hull - e-mail: [g.owen@hull.ac.uk](mailto:g.owen@hull.ac.uk)

Word Count: 4094

Key Words: Coronary Heart Disease, Exercise Training, Atherosclerosis,  $VO_{2peak}$ ,

Conflicts of interest: None

Acknowledgements: We would like to acknowledge the significant contribution of Hull's cardiac rehabilitation nurses - W.Summer, L.Richardson and E.Smith

1  
2  
3 Author Contributions

4 **Nichols, S** - Is responsible for protocol design, study approval, data collection and analysis and,  
5 presentation of findings. He was also responsible for drafting this manuscript.  
6  
7

8 **F. Nation** - Is responsible for drafting this manuscript and is involved in data collection and analysis.  
9

10 **T. Goodman** - Is responsible for protocol design and patient recruitment.  
11

12 **A.L. Clark** - Is responsible for drafting this manuscript and facilitating patient testing.  
13

14 **S. Carroll** - Is responsible for protocol design, study approval and drafting this manuscript.  
15

16 **L. Ingle** - Is the Principal Investigator and was responsible for protocol design, study approval and  
17 drafting this manuscript.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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 27<sup>th</sup> 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.**

## INTRODUCTION

Coronary heart disease (CHD) affects 2.3 million people in the UK and is a leading cause of premature death<sup>1</sup>. 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<sup>2,3</sup>. 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<sup>2,4</sup>. Although variations in service provision exist across the UK<sup>5</sup>, 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<sup>2,6,7</sup> and may make the largest contribution to increasing patient survival<sup>8,9</sup>. Exercise training alone is associated with a 28% all-cause mortality reduction<sup>10</sup>. Contemporary evidence suggests that all-cause and CVD mortality, recurrent cardiac events,<sup>11</sup> and hospital admissions are reduced whilst quality of life is improved<sup>9</sup>. 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<sup>9,12</sup>.

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

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

1  
2  
3 However, a recent multicentre study of routine UK-based CR (current clinical practice)  
4 indicates that the “exercise dose” within outpatient CR may be insufficient to meaningfully  
5 improve CRF<sup>24 25</sup> (~0.5 METs; or  $\text{VO}_2$   $1.75 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) when compared to international  
6 programmes [ $\sim 1.5$  METs; or  $\text{VO}_2$   $1.75 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ]<sup>26</sup>. Fewer than 50% of patients completing  
7 a ‘typical’ UK CR programme may achieve minimal clinically important improvements to CRF,  
8 (70 metres) derived from incremental shuttle walk testing<sup>27</sup>. These findings may explain why  
9 UK CR programmes do not appear to improve patient survival<sup>14-16</sup>. However, UK studies  
10 typically estimate CRF changes from submaximal exercise testing protocols. This may lead  
11 to inaccurate reporting of  $\text{VO}_{2\text{peak}}$  changes following CR in patients with CHD<sup>28</sup>. There is a  
12 need to investigate the exercise-based CR findings of Sandercock, et al.<sup>29</sup> using ‘gold-  
13 standard’ CPET testing methods.  
14  
15  
16  
17  
18  
19  
20  
21

22 Numerous mechanisms may be responsible for improving survival associated with exercise-  
23 based CR and improved CRF, including cardiovascular risk factor modification (smoking,  
24 lipids, blood pressure, glucose metabolism). Within one meta-analysis, approximately half of  
25 the 28% reduction in cardiac mortality achieved with exercise-based CR was attributed to  
26 reductions in major cardiovascular risk factors, particularly reduced smoking<sup>9</sup>. Anti-  
27 ischaemic/thrombotic effects, cardiac remodelling, and anti-atherosclerotic and vascular  
28 conditioning have also been documented<sup>30 31</sup>. Larger volumes of exercise training  
29 (associated with higher energy expenditures) have been shown to underline regression of  
30 atherosclerosis<sup>32</sup>. Carotid intima-media thickness (C-IMT) is a practical, valid and reliable  
31 non-invasive surrogate marker of sub-clinical atherosclerosis<sup>33-35</sup>. Carotid ultrasound has  
32 been used to non-invasively characterise dynamic changes in atherosclerotic plaque  
33 characteristics. Whilst some data suggest that exercise training may reduce C-IMT in  
34 patients at elevated CV risk<sup>36 37</sup>, the evidence is still unclear<sup>38</sup>. Furthermore, no UK study has  
35 investigated the effects of a short-term, routine CR exercise training programme on longer-  
36 term atherosclerotic disease progression. The modest improvements in CRF reported within  
37 UK CR patients<sup>39 40</sup>, and the reported absence of improved survival outcomes, may indicate  
38 that the exercise dose prescribed to patients is too low to meaningfully influence CRF,  
39 cardiometabolic risk factors and atherosclerotic plaque progression. Therefore, the  
40 objectives of this controlled trial are:  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52

53 To determine, when compared to CR without exercise training, the short (eight-week) and  
54 longer-term (12-month) effects of a routine, eight week, low to moderate intensity UK CR  
55 exercise training programme on:  
56  
57  
58

- 1
- 2
- 3
- 4 1. Changes in  $VO_{2peak}$  assessed using 'gold-standard' cardiopulmonary exercise testing
- 5 (CPET)
- 6
- 7
- 8
- 9 2. Subclinical and clinical atherosclerosis progression using C-IMT measurements
- 10
- 11
- 12
- 13 3. Standard risk factors including lipid profiles, blood pressure and blood glucose,
- 14 measurement, and cardiometabolic markers including NT-Pro BNP and hs-CRP)
- 15
- 16 4.
- 17 5. Estimated all-cause 5-year mortality risk using the comprehensive CALIBER score<sup>41)</sup>
- 18
- 19

## 20

## 21 **METHODS**

### 22 **Ethical Approval**

23 Ethical approval has been obtained from the Humber Bridge NHS Research Ethics  
24 Committee - Yorkshire and the Humber (12/YH/0278). Any protocol amendments will be  
25 submitted to the committee prior to implementation.  
26  
27  
28  
29

### 30 **Study Design**

31 This study will be a pragmatic, single-centre longitudinal controlled study of a routine NHS  
32 outpatient CR programme. Patients recruited to the study will have the option to attend a  
33 routine low to moderate intensity, eight-week circuit-based CR exercise training programme  
34 (routine CR), or voluntarily abstain (control group) from the structured exercise training  
35 component of the CR programme. Study measures will be made before starting exercise  
36 training, or approximately two weeks after recruitment for patients who decline the exercise  
37 programme (visit 1). Follow-up assessment will be conducted after completion of a patients  
38 CR programme (visit 2) or approximately 10 weeks after recruitment for controls. The  
39 difference in planned reassessment times accounts for a typical two week waiting time to  
40 receive NHS treatment (exercise training) and will allow both groups to be reassessed within  
41 a similar timeframe. Patients will also be invited for assessment 12-months after visit 1 (visit  
42 3).  
43  
44  
45  
46  
47  
48  
49  
50  
51

52 Routine CR will be delivered by clinical (not research) staff within existing NHS secondary  
53 prevention care pathways. The study will be conducted in collaboration with Hull's CR team  
54 (City Health Care Partnership CIC) who follow the Department of Health <sup>42</sup> 'best care  
55  
56  
57  
58



1  
2  
3 pathway' for referral and delivery of CR. Adherence to national guidelines on exercise  
4 prescription will allow broad generalisability of the findings to UK-based CR programmes.  
5 The trial protocol adheres to the Standard Protocol Items: Recommendations for Clinical  
6 Trials (SPIRIT) guidelines.  
7  
8  
9

## 10 11 **Setting**

12  
13 Patients can attend CR at three sites across Hull; The University of Hull (West Hull), Hull  
14 Royal Infirmary (Hull Centre) and the Freedom Centre (Community Centre, East Hull).  
15 Testing will be conducted at the Academic Cardiology Research Laboratory at Castle Hill  
16 Hospital, Hull.  
17  
18  
19

## 20 21 22 **Participants**

23  
24 Patients who have had a recent hospital admission for stable angina, MI (STEMI and Non-  
25 STEMI), coronary artery bypass graft (CABG) surgery, and elective percutaneous coronary  
26 intervention (PCI) will be recruited recruitment by a specialist CR, typically within two-week  
27 of sustaining a cardiac event. Patients will be offered all CR secondary prevention  
28 components recommended by the BACPR <sup>2</sup>, including exercise training. Those opting to  
29 take part in structured, supervised exercise training will be referred to as the treatment group  
30 (TG). Those who decline exercise training will be known as the control group (CG). Group  
31 randomisation was not performed as this was deemed unethical given the current evidence  
32 for the benefits of exercise-based CR<sup>9</sup>. Patients in both groups will be advised to increase  
33 unsupervised physical activity levels.  
34  
35  
36  
37  
38  
39  
40  
41

### 42 **General inclusion criteria**

- 43  
44 1. Primary diagnosis of CHD including recent MI, coronary artery bypass graft CABG  
45 surgery, elective percutaneous coronary intervention (PCI) or exertional angina.
- 46  
47 2. Clinically stable patients.
- 48  
49 3. Aged 30-85 years.
- 50  
51 4. Absence of contraindications to exercise testing and exercise training.
- 52  
53 5. Capable and mentally able to understand and follow the instructions of the health  
54 professional team.  
55  
56  
57  
58

### 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<sup>43</sup> 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.

### **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 be reported as  $\text{kg m}^{-2}$ , where kg is a patients' body mass and  $\text{m}^2$  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<sup>44</sup>.

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  $\text{O}_2$  and expired  $\text{CO}_2$  concentrations (control gases:  $\text{O}_2$  16.4%;  $\text{CO}_2$  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<sup>43-45-47</sup>. A description of the CPET protocol, RPE scale, potential adverse symptoms and CPET stop procedures will be given to participants. The Modified Bruce Protocol<sup>48</sup> will be used for all CPETs (Table 1).

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<sub>2</sub>) 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<sup>41</sup>.

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<sub>2peak</sub> (mean VO<sub>2</sub> over final 30 seconds of a CPET). Secondary CRF outcome measures including the ventilatory anaerobic threshold (VAT), VE/VCO<sub>2</sub> slope, peak O<sub>2</sub> pulse (VO<sub>2</sub>/HR) and O<sub>2</sub> uptake efficiency slope and plateaus (OUES and OUEP) will be assessed.

**Table 2** – Exercise test termination criteria

---

**Indications for exercise test termination**

---

Chest pain suggestive ischemia

Ischemic ECG Changes (&gt;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<sub>2</sub> 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<sub>2</sub> = Peripheral Capillary O<sub>2</sub> saturation

**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

## 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  $\leq 0.150$  L difference between the largest and second largest forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) measurements<sup>49</sup>. FEV<sub>1</sub>, 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<sup>53</sup>. LVSD will be diagnosed if LVEF is  $\leq 45\%$ . When LVEF cannot be calculated, LVSD will be diagnosed were LVEF  $\leq 45$  or there was at least "mild-to-moderate" impairment.

### **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<sup>34 54</sup>. C-IMT will be assessed using previously outlined methods<sup>34</sup>. 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>)<sup>41</sup>. 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.



### 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<sup>55</sup>. Estimated training zones will be calculated using the Karvonen formula:

$$((206 - (0.7 \times \text{age})) - \text{resting heart rate} (- 30 \text{ if taking beta-blockers}))$$

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<sup>56</sup> and the British Association of Cardiac Prevention and Rehabilitation<sup>57 58</sup> (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.

## Statistical analysis

The primary end point for statistical analysis is the mean change in  $VO_{2\text{ peak}}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) 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  $VO_{2\text{ peak}}$  will be investigated using a general linear model (parametric approach). The number of patients achieving a  $VO_{2\text{ peak}}$  improvement greater than 0.5 and 1.5 METs will also be reported<sup>24 26</sup>. 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  $VO_{2\text{ peak}}$ , 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  $VO_{2\text{ peak}}$  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<sup>49</sup>.

Power analysis, performed in G-Power<sup>59</sup> 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)  $VO_{2\text{ peak}}$  difference of  $2\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  with a pooled standard deviation of  $4\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .  $2\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  was selected based on a predicted 0.52 MET ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) CRF increase recently reported in UK CR programmes<sup>24</sup>.

1  
2  
3 A power of 90% and a group allocation ratio of 70% TG (123 participants) to 30% CG (80  
4 participants) and a predicted study attrition rate of 15% were applied. The assumption of  
5 uneven group sizes was made based on a local audit reporting that more patients participate  
6 in structured exercise than decline (TG 57%; CG 43%).  
7  
8

9 Approximately 440 patients attend the local nurse led CR clinic each year. With a  
10 recruitment rate of 10%, (44 patients per year) the study duration is estimated to be 5 years.  
11 The first patient was recruited in March 2014 and recruitment is ongoing. The study is  
12 expected to complete in March 2019. A formal interim analysis<sup>60</sup> on the primary and  
13 secondary outcomes will be conducted when 70 patients have completed the study (one  
14 third of the cohort required on the a priori determined sample size). A decision on trial  
15 progression will be collectively made by the research team (estimated to be January 2018).  
16 A data monitoring committee will not be used owing to the observational nature of the study.  
17  
18  
19  
20  
21  
22  
23

#### 24 **Cardiac Rehabilitation Exercise Prescription Analysis**

25  
26 Recent evidence<sup>11</sup> suggests that no single exercise component within CR is predictive of  
27 mortality outcomes. However, reductions in both total and cardiovascular mortality were  
28 reported in trials which reported high levels of participant exercise adherence compared to  
29 those recording lower levels<sup>11</sup>. Patients' exercise doses have also been related to long-term  
30 survival outcomes<sup>61</sup>. Accordingly, all exercise training characteristics including adherence to  
31 the programme, will be recorded. CV exercise duration achieved by each patient at each of  
32 their 16 CR sessions will be calculated and summed to report a total exercise training  
33 duration. To characterise exercise intensity during each exercise session, the mean of  
34 patients' HR following completion of all CV exercises for each session will be calculated.  
35 Patients' 'mean peak HR' for each exercise session will be pooled for analysis. A 'median of  
36 the mean' HR will be reported. 'Median peak HR' will be expressed as a percentage of the VAT  
37 determined from visit 1 CPET and relative to HRR obtained from visit 1 CPET. A simple  
38 composite score of intensity and CV exercise duration for each training session will be  
39 calculated and summed to provide an overall "exercise dose" for each participant. The  
40 composite score will be:  
41  
42  
43  
44  
45  
46  
47  
48  
49

$$50 \quad \frac{\text{Mean peak HR}}{\text{Patients' CPET HRR}} \times \text{CV exercise duration}$$

51  
52

53 As an additional marker of exercise intensity the mean of a patient's RPE following  
54 completion of an exercise session will be calculated (mean RPE). As with HR, patient's RPE  
55 scores for each exercise session will be pooled for analysis.  
56  
57  
58

## 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.

For peer review only

## References

1. Townsend N, Bhatnager P, Wilkins E, et al. Cardiovascular Disease Statistics 2015. 2015.
2. BACPR. Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. . 2017. <http://www.bacpr.com>.
3. Bethell H, Lewin R, Dalal H. Cardiac rehabilitation in the United Kingdom. *Heart* 2009;95(4):271-75. doi: doi:10.1136/hrt.2007.134338
4. Dalal HM, Zawada A, Jolly K, et al. Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. *Bmj* 2010;340:b5631.
5. Doherty P, Salman A, Furze G, et al. Does cardiac rehabilitation meet minimum standards: an observational study using UK national audit? *Open Heart* 2017;4(1) doi: 10.1136/openhrt-2016-000519
6. Joint British Society. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100(Suppl 2):ii1-ii67. doi: 10.1136/heartjnl-2014-305693
7. Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol* 2014;21(6):664-81. doi: 10.1177/2047487312449597 [published Online First: 2012/06/22]
8. Jolliffe J, Rees K, Taylor RR, et al. Exercise-based rehabilitation for coronary heart disease. *The Cochrane Library* 2001
9. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart DiseaseCochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044
10. Taylor RS, Unal B, Critchley JA, et al. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation* 2006;13(3):369-74. doi: 10.1097/01.hjr.0000199492.00967.11
11. Abell B, Glasziou P, Hoffmann T. The Contribution of Individual Exercise Training Components to Clinical Outcomes in Randomised Controlled Trials of Cardiac Rehabilitation: A Systematic Review and Meta-regression. *Sports medicine - open* 2017;3(1):19. doi: 10.1186/s40798-017-0086-z [published Online First: 2017/05/10]
12. van Halewijn G, Deckers J, Tay HY, et al. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. *Int J Cardiol* 2017;232:294-303. doi: 10.1016/j.ijcard.2016.12.125 [published Online First: 2017/01/18]
13. Heran BS, Chen J, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011;7
14. Bethell HJN, Turner SC, Mullee MA. Cardiac rehabilitation in the community: 11 year follow-up after a randomized controlled trial. *Coronary Health Care* 1999;3:183-88.
15. Carson P, Phillips R, Lloyd M, et al. Exercise after myocardial infarction: a controlled trial1982.
16. West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart* 2012;98(8):637-44. doi: 10.1136/heartjnl-2011-300302
17. Ross R, Blair SN, Arena R, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* 2016:CIR. 0000000000000461.

18. Martin B-J, Arena R, Haykowsky M, et al. Cardiovascular Fitness and Mortality After Contemporary Cardiac Rehabilitation. *Mayo Clinic proceedings Mayo Clinic* 2013;88(5):455-63.
19. Mandic S, Myers J, Oliveira RB, et al. Characterizing differences in mortality at the low end of the fitness spectrum in individuals with cardiovascular disease. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2010;17(3):289-95. doi: 10.1097/HJR.0b013e32833163e2
20. Vanhees L, Fagard R, Thijs L, et al. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American journal of cardiology* 1995;76(14):1014-19.
21. Barons MJ, Turner S, Parsons N, et al. Fitness predicts long-term survival after a cardiovascular event: a prospective cohort study. *BMJ Open* 2015;5(10) doi: 10.1136/bmjopen-2015-007772
22. Taylor C, Tsakirides C, Moxon J, et al. Submaximal fitness and mortality risk reduction in coronary heart disease: a retrospective cohort study of community-based exercise rehabilitation. *BMJ open* 2016;6(6):e011125.
23. Dugmore L, Tipson R, Phillips M, et al. Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. *Heart* 1999;81(4):359-66.
24. Ingle L, Carroll S. Cardiac rehabilitation and exercise training. *Heart* 2013 doi: 10.1136/heartjnl-2013-304015
25. Sandercock G, Cardoso F, Almodhy M. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013;99(17):1298-99. doi: 10.1136/heartjnl-2013-304085
26. Sandercock G, Hurtado V, Cardoso F. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International journal of cardiology* 2011 doi: 10.1016/j.ijcard.2011.11.068
27. Houchen-Wolloff L, Boyce S, Singh S. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. *European Journal of Preventive Cardiology* 2014 doi: 10.1177/2047487314540840
28. Nichols S, Gleadall-Sidall DO, Antony R, et al. Estimated peak functional capacity; an accurate method for assessing change in peak oxygen consumption after cardiac rehabilitation? *Clinical Physiology and Functional Imaging* 2017;Ahead of print doi: 10.1111/cpf.12468
29. Sandercock GR, Cardoso F, Almodhy M, et al. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013;99(11):785-90. doi: 10.1136/heartjnl-2012-303055
30. Boden WE, Franklin BA, Wenger NK. Physical activity and structured exercise for patients with stable ischemic heart disease. *JAMA* 2013;309(2):143-44.
31. Kachur S, Chongthammakun V, Lavie CJ, et al. Impact of Cardiac Rehabilitation and Exercise Training Programs in Coronary Heart Disease. *Progress in Cardiovascular Diseases* 2017
32. Hambrecht R, Walther C, Möbius-Winkler S, et al. Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial. *Circulation* 2004;109(11):1371-78. doi: 10.1161/01.cir.0000121360.31954.1f
33. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986;74(6):1399-406. doi: 10.1161/01.cir.74.6.1399
34. Nichols S, Milner M, Meijer R, et al. Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging* 2014
35. Amato M, Montorsi P, Ravani A, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography

- and coronary intravascular ultrasound findings. *European Heart Journal* 2007;28(17):2094-101. doi: 10.1093/eurheartj/ehm244
36. Fearheller DL, Diaz KM, Kashem MA, et al. Effects of moderate aerobic exercise training on vascular health and blood pressure in african americans. *The Journal of Clinical Hypertension* 2014;16(7):504-10.
37. Kim SH, Lee SJ, Kang ES, et al. Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metabolism* 2006;55(8):1053-59. doi: <http://dx.doi.org/10.1016/j.metabol.2006.03.017>
38. Byrkjeland R, Stensaeth KH, Anderssen S, et al. Effects of exercise training on carotid intima-media thickness in patients with type 2 diabetes and coronary artery disease. Influence of carotid plaques. *Cardiovasc Diabetol* 2016;15:13. doi: 10.1186/s12933-016-0336-2 [published Online First: 2016/01/24]
39. Brodie D, Bethell H, Breen S. Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation* 2006;13(1):122-28. doi: 10.1097/01.hjr.0000192741.04103.d3
40. Sandercock G, Cardoso F, Almodhy M, et al. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013;99(11):785-90. doi: 10.1136/heartjnl-2012-303055
41. Rapsomaniki E, Shah A, Perel P, et al. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. *Eur Heart J* 2014;35(13):844-52. doi: 10.1093/eurheartj/ehf533 [published Online First: 2013/12/20]
42. Department of Health. Department of Health's commissioning pack on cardiac rehabilitation In: Health Do, ed., 2010.
43. American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine* 2003;167(2):211. doi: 10.1164/rccm.167.2.211
44. ACSM. ACSM's Guidelines for exercise testing and prescription. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health 2013.
45. Taylor C, Nichols S, Ingle L. A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *British Journal of Hospital Medicine* 2015;76(4):192-5. doi: 10.12968/hmed.2015.76.4.192 [published Online First: 2015/04/09]
46. Nichols S, Taylor C, Ingle L. A clinician's guide to cardiopulmonary exercise testing 2: test interpretation. *British Journal of Hospital Medicine* 2015;76(5):281-89. doi: doi:10.12968/hmed.2015.76.5.281
47. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation* 2010;122(2):191-225. doi: 10.1161/CIR.0b013e3181e52e69
48. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85(4):546-62. doi: [http://dx.doi.org/10.1016/0002-8703\(73\)90502-4](http://dx.doi.org/10.1016/0002-8703(73)90502-4)
49. American Thoracic Society/European Respiratory Society. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38. doi: 10.1183/09031936.05.00034805
50. Hansen J, Sue D, Wasserman K. Predicted values for clinical exercise testing. *The American review of respiratory disease* 1984;129(2 Pt 2):S49-55.
51. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *Journal of Occupational and Environmental Medicine* 1982;24(7):531-33.
52. Blackie SP, Fairbairn MS, McElvaney NG, et al. Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest* 1991;100(1):136-42. doi: 10.1378/chest.100.1.136

- 1  
2  
3 53. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle  
4 by two-dimensional echocardiography. American Society of Echocardiography Committee on  
5 Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc*  
6 *Echocardiogr* 1989;2(5):358-67. [published Online First: 1989/09/01]  
7 54. Vanoli D, Wiklund U, Lindqvist P, et al. Successful novice's training in obtaining accurate  
8 assessment of carotid IMT using an automated ultrasound system. *European Heart Journal –*  
9 *Cardiovascular Imaging* 2013;15(6):637-42. doi: 10.1093/ehjci/jet254  
10 55. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-81.  
11 56. ACPICR. Standards for physical activity and exercise in the cardiovascular population. 3rd ed:  
12 Association of Chartered Physiotherapists in Cardiac Rehabilitation 2015.  
13 57. BACPR. Standards and Core Components for Cardiovascular Disease Prevention and  
14 Rehabilitation. 2012. <http://www.bacpr.com/resources/>.  
15 58. BACR. British Association For Cardiac Rehabilitation: Exercise instructor training module. 4th ed.  
16 Leeds: Human Kinetics 2006.  
17 59. Faul F, Erdfelder E, Buchner A, et al. Statistical power analyses using G\*Power 3.1: Tests for  
18 correlation and regression analyses. *Behavior Research Methods* 2009;41(4):1149-60. doi:  
19 10.3758/brm.41.4.1149  
20 60. Herson J, Wittes J. The Use of Interim Analysis for Sample Size Adjustment. *Drug Information*  
21 *Journal* 1993;27(3):753-60. doi: doi:10.1177/009286159302700317  
22 61. Taylor C, Tsakirides C, Moxon J, et al. Exercise dose and all-cause mortality within extended  
23 cardiac rehabilitation: a cohort study. *Open Heart* 2017;4(2):e000623. doi: 10.1136/openhrt-  
24 2017-000623 [published Online First: 2017/09/08]  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figures**

**Figure 1** – Study flow diagram

For peer review only

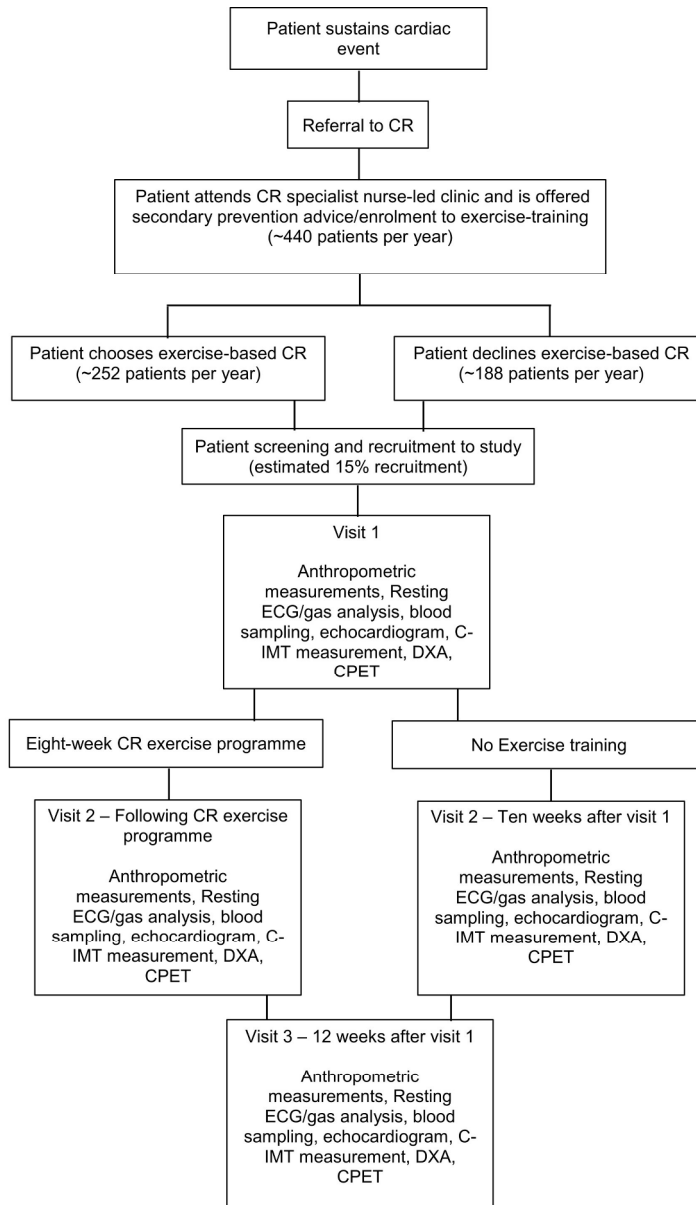


Figure 1 - Study flow diagram

152x242mm (300 x 300 DPI)



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

1 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint  
 2 adjudication committee, data management team, and other individuals or groups overseeing the trial, if  
 3 applicable (see Item 21a for data monitoring committee)  
 4  
 5  
 6  
 7  
 8  
 9

N/A

## 10 Introduction

11 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant  
 12 rationale studies (published and unpublished) examining benefits and harms for each intervention 4 to 6  
 13  
 14 6b Explanation for choice of comparators 6 to 7  
 15  
 16 Objectives 7 Specific objectives or hypotheses 5 to 6  
 17  
 18 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 19 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 6 to 8  
 20  
 21

## 22 Methods: Participants, interventions, and outcomes

23  
 24 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will  
 25 be collected. Reference to where list of study sites can be obtained 6 (also Figure 1  
 26 and page 8)  
 27  
 28 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  
 29 individuals who will perform the interventions (eg, surgeons, psychotherapists) 7 (echocardiogram  
 30 on 11)  
 31 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be  
 32 administered Figure 1, Table  
 33 1,2,3 and 4. Page  
 34 8 to 14  
 35 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  
 36 change in response to harms, participant request, or improving/worsening disease) Page 13 - Interim  
 37 power analysis  
 38 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence  
 39 (eg, drug tablet return, laboratory tests) N/A - Assessment  
 40 of routine care  
 41  
 42  
 43  
 44  
 45  
 46

1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
2	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
3				
4				
5				
6	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
7				
8	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
9				
10	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6 to 7
11				
12	<b>Methods: Assignment of interventions (for controlled trials)</b>			
13	Allocation:			
14	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
15				
16				
17	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
18				
19	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6 to 7
20				
21	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				

1 **Methods: Data collection, management, and analysis**

2

3 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 7 to 14

4 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of

5 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.

6 Reference to where data collection forms can be found, if not in the protocol

7

8

9 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be N/A

10 collected for participants who discontinue or deviate from intervention protocols

11

12 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality 13

13 (eg, double data entry; range checks for data values). Reference to where details of data management

14 procedures can be found, if not in the protocol

15

16

17 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the 13

18 statistical analysis plan can be found, if not in the protocol

19

20 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) 13 to 14

21

22 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any

23 statistical methods to handle missing data (eg, multiple imputation) 13

24

25

26 **Methods: Monitoring**

27

28 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of 13

29 whether it is independent from the sponsor and competing interests; and reference to where further details

30 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not

31 needed

32

33 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim 13

34 results and make the final decision to terminate the trial

35

36

37 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse 8

38 events and other unintended effects of trial interventions or trial conduct

39

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

41 from investigators and the sponsor

42

43

44

45

46

## Ethics and dissemination

1				
2				
3	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1 and 6
4	approval			
5				
6	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	6
7	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
8			regulators)	
9				
10				
11	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and	8
12			how (see Item 32)	
13				
14		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	N/A
15			studies, if applicable	
16				
17	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained	7
18			in order to protect confidentiality before, during, and after the trial	
19				
20	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
21	interests			
22				
23				
24	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	13
25			limit such access for investigators	
26				
27	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	N/A
28	trial care		participation	
29				
30	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	3 and 14
31			the public, and other relevant groups (eg, via publication, reporting in results databases, or other data	
32			sharing arrangements), including any publication restrictions	
33				
34				
35		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 2
36				
37		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
38				

## Appendices

1	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
2	materials			
3				
4	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	11 to 12
5	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
6				

7 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
8 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
9 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

For peer review only