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Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Key words: Coronary heart disease, coronary artery bypass graft, valve replacement, muscle atrophy, cardiovascular fitness

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Abstract

Introduction: Current guidelines recommend abstinence from supervised cardiac rehabilitation (CR) exercise training for six weeks post-sternotomy. This practice is not based on empirical evidence, thus imposing potentially unnecessary activity restrictions. Delayed participation in CR exercise training promotes muscle atrophy, reduces cardiovascular fitness, and prolongs recovery. Limited data suggest no detrimental effect of beginning CR exercise training as early as two weeks post-surgery, but randomised controlled trials are yet to confirm this. The purpose of this trial is to compare CR exercise training commenced early (2 weeks post-surgery) with current usual care (6 weeks post-surgery) with a view to informing future CR guidelines for patients recovering from sternotomy.

Methods and analysis: In this assessor-blind randomised controlled trial, 170 cardiac surgery patients, recovering from sternotomy, will be assigned to eight weeks of twice weekly supervised CR exercise training commencing at either two weeks (early CR) or 6 weeks (usual care CR) post-surgery. Usual care exercise training will adhere to current UK recommendations. Participants in the early CR group will undertake a highly individualised 2-3 week programme of functional mobility, strength and cardiovascular exercise before progressing to a usual care CR programme. Outcomes will be assessed at baseline (in-patient), pre-CR (2 or 6 weeks post-surgery), post CR (10 or 14 weeks post-surgery) and 12 months. The primary outcome will be change in six-minute walk distance. Secondary outcomes will include measures of functional fitness, quality of life and cost effectiveness.

Ethics and dissemination: The study protocol v.1.0, dated 25th January 2017 was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee (17/WM/0057). Recruitment commenced July 2017 and will complete by December 2019. Results will be disseminated via national governing bodies, scientific meetings and peer-reviewed journals.

Trial registration number: This study is registered with ClinicalTrials.gov: NCT03223558

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Strengths and limitations of this study:

- This trial will be conducted in a 'real world' community cardiac rehabilitation environment, ensuring a high degree of ecological validity.
- Randomisation and blinding will minimise any potential bias.
- As a limitation, this trial will only be performed in a single centre, thus potentially reducing external validity. Future trials should consider a multi-centre design.

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Introduction

Every year approximately 35,000 patients undergo coronary artery bypass graft (CABG) or aortic/mitral valve replacement surgery in the UK (1). Functional limitation is common and persistent after surgery, mediated by chest wall pain, respiratory complications, fatigue, and anxiety concerning the resumption of daily activities (2-4). At 12 months, previous studies have reported sternal wound pain in nearly 50% of patients (2), and 'unsatisfactory' functional status and quality of life in a third of patients (5). These issues can delay return to work, particularly for those with physically demanding jobs, and the financial consequences can be significant (6, 7).

The benefits of cardiac rehabilitation (CR) exercise training after sternotomy are well documented. A recent Cochrane review reported reduced cardiovascular mortality and hospital readmissions, in addition to improved quality of life (8). Higher fitness levels following CR exercise training also predict better outcomes and lower mortality rates (9). Historically, supervised CR exercise training does not commence until 42 days (6 weeks) after surgery, during which time functional capacity can deteriorate rapidly (8). This guideline emanates from concerns that exercise may slow healing or increase the likelihood of sternal instability and infection (6). These concerns may be justified given that serious complications, such as mediastinitis, are associated with significant mortality (10, 11). To date, however, there is no evidence directly linking early post-operative physical activity to an increased risk of sternal complications (6).

Existing sternal precautions are likely the product of expert opinion and anecdotal evidence. Consequently, practice varies considerably in hospitals and CR centres around the world (7). Sternal precautions, which often lack individualisation, may be overly

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restrictive, reinforcing fear of activity, and delaying recovery (12, 13). Indeed, long periods of inactivity, particularly in the elderly, can slow healing and promote muscle atrophy. The Dallas bed rest studies demonstrated that three weeks of total inactivity had a more profound impact on exercise capacity than 30 years of aging (14, 15). Cardiac muscle mass has also been shown to decrease by 8% after six weeks of bed rest (15). Additionally, inactivity of 10-12 days is sufficient to lead to a loss of skeletal muscle mass of 0.5-0.6% per day (16). This avoidable muscle wasting is likely to be accelerated in elderly patients, with potentially significant consequences. The increased risk of falls associated with muscle atrophy can lead to hip or pelvic fractures, for which the one year mortality rate can be as high as 40% (17).

Evidence for the safety of earlier CR (<6 weeks post-surgery) exercise training in sternotomy patients is accumulating (18). Studies have shown that in-patient walking and cycling, 1-7 days post-surgery, is safe and effective (19, 20). Further, no difference was found in hospital readmissions, infection rates or sternal instability between patients who started CR exercise training 10 days or 4-7 weeks post-discharge (21). Consequently, current post-sternotomy activity restrictions may be overly cautious. On the grounds of safety, surgical patients are commonly advised to avoid lifting more than 5 lbs for 12 weeks after surgery. Adams and colleagues, however, reported that the forces generated by sneezing and coughing (commonly endured without incident) far exceed that of upper-body dumbbell exercise and other restricted daily activities such as lifting a coffee pot and pushing a lawn mower (7, 12). There is little empirical evidence to support universal restriction of such activities for 12 weeks post sternotomy.

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A number of studies have highlighted the detrimental effects of delayed enrolment on CR programmes following cardiac surgery. In the UK, the National Audit for Cardiac Rehabilitation (NACR), recently reported that, for every 1-day increase in CR wait time, patients were 1% less likely to improve across all fitness-related measures (22). This finding is supported by Canadian data which, in an analysis of 6497 CABG patients, found that longer wait times before CR initiation were associated with lesser improvement in cardiovascular fitness (23). Attendance on CR programmes is also negatively impacted by extended waits. Studies have consistently determined that patients are less likely to attend and adhere to CR, the longer they are required to wait post-cardiac event (24, 25)

Evidence to support the earlier initiation of post-sternotomy CR exercise training is, therefore, apparent in a number of areas. Muscle mass and cardiovascular fitness decline rapidly with post-surgical inactivity, and when CR programme initiation is delayed, attendance is lower, and the benefits of exercise training are reduced. Moreover, there is insufficient evidence to support the current guideline of a six week wait post-surgery, and safety does not appear to be compromised by earlier CR. Whilst the growing evidence base for earlier post-sternotomy CR exercise training is relatively compelling, good quality prospective trials have not been performed. As such, randomised controlled trials are required to confirm benefit, safety and cost effectiveness. Results of such studies are essential before national guidelines can be established, allowing policymakers and clinicians to be confident in altering practice.

The early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR) trial is a single-centre randomised controlled trial, and economic evaluation, comparing supervised

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exercise training commenced at two weeks (early CR) with exercise training commenced at six weeks (usual care CR) post-sternotomy. The main objectives of the trial are:

1. To assess the effect of early CR on functional fitness.
2. To assess the effect of early CR on anxiety, depression and health related quality of life (HR-QoL).
3. To assess compliance and adherence to early CR.
4. To assess the cost effectiveness of early CR.
5. To assess the safety of early CR

In cardiac surgery patients recovering from sternotomy, our primary hypothesis is that early CR will improve walking distance to the same extent as usual care CR. With limited data on early CR in this population, particularly in the UK, we propose a holistic investigation including the following secondary hypotheses: early CR will 1) be as effective as usual care CR in improving functional fitness; 2) be as effective as usual care CR in improving anxiety and depression; 3) be as effective as usual care CR in improving HR-QoL; 4) demonstrate equivalent adherence and compliance to usual care CR; 5) be as cost effective as usual care CR; 6) be as safe as usual care CR.

Methods and analysis

The SCAR study is an assessor-blind parallel group, randomised controlled trial and economic evaluation. Participants will be randomly allocated to eight weeks of CR exercise training commencing at either two weeks (early CR) or six weeks (usual care CR) post-surgery. Outcomes will be measured at baseline (within 7 days of surgery), start of CR (2 or 6

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weeks), end of CR (10 or 14 weeks), and at 12 months. Assessors will be blinded to group allocation. The trial protocol adheres to the Standard Protocol Items: Recommendations for Clinical Trials (SPIRIT) guidelines (26).

Setting

The SCAR trial will be conducted at two cardiac rehabilitation venues provided by University Hospitals Coventry & Warwickshire (UHCW) NHS Trust, 1) Atrium Health, Centre for Exercise & Health, Coventry, and 2) Hospital of St. Cross, Rugby. Both CR programmes are certified by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR), thus, providing the necessary infrastructure and expertise for the delivery of the SCAR intervention. All cardiac surgery will be performed at University Hospital, Coventry, a national specialist tertiary cardiac centre. One hundred and seventy patients will be recruited over a two-year period, commencing July 2017.

Participants

All patients who are to undergo elective or emergency sternotomy for coronary artery bypass graft surgery or mitral/aortic valve replacement will be screened for eligibility. Inclusion and exclusion criteria are summarised in table 1.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria
▪ Coronary artery bypass graft and mitral/aortic valve replacement patients recovering from sternotomy, and eligible for cardiac rehabilitation exercise training in accordance with UK standards (27)	▪ Serious cardiac arrhythmias ▪ Current neurological disorders or previous cerebral vascular accident with residual neurological deficit significant enough to limit exercise
▪ Able to provide written informed consent	▪ Unable to enrol for the full study duration ▪ Inability to comply with guidelines for participation in exercise training (28, 29)
▪ Male or female	▪ Significant limiting comorbidities that would prevent full participation
▪ 18-90 years of age	

Study Procedures

The participant study pathway is illustrated in figure 1. All cardiac surgery patients will be screened and assessed for eligibility by the research team in consultation with the trial clinical lead. Patients meeting the inclusion criteria will be informed of the study at the first available opportunity. For elective patients, this will take place at either the pre-operative assessment clinic appointment (approximately two weeks prior to surgery), or on admission for surgery. For emergency admissions, patients will be informed of the study early in the post-operative period if it is inappropriate for the study to be discussed pre-surgery. Those who may be interested in participating will be given the patient information leaflet and permitted a minimum of 24 hours to consider their involvement prior to a follow-up phone call or in-patient visit from the research team. Non-English speaking patients will have access to translation services. Informed consent will be obtained on admission for surgery or early in the post-operative period. Baseline data collection will include clinical examination, 6-minute walk test (6-MWT), five times sit-to-stand test (FTSTS), hand grip strength, and isometric leg muscle strength. Instruments to assess anxiety and depression, HR-QoL, and health and

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social care use, will also be administered. Subsequently, participants will be randomised to twice weekly CR exercise training, commencing at either two weeks post-surgery (early CR) or six weeks post-surgery (usual care CR). All measures will be repeated immediately prior to starting CR (2 or 6 weeks post-surgery), on completion of 8 weeks of CR exercise training (10 or 14 weeks post-surgery), and at 12 months follow-up. Transport to and from the CR venues will be offered to patients who are not permitted to drive due to post-surgical Driving and Vehicle Licencing Agency (DVLA) restrictions.

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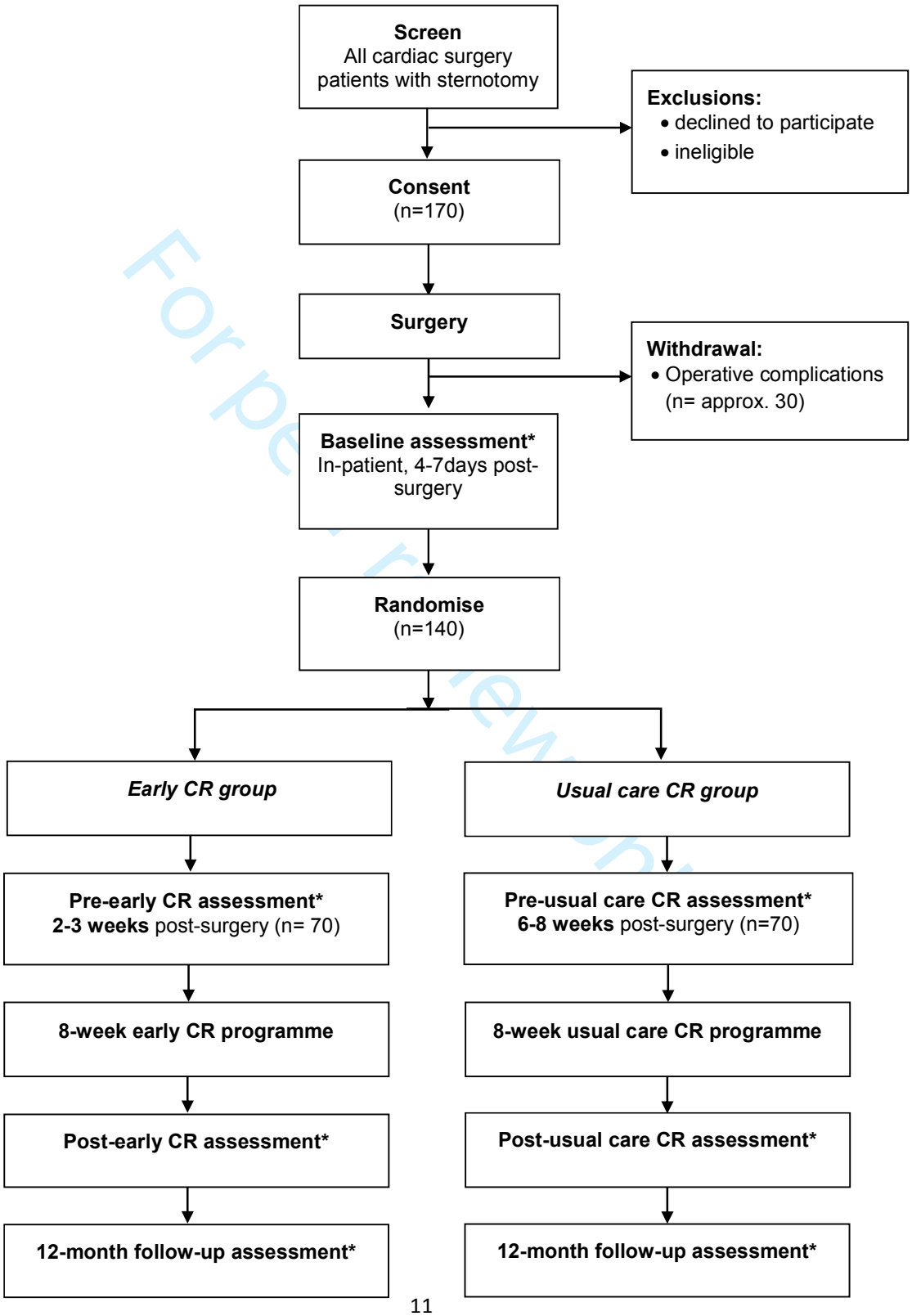
Figure 1. Study flow chart



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UHCW, University Hospitals Coventry & Warwickshire; CR, cardiac rehabilitation; *Assessment to include six-minute walk, five times sit-to-stand, grip strength, isometric leg strength, Generalised Anxiety Disorder assessment (GAD-7), Patient Health Questionnaire (PHQ-9), 12-Item Short Form Survey (SF-12), 5-Item EuroQol (EQ-5D), client service receipt inventory (CSRI).

Interventions

Participants in both groups will attend eight weeks of twice-weekly supervised CR exercise training. The usual care CR group will adhere to current UK standards (BACPR/ACPICR) (27), commencing exercise training at six weeks post-surgery. In brief, a 15-minute warm-up will incorporate light cardiovascular and mobility exercises (<40% heart rate reserve, HRR). The subsequent cardiovascular exercise component will involve moderate intensity interval training, progressing to 20-40 minutes of continuous cardiovascular exercise at 40-70% HRR. After a 10-minute cool-down, a full programme of functional muscular strength, flexibility and proprioception exercises will be undertaken. Care will be taken to ensure upper body exercises are performed in such a way to avoid sternal and leg wound pain/complications. Exercise intensity will be prescribed using estimated metabolic equivalents (METs) from the six-minute walk test (6-MWT). Duration and workload will be increased, as tolerated, based on heart rate and patient reported rating of perceived exertion (RPE). Written home exercise guidance will be provided for the six weeks preceding CR enrolment. This guidance has been produced locally and recommends short bouts (5 minutes) of light-moderate intensity walking, progressing in duration each week after surgery. In addition, a series of shoulder mobility exercises will be completed, with the advice to avoid pain and/or undue post-exercise fatigue.

Currently there are no specific exercise prescription guidelines for outpatient CR in patients who have undergone recent sternotomy (<6 weeks). In the first 2-3 weeks of early CR, participants will follow a highly individualised exercise programme dictated by their current

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level of fitness and post-surgery symptoms/limitations. General guidance will be taken from previous exploratory work (7) aimed at maintaining and increasing mobility and functional strength. Shoulder and chest mobility/strength exercises will be performed when they can be completed with minimal discomfort, and moderate intensity cardiovascular interval training will be gradually introduced. By weeks 2-3 of early CR, participants will progress towards achieving current UK standards (BACPR/ACPICR) (27). Initially, warm-up and cool-down will be specifically tailored to the planned exercises, without adhering to current guidelines. Table 2 provides an overview of the early CR exercise intervention.

Table 2. General principles of exercise training for early CR (first 2-3 weeks of CR)

- Highly individualised programme based on current limitations, mobility, fitness and symptoms
- Shortened warm-up and cool down where required, appropriate to the main exercise component
- Focus on improvement of posture, mobility, proprioception and functional strength
- Range of movement dictated by sternal and leg wound pain – pain free exercise advised
- Low-moderate intensity CV exercise (excluding rowing machine and arm ergometer for 2 weeks) i.e treadmill, cycle ergometer, step-ups
- Seated exercise where necessary

Extension of the CR programme beyond 8 weeks will be permitted in both groups where two or more consecutive exercise sessions are missed. This is in keeping with standard practice in UK cardiac rehabilitation programmes, and the pragmatic nature of the trial. Sufficient adherence to the study protocol will be determined by the following criteria:

- A minimum of 66% of sessions completed (12 of 18).
- 20 minutes continuous cardiovascular exercise achieved by week four of the CR programme.

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Randomisation and blinding:

Trial participants will be allocated to early CR or usual care CR, on a 1:1 basis, via block randomisation. The random allocation sequence will be generated by the trial statistician, implemented by an independent CR team member, and compliance will be ensured by UHCW NHS Trust R&D department. Randomisation requests will only be submitted further to completion of all baseline assessments, thus ensuring allocation concealment. At all time points, outcome assessors will be blinded to group allocation, as will the cardiac surgeons. Due to the nature of the trial, it will not be possible to blind the CR staff involved in the delivery of the exercise training interventions. Likewise, participants cannot be blinded.

Study outcome measures:

The primary outcome measure is the change in six-minute walk distance at the end of the CR exercise training programme. Secondary outcomes will include measures of 1) functional fitness; 2) anxiety and depression; 3) HR-QoL; 4) compliance and adherence; 5) cost effectiveness, and 6) safety. Table 3 outlines the full schedule of outcome assessments.

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Table 3. Outcome measures and schedule of assessments

Measure	Instrument	Assessment time point
Primary outcome		
Walking distance	Six-minute walk test	Baseline, start CR, end CR, 12 months
Secondary outcomes		
Functional fitness	Five times sit-to-stand	Baseline, start CR, end CR, 12 months
	Handgrip strength	Baseline, start CR, end CR, 12 months
	Isometric leg strength	Baseline, start CR, end CR, 12 months
Anxiety and depression	GAD-7	Baseline, start CR, end CR, 12 months
	PHQ-9	Baseline, start CR, end CR, 12 months
HR-QOL	SF-12	Baseline, start CR, end CR, 12 months
Compliance, adherence	Compliance/adherence/drop-out rates	Continuous
Cost effectiveness	EQ-5D	Baseline, start CR, end CR, 12 months
	CSRI	Start CR, end CR, 12 months
Safety	Adverse event monitoring	Continuous

CR, cardiac rehabilitation; GAD-7, Generalised Anxiety Disorder assessment; PHQ-9, Patient Health Questionnaire; HR-QoL, health related quality of life; SF-12; 12-Item Short Form Survey; EQ-5D, 5-Item EuroQol; CSRI, client service receipt inventory.

Primary outcome

The six-minute walk test (6-MWT) is a general measure of functional capacity, and an important prognostic indicator in cardiac surgery populations (30-32). Tests will be conducted in accordance with American Thoracic Society (ATS) guidelines (33). Participants will be instructed to walk as far as possible along a 30m, flat, obstacle free corridor, turning 180 degrees every 30m, in the allotted time of six minutes.

Functional fitness

The five times sit-to-stand test is often used in clinical and research settings (34) for the measurement of functional lower-extremity muscular strength and power. To complete the FTSTS, the participant will be instructed to stand up and sit down five times as quickly as

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possible without using their arms for assistance. To ensure good test-retest reliability (35), standardised foot placement and chair height will be required for each participant. A Jamar hand dynamometer (Sammons Preston Inc; Bollingbrook, Illinois) will be used to evaluate hand grip strength in the dominant hand. The position of the participant's arm will adhere to American Society of Hand Therapists recommendations (36) and participants will be instructed to maintain maximal grip contraction for 2-5 seconds. Isometric quadriceps strength will be assessed using a hand held dynamometer (MicroFET2 Torque/Force indicator, Hoggan Health Industries, Utah, US) (37). Whilst sitting in an elevated chair, with hips and knees aligned at 90 degrees and the lower leg vertical, participants will exert maximal force against equal and opposite resistance provided by the assessor.

Anxiety, depression and HR-QoL

The seven item Generalised Anxiety Disorder assessment (GAD-7) and nine-item Patient Health Questionnaire (PHQ-9) are well validated for the assessment of anxiety and depression (38, 39). Both are widely used as brief diagnostic tools, and measures of severity. Furthermore, they are routinely recorded in the CR population as part of standard clinical practice with the results reported in the National Audit of Cardiac Rehabilitation (NACR) (40). The 12-Item Short Form Survey (SF-12) will be used to evaluate HR-QoL (41). The 12 items of the questionnaire are summarised in two weighted summary scales; mental health score (MCS) and physical health score (PCS), where lower scores indicate more severe disability.

Compliance and adherence

Compliance and adherence is an important outcome in patients commencing CR exercise training early post-surgery. Attendance at CR exercise sessions will be closely monitored

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along with compliance to the prescribed exercise regimen. The number of sessions attended will be documented, as will the number of sessions successfully completed. Detailed reasons for incomplete sessions, and drop out, will be recorded where the participant is happy to provide this information.

Economic evaluation

The EQ-5D questionnaire is a commonly used generic measure of health status. A key feature is the availability of 'value sets' to weight the EQ-5D health states reported by participants and populations. The UK value set reported by Dolan (1997) (42) is recommended by NICE for use in its health technology appraisal process (43). An adapted client service receipt inventory (CSRI), based on examples in the DIRUM database (44) will be administered at each time point to capture participant health and social care service use since the last time point. The cost of delivering early CR and usual care CR (i.e. staff, equipment, facility) will be recorded throughout the CR programme.

Safety

To verify the safety of early CR exercise training, all adverse and serious adverse events will be carefully monitored, recorded and reported. In line with the principles of Good Clinical Practice (GCP), the nature and severity of the event, in addition to its potential association with study participation, will be recorded (45). As with current usual care, the local CR team, in conjunction with the trial clinician, will decide if participants with sternal instability or wound infection should be delayed or withdrawn.

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Sample size

The sample size calculation is based on the primary analysis of change in 6-MWT distance post-CR from baseline. A recent systematic review and meta-analysis of over 2500 CR patients (46) showed standard deviations of changes in 6-MWT distances after CR ranging from 57 to 160m, with the pooled standard deviation being 102m. Using a conservative standard deviation of 112m, and assuming that mean changes in 6-MWT distances at the end of CR sessions for both early CR and usual care CR are equal, 60 patients are required in each group (120 in total) to conclude non-inferiority (non-inferiority margin of 60) with 90% power. To allow for approximate dropout rate of 15%, 70 patients will need to be randomised to each group (140 in total).

Data collection and management

Data will be collected by research staff on case report forms at four time points; baseline, pre-CR, post-CR and 12 months follow up. Local policy and national data protection guidance will be followed with study data anonymously recorded on a bespoke trial database using unique study identification numbers.

Statistical analysis

The primary analysis will test non-inferiority of the early CR group compared to usual care CR based on changes in 6-MWT distances and will allow a switch to a superiority test. The non-inferiority margin has been set at 60m by the research team, Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% confidence interval for the mean difference of changes at the end of CR is above 60m. The non-inferiority margin was informed by the fact that a 6-MWT distance of 60m equates to an improvement of approximately 0.5 metabolic equivalents (METs) which leads to a 10% reduction in all-cause

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mortality (47). If the lower bound of the 95% confidence interval for the mean difference in changes at the end of CR is above 0, early CR will be concluded superior to usual care CR. The 95% confidence interval will be based on the t-distribution for the mean difference in changes between early and usual care CR.

In secondary analysis, a linear mixed model will include all 6-MWT distances taken from each patient at different time points, from baseline (at randomisation) to 14 weeks. Fourteen weeks is the time point at which CR exercise training will be complete in the usual care CR group. The model will include terms for group (early or usual care CR), and time (baseline, pre-CR, post-CR, 12 months). To assess if the trends for early CR and usual care CR are different, an interaction term for group and time will be included in the linear mixed models. All data will be summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (48).

Cost effectiveness analysis

Economic evaluation will complement the trail's clinical effectiveness results and inform decision-making on the commissioning of early CR. The costs and effects for participants in each group will be compared for the economic evaluation of the intervention. Given that the primary outcome is measured in natural units, and that the trial lasts 12 months, a cost-effectiveness (CE) approach will be used to perform the economic evaluation (49). A service provider perspective will be adopted: a client service receipt inventory (CSRI), administered pre-CR, post CR and at 12 months, will capture participant health and social care service use (direct medical and non-medical resources) since the last time point. Resource use, presented along with cost items in table 4, will be measured as per the recommendations of the Expert Delphi Consensus Survey (50). The collected resource use and effects data will be handled

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with Stata software for statistical analysis of economic evaluation (51). The missing values will be analysed through multiple imputation. The incremental cost and effectiveness ratios will be estimated for early CR and obtained by dividing the incremental cost by the incremental gain in meters from the 6-MWT. Incremental cost and effectiveness ratios and Cost-Effectiveness Acceptability Curves will be used to evaluate if the health benefit generated by early CR is worth any additional cost associated with the intervention. A non-parametric bootstrap technique will be employed to report uncertainty around CE measures. The CE analysis will adhere to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of published economic evaluations (52).

Table 4. Resource use and intervention cost measures

Measure	Instrument	Assessment time point
Secondary care		
Number and length of admissions (inpatient stay or day case) Number of outpatient appointments	CSRI	Start CR, end CR, 12 months
Emergency care		
Number of visits to A&E Number of admissions to hospital, after A&E	CSRI	Start CR, end CR, 12 months
Primary care		
Type of professional seen Number and length of visits	CSRI	Start CR, end CR, 12 months
Health care at home		
Type of professional seen Number and length of visits	CSRI	Start CR, end CR, 12 months
Medication Name/class/dose	CSRI	Start CR, end CR, 12 months
Cost of intervention Staff, equipment, facility	Cost diary	Every participant contact

CSRI, client service receipt inventory; CR, cardiac rehabilitation; A&E, accident and emergency

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Patient and public involvement

Patient and public involvement (PPI) has shaped the study design. Our patient forum endorsed the acceptability of early CR exercise training after surgery, and stressed the importance of returning to work/activities of daily living as soon as possible. Our PPI co-investigator, with lived experience of cardiac surgery, met with several surgical patients, each of whom was sent an overview of the early research protocol. The feedback helped researchers select outcome measures that were relevant to patients' daily experiences and, that crucially, would not unduly inconvenience participants. Multiple, time consuming, invasive outcome measures were considered unethical so early after major surgery.

Ethics

The study protocol v1.0, dated 25th January 2017, was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee on 24th February 2017 (17/WM/0057).

Dissemination and impact

Research findings will be presented at scientific meetings and published in peer-reviewed journals. All authors will approve the prepared manuscripts and authorship will be agreed based on international recommendations (ICMJE). The trial is anticipated to influence the direction of future research into CR in sternotomy patients. It is also expected that results from this trial will influence national CR guidelines. As such, findings, relating to both scientific outcomes and CR service provision will be disseminated amongst national governing bodies, and associated organisations, via newsletters and conferences.

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Contributions: SE is the Chief Investigator for the trial, leading on protocol development and the research ethics application. SE, GL, SW, TB, GM, PK, AK, RP and PB all contributed fully to the study design. TB (cardiothoracic surgery) PK (statistics), AK (health economics), provided discipline specific expertise and authored the relevant sections of the protocol and manuscript. GM prepared the manuscript which was edited by SE, TB, PK and AK. All authors read and approved the final version of the manuscript.

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Competing interests: none.

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	throughout
Protocol version	3	Date and version identifier	all
Funding	4	Sources and types of financial, material, and other support	n/a
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	3
	5b	Name and contact information for the trial sponsor	4
	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	n/a
	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)	24-26

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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	12-16
	6b	Explanation for choice of comparators	12-16
Objectives	7	Specific objectives or hypotheses	13
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)	4
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	18
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)	18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
	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)	16,22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	17-21
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)	6

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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	23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	12
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	19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19
	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	20
	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	22

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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	24
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	22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22
	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)	22
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	N/A
	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	N/A
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	26
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24-25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
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)	X

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	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	24-26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
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	26
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	ethics
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	ethics
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Site file/ethics
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	N/A

*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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Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Manuscripts

Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Abstract

Introduction: Current guidelines recommend abstinence from supervised cardiac rehabilitation (CR) exercise training for six weeks post-sternotomy. This practice is not based on empirical evidence, thus imposing potentially unnecessary activity restrictions. Delayed participation in CR exercise training promotes muscle atrophy, reduces cardiovascular fitness, and prolongs recovery. Limited data suggest no detrimental effect of beginning CR exercise training as early as two weeks post-surgery, but randomised controlled trials are yet to confirm this. The purpose of this trial is to compare CR exercise training commenced early (2 weeks post-surgery) with current usual care (6 weeks post-surgery) with a view to informing future CR guidelines for patients recovering from sternotomy.

Methods and analysis: In this assessor-blind randomised controlled trial, 170 cardiac surgery patients, recovering from sternotomy, will be assigned to eight weeks of twice weekly supervised CR exercise training commencing at either two weeks (early CR) or 6 weeks (usual care CR) post-surgery. Usual care exercise training will adhere to current UK recommendations. Participants in the early CR group will undertake a highly individualised 2-3 week programme of functional mobility, strength and cardiovascular exercise before progressing to a usual care CR programme. Outcomes will be assessed at baseline (in-patient), pre-CR (2 or 6 weeks post-surgery), post CR (10 or 14 weeks post-surgery) and 12 months. The primary outcome will be change in six-minute walk distance. Secondary outcomes will include measures of functional fitness, quality of life and cost effectiveness.

Ethics and dissemination: The study protocol v.1.0, dated 25th January 2017 was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee (17/WM/0057). Recruitment commenced July 2017 and will complete by December 2019. Results will be disseminated via national governing bodies, scientific meetings and peer-reviewed journals.

Trial registration number: This study is registered with ClinicalTrials.gov: NCT03223558

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Strengths and limitations of this study:

- This trial will be conducted in a 'real world' community cardiac rehabilitation environment, ensuring a high degree of ecological validity.
- Randomisation and blinding will minimise any potential bias.
- As a limitation, this trial will only be performed in a single centre, thus potentially reducing external validity. Future trials should consider a multi-centre design.

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Introduction

Every year approximately 35,000 patients undergo coronary artery bypass graft (CABG) or aortic/mitral valve replacement surgery in the UK (1). Functional limitation is common and persistent after surgery, mediated by chest wall pain, respiratory complications, fatigue, and anxiety concerning the resumption of daily activities (2-4). At 12 months, previous studies have reported sternal wound pain in nearly 50% of patients (2), and 'unsatisfactory' functional status and quality of life in a third of patients (5). These issues can delay return to work, particularly for those with physically demanding jobs, and the financial consequences can be significant (6, 7).

The benefits of cardiac rehabilitation (CR) exercise training after sternotomy are well documented. A recent Cochrane review reported reduced cardiovascular mortality and hospital readmissions, in addition to improved quality of life (8). Higher fitness levels following CR exercise training also predict better outcomes and lower mortality rates (9). Historically, supervised CR exercise training does not commence until 42 days (6 weeks) after surgery, during which time functional capacity can deteriorate rapidly (8). This guideline emanates from concerns that exercise may slow healing or increase the likelihood of sternal instability and infection (6). These concerns may be justified given that serious complications, such as mediastinitis, are associated with significant mortality (10, 11). To date, however, there is no evidence directly linking early post-operative physical activity to an increased risk of sternal complications (6).

Existing sternal precautions are likely the product of expert opinion and anecdotal evidence. Consequently, practice varies considerably in hospitals and CR centres around the world (7). Sternal precautions, which often lack individualisation, may be overly

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restrictive, reinforcing fear of activity, and delaying recovery (12, 13). Indeed, long periods of inactivity, particularly in the elderly, can slow healing and promote muscle atrophy. The Dallas bed rest studies demonstrated that three weeks of total inactivity had a more profound impact on exercise capacity than 30 years of aging (14, 15). Cardiac muscle mass has also been shown to decrease by 8% after six weeks of bed rest (15). Additionally, inactivity of 10-12 days is sufficient to lead to a loss of skeletal muscle mass of 0.5-0.6% per day (16). This avoidable muscle wasting is likely to be accelerated in elderly patients, with potentially significant consequences. The increased risk of falls associated with muscle atrophy can lead to hip or pelvic fractures, for which the one year mortality rate can be as high as 40% (17).

Evidence for the safety of earlier CR (<6 weeks post-surgery) exercise training in sternotomy patients is accumulating (18). Studies have shown that in-patient walking and cycling, 1-7 days post-surgery, is safe and effective (19, 20). Further, no difference was found in hospital readmissions, infection rates or sternal instability between patients who started CR exercise training 10 days or 4-7 weeks post-discharge (21). Consequently, current post-sternotomy activity restrictions may be overly cautious. On the grounds of safety, surgical patients are commonly advised to avoid lifting more than 5 lbs for 12 weeks after surgery. Adams and colleagues, however, reported that the forces generated by sneezing and coughing (commonly endured without incident) far exceed that of upper-body dumbbell exercise and other restricted daily activities such as lifting a coffee pot and pushing a lawn mower (7, 12). There is little empirical evidence to support universal restriction of such activities for 12 weeks post sternotomy.

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A number of studies have highlighted the detrimental effects of delayed enrolment on CR programmes following cardiac surgery. In the UK, the National Audit for Cardiac Rehabilitation (NACR), recently reported that, for every 1-day increase in CR wait time, patients were 1% less likely to improve across all fitness-related measures (22). This finding is supported by Canadian data which, in an analysis of 6497 CABG patients, found that longer wait times before CR initiation were associated with lesser improvement in cardiovascular fitness (23). Attendance on CR programmes is also negatively impacted by extended waits. Studies have consistently determined that patients are less likely to attend and adhere to CR, the longer they are required to wait post-cardiac event (24, 25)

Evidence to support the earlier initiation of post-sternotomy CR exercise training is, therefore, apparent in a number of areas. Muscle mass and cardiovascular fitness decline rapidly with post-surgical inactivity, and when CR programme initiation is delayed, attendance is lower, and the benefits of exercise training are reduced. Moreover, there is insufficient evidence to support the current guideline of a six week wait post-surgery, and safety does not appear to be compromised by earlier CR. Whilst the growing evidence base for earlier post-sternotomy CR exercise training is relatively compelling, good quality prospective trials have not been performed. As such, randomised controlled trials are required to confirm benefit, safety and cost effectiveness. Results of such studies are essential before national guidelines can be established, allowing policymakers and clinicians to be confident in altering practice.

The early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR) trial is a single-centre randomised controlled trial, and economic evaluation, comparing supervised

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exercise training commenced at two weeks (early CR) with exercise training commenced at six weeks (usual care CR) post-sternotomy. The main objectives of the trial are:

1. To assess the effect of early CR on functional fitness.
2. To assess the effect of early CR on anxiety, depression and health related quality of life (HR-QoL).
3. To assess compliance and adherence to early CR.
4. To conduct a cost-effectiveness analysis of early CR compared to usual care CR.
5. To assess the safety of early CR

In cardiac surgery patients recovering from sternotomy, our primary hypothesis is that early CR will improve walking distance to the same extent as usual care CR. With limited data on early CR in this population, particularly in the UK, we propose a holistic investigation including the following secondary hypotheses: early CR will 1) be as effective as usual care CR in improving functional fitness; 2) be as effective as usual care CR in improving anxiety and depression; 3) be as effective as usual care CR in improving HR-QoL; 4) demonstrate equivalent adherence and compliance to usual care CR; 5) be as cost effective as usual care CR; 6) be as safe as usual care CR.

Methods and analysis

The SCAR study is an assessor-blind parallel group, randomised controlled trial and economic evaluation. Participants will be randomly allocated to eight weeks of CR exercise training commencing at either two weeks (early CR) or six weeks (usual care CR) post-surgery. Outcomes will be measured at baseline (within 7 days of surgery), start of CR (2 or 6

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weeks), end of CR (10 or 14 weeks), and at 12 months. Assessors will be blinded to group allocation. The trial protocol adheres to the Standard Protocol Items: Recommendations for Clinical Trials (SPIRIT) guidelines (26).

Setting

The SCAR trial will be conducted at two cardiac rehabilitation venues provided by University Hospitals Coventry & Warwickshire (UHCW) NHS Trust, 1) Atrium Health, Centre for Exercise & Health, Coventry, and 2) Hospital of St. Cross, Rugby. Both CR programmes are certified by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR), thus, providing the necessary infrastructure and expertise for the delivery of the SCAR intervention. All cardiac surgery will be performed at University Hospital, Coventry, a national specialist tertiary cardiac centre. One hundred and seventy patients will be recruited over a two-year period, commencing July 2017.

Participants

All patients who are to undergo elective or emergency sternotomy for coronary artery bypass graft surgery or mitral/aortic valve replacement will be screened for eligibility. Inclusion and exclusion criteria are summarised in table 1.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria
▪ Coronary artery bypass graft and mitral/aortic valve replacement patients recovering from sternotomy, and eligible for cardiac rehabilitation exercise training in accordance with UK standards (27)	▪ Serious cardiac arrhythmias ▪ Current neurological disorders or previous cerebral vascular accident with residual neurological deficit significant enough to limit exercise
▪ Able to provide written informed consent	▪ Unable to enrol for the full study duration ▪ Inability to comply with guidelines for participation in exercise training (28, 29)
▪ Male or female	▪ Significant limiting comorbidities that would prevent full participation
▪ 18-90 years of age	

Study Procedures

The participant study pathway is illustrated in figure 1. All cardiac surgery patients will be screened and assessed for eligibility by the research team in consultation with the trial clinical lead. Patients meeting the inclusion criteria will be informed of the study at the first available opportunity. For elective patients, this will take place at either the pre-operative assessment clinic appointment (approximately two weeks prior to surgery), or on admission for surgery. For emergency admissions, patients will be informed of the study early in the post-operative period if it is inappropriate for the study to be discussed pre-surgery. Those who may be interested in participating will be given the patient information leaflet and permitted a minimum of 24 hours to consider their involvement prior to a follow-up phone call or in-patient visit from the research team. Non-English speaking patients will have access to translation services. Informed consent will be obtained on admission for surgery or early in the post-operative period. Baseline data collection will include clinical examination, 6-minute walk test (6-MWT), five times sit-to-stand test (FTSTS), hand grip strength, and isometric leg muscle strength. Instruments to assess anxiety and depression, HR-QoL, and health and

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social care use, will also be administered. Subsequently, participants will be randomised to twice weekly CR exercise training, commencing at either two weeks post-surgery (early CR) or six weeks post-surgery (usual care CR). All measures will be repeated immediately prior to starting CR (2 or 6 weeks post-surgery), on completion of 8 weeks of CR exercise training (10 or 14 weeks post-surgery), and at 12 months follow-up. Transport to and from the CR venues will be offered to patients who are not permitted to drive due to post-surgical Driving and Vehicle Licencing Agency (DVLA) restrictions.

Interventions

Participants in both groups will attend eight weeks of twice-weekly supervised CR exercise training. Both groups will exercise at the same time, in the same facility, with equal levels of supervision, and each session will last approximately one hour. The usual care CR group will adhere to current UK standards (BACPR/ACPICR) (27), commencing exercise training at six weeks post-surgery. In brief, a 15-minute warm-up will incorporate light cardiovascular and mobility exercises (<40% heart rate reserve, HRR). The subsequent cardiovascular exercise component (cycle ergometer, rowing ergometer, treadmill, arm ergometer, cross trainer) will involve 20 minutes of moderate intensity interval training (1-2 minute intervals), progressing to 20-40 minutes of continuous cardiovascular exercise at 40-70% HRR. After a 10-minute cool-down, a full programme of functional muscular strength, flexibility and proprioception exercises will be undertaken (e.g. resistance machines, free weights, multi-plane functional daily living exercise). Care will be taken to ensure upper body exercises are performed in such a way to avoid sternal and leg wound pain/complications. Exercise intensity will be prescribed using estimated metabolic equivalents (METs) from the six-minute walk test (6-MWT). Duration and workload will be increased, as tolerated, based on heart rate and patient reported rating of perceived exertion (RPE). Written home exercise guidance will be

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provided for the six weeks preceding CR enrolment. This guidance has been produced locally and recommends short bouts (5 minutes) of light-moderate intensity walking, progressing in duration each week after surgery. In addition, a series of shoulder mobility exercises will be completed, with the advice to avoid pain and/or undue post-exercise fatigue.

Currently there are no specific exercise prescription guidelines for outpatient CR in patients who have undergone recent sternotomy (<6 weeks). In the first 2-3 weeks of early CR, participants will follow a highly individualised exercise programme dictated by their current level of fitness and post-surgery symptoms/limitations. General guidance will be taken from previous exploratory work (7) aimed at maintaining and increasing mobility and functional strength. Shoulder and chest mobility/strength exercises will be performed when they can be completed with minimal discomfort, and moderate intensity cardiovascular interval training will be gradually introduced. By weeks 2-3 of early CR, participants will progress towards achieving current UK standards as above (BACPR/ACPICR) (27). Initially, warm-up and cool-down will be specifically tailored to the planned exercises, without adhering to current guidelines. Table 2 provides an overview of the early CR exercise intervention.

Table 2. General principles of exercise training for early CR (first 2-3 weeks of CR)

- Highly individualised programme based on current limitations, mobility, fitness and symptoms
- Shortened warm-up and cool down where required, appropriate to the main exercise component
- Focus on improvement of posture, mobility, proprioception and functional strength
- Range of movement dictated by sternal and leg wound pain – pain free exercise advised
- Low-moderate intensity CV exercise (excluding rowing machine and arm ergometer for 2 weeks) i.e treadmill, cycle ergometer, step-ups
- Seated exercise where necessary

Extension of the CR programme beyond 8 weeks will be permitted in both groups

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where two or more consecutive exercise sessions are missed. This is in keeping with standard practice in UK cardiac rehabilitation programmes, and the pragmatic nature of the trial. Sufficient adherence to the study protocol will be determined by the following criteria:

- A minimum of 66% of sessions completed (12 of 18).
- 20 minutes continuous cardiovascular exercise achieved by week four of the CR programme.

Randomisation and blinding:

Trial participants will be allocated to early CR or usual care CR, on a 1:1 basis, via block randomisation. The random allocation sequence will be generated by the trial statistician, implemented by an independent CR team member, and compliance will be ensured by UHCW NHS Trust R&D department. Randomisation requests will only be submitted further to completion of all baseline assessments, thus ensuring allocation concealment. At all time points, outcome assessors will be blinded to group allocation, as will the cardiac surgeons. Due to the nature of the trial, it will not be possible to blind the CR staff involved in the delivery of the exercise training interventions. Likewise, participants cannot be blinded.

Study outcome measures:

The primary outcome measure is the change in six-minute walk distance at the end of the CR exercise training programme. Secondary outcomes will include measures of 1) functional fitness; 2) anxiety and depression; 3) HR-QoL; 4) compliance and adherence; 5) cost effectiveness, and 6) safety. Table 3 outlines the full schedule of outcome assessments.

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Table 3. Outcome measures and schedule of assessments

Measure	Instrument	Assessment time point
Primary outcome		
Walking distance	Six-minute walk test	Baseline, start CR, end CR, 12 months
Secondary outcomes		
Functional fitness	Five times sit-to-stand	Baseline, start CR, end CR, 12 months
	Handgrip strength	Baseline, start CR, end CR, 12 months
	Isometric leg strength	Baseline, start CR, end CR, 12 months
Anxiety and depression	GAD-7	Baseline, start CR, end CR, 12 months
	PHQ-9	Baseline, start CR, end CR, 12 months
HR-QOL	SF-12	Baseline, start CR, end CR, 12 months
Compliance, adherence	Compliance/adherence/drop-out rates	Continuous
Cost effectiveness	EQ-5D	Baseline, start CR, end CR, 12 months
	CSRI	Start CR, end CR, 12 months
Safety	Adverse event monitoring	Continuous

CR, cardiac rehabilitation; GAD-7, Generalised Anxiety Disorder assessment; PHQ-9, Patient Health Questionnaire; HR-QoL, health related quality of life; SF-12; 12-Item Short Form Survey; EQ-5D, 5-Item EuroQol; CSRI, client service receipt inventory.

Primary outcome

The six-minute walk test (6-MWT) is a general measure of functional capacity, and an important prognostic indicator in cardiac surgery populations (30-32). Tests will be conducted in accordance with American Thoracic Society (ATS) guidelines (33). Participants will be instructed to walk as far as possible along a 30m, flat, obstacle free corridor, turning 180 degrees every 30m, in the allotted time of six minutes.

Functional fitness

The five times sit-to-stand test is often used in clinical and research settings (34) for the measurement of functional lower-extremity muscular strength and power. To complete the FTSTS, the participant will be instructed to stand up and sit down five times as quickly as

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possible without using their arms for assistance. To ensure good test-retest reliability (35), standardised foot placement and chair height will be required for each participant. A Jamar hand dynamometer (Sammons Preston Inc; Bollingbrook, Illinois) will be used to evaluate hand grip strength in the dominant hand. The position of the participant's arm will adhere to American Society of Hand Therapists recommendations (36) and participants will be instructed to maintain maximal grip contraction for 2-5 seconds. Isometric quadriceps strength will be assessed using a hand held dynamometer (MicroFET2 Torque/Force indicator, Hoggan Health Industries, Utah, US) (37). Whilst sitting in an elevated chair, with hips and knees aligned at 90 degrees and the lower leg vertical, participants will exert maximal force against equal and opposite resistance provided by the assessor.

Anxiety, depression and HR-QoL

The seven item Generalised Anxiety Disorder assessment (GAD-7) and nine-item Patient Health Questionnaire (PHQ-9) are well validated for the assessment of anxiety and depression (38, 39). Both are widely used as brief diagnostic tools, and measures of severity. Furthermore, they are routinely recorded in the CR population as part of standard clinical practice with the results reported in the National Audit of Cardiac Rehabilitation (NACR) (40). The 12-Item Short Form Survey (SF-12) will be used to evaluate HR-QoL (41). The 12 items of the questionnaire are summarised in two weighted summary scales; mental health score (MCS) and physical health score (PCS), where lower scores indicate more severe disability.

Compliance and adherence

Compliance and adherence is an important outcome in patients commencing CR exercise training early post-surgery. Attendance at CR exercise sessions will be closely monitored

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along with compliance to the prescribed exercise regimen. The number of sessions attended will be documented, as will the number of sessions successfully completed. Detailed reasons for incomplete sessions, and drop out, will be recorded where the participant is happy to provide this information.

Economic evaluation

The EQ-5D questionnaire is a commonly used generic measure of health status. A key feature is the availability of 'value sets' to weight the EQ-5D health states reported by participants and populations. The UK value set reported by Dolan (1997) (42) is recommended by NICE for use in its health technology appraisal process (43). An adapted client service receipt inventory (CSRI), based on examples in the DIRUM database (44) will be administered at each time point to capture participant health and social care service use since the last time point. The cost of delivering early CR and usual care CR (i.e. staff, equipment, facility) will be recorded throughout the CR programme.

Safety

To verify the safety of early CR exercise training, all adverse and serious adverse events will be carefully monitored, recorded and reported. In line with the principles of Good Clinical Practice (GCP), the nature and severity of the event, in addition to its potential association with study participation, will be recorded (45). As with current usual care, the local CR team, in conjunction with the trial clinician, will decide if participants with sternal instability or wound infection should be delayed or withdrawn.

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Sample size

The sample size calculation is based on the primary analysis of change in 6-MWT distance post-CR from baseline. A recent systematic review and meta-analysis of over 2500 CR patients (46) showed standard deviations of changes in 6-MWT distances after CR ranging from 57 to 160m, with the pooled standard deviation being 102m. Using a conservative standard deviation of 112m, and assuming that mean changes in 6-MWT distances at the end of CR sessions for both early CR and usual care CR are equal, 60 patients are required in each group (120 in total) to conclude non-inferiority (non-inferiority margin of 60 m) with 90% power. To allow for approximate dropout rate of 15%, 70 patients will need to be randomised to each group (140 in total).

Data collection and management

Data will be collected by research staff on case report forms at four time points; baseline, pre-CR, post-CR and 12 months follow up. Local policy and national data protection guidance will be followed with study data anonymously recorded on a bespoke trial database using unique study identification numbers.

Statistical analysis

The primary analysis will test non-inferiority of the early CR group compared to usual care CR based on changes in 6-MWT distances. The non-inferiority margin has been set at 60m by the research team. Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% confidence interval for the mean difference of changes at the end of CR is less than 60m. The non-inferiority margin was informed by the fact that a mean improvement in 6-MWT distance of 60m (in a population with a mean baseline distance of 250m) equates to an improvement of approximately 1.0 $ml.kg.^{-1}min^{-1}$ in estimated $VO_{2\ peak}$ (30), which in-

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turn leads to an approximate 10-15% reduction in all-cause mortality (47). If the lower bound of the 95% confidence interval for the mean difference in changes at the end of CR is above 0, early CR will be concluded superior to usual care CR. The 95% confidence interval will be based on the t-distribution for the mean difference in changes between early and usual care CR.

In secondary analysis, a linear mixed model will include all 6-MWT distances taken from each patient at different time points, from baseline (at randomisation) to 14 weeks. Fourteen weeks is the time point at which CR exercise training will be complete in the usual care CR group. The model will include terms for group (early or usual care CR), and time (baseline, pre-CR, post-CR, 12 months). To assess if the trends for early CR and usual care CR are different, an interaction term for group and time will be included in the linear mixed models. All data will be summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (48).

Economic evaluation

Economic evaluation will complement the trail's clinical effectiveness results and inform decision-making on the commissioning of early CR. We will conduct a cost-effectiveness analysis to estimate cost per unit of health gains due to early CR compared to usual CR (e.g. cost per additional distance covered in the 6-MWT). The costs and effects for participants in each group will be compared for the economic evaluation of the intervention. Given that the primary outcome is measured in natural units, and that the trial lasts 12 months, a cost-effectiveness (CE) approach is preferred for the economic evaluation (49). A service provider perspective will be adopted: a client service receipt inventory (CSRI), administered pre-CR, post CR and at 12 months, will collect data for participants' health and social care resource

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use (direct medical and non-medical resources) since the last data collection point. Health outcome measures for effectiveness, reported in table 3, and economic resource use, listed in table 4, will be measured as per the recommendations of the Expert Delphi Consensus Survey (50). The collected resource use and effects data will be handled with Stata software for statistical analysis of economic evaluation (51). The missing values will be analysed through multiple imputation. The incremental cost and effectiveness ratios will be estimated for early CR and obtained by dividing the incremental cost by the incremental gain in meters from the 6-MWT. Incremental cost and effectiveness ratios and Cost-Effectiveness Acceptability Curves will be used to evaluate if the health benefit generated by early CR is worth any additional cost associated with the intervention. A non-parametric bootstrap technique will be employed to report uncertainty around CE measures. The CE analysis will adhere to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of published economic evaluations (52).

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Table 4. Resource use and intervention cost measures

Measure	Instrument	Assessment time point
Secondary care		
Number and length of admissions (inpatient stay or day case)	CSRI	Start CR, end CR, 12 months
Number of outpatient appointments		
Emergency care		
Number of visits to A&E	CSRI	Start CR, end CR, 12 months
Number of admissions to hospital, after A&E		
Primary care		
Type of professional seen	CSRI	Start CR, end CR, 12 months
Number and length of visits		
Health care at home		
Type of professional seen	CSRI	Start CR, end CR, 12 months
Number and length of visits		
Medication	CSRI	Start CR, end CR, 12 months
Name/class/dose		
Cost of intervention	Cost diary	Every participant contact
Staff, equipment, facility		

CSRI, client service receipt inventory; CR, cardiac rehabilitation; A&E, accident and emergency

Patient and public involvement

Patient and public involvement (PPI) has shaped the study design. Our patient forum endorsed the acceptability of early CR exercise training after surgery, and stressed the importance of returning to work/activities of daily living as soon as possible. Our PPI co-investigator, with lived experience of cardiac surgery, met with several surgical patients, each of whom was sent an overview of the early research protocol. The feedback helped researchers select outcome measures that were relevant to patients' daily experiences and, that crucially, would not unduly inconvenience participants. Multiple, time consuming, invasive outcome measures were considered unethical so early after major surgery.

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Ethics

The study protocol v1.0, dated 25th January 2017, was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee on 24th February 2017 (17/WM/0057).

Dissemination and impact

Research findings will be presented at scientific meetings and published in peer-reviewed journals. All authors will approve the prepared manuscripts and authorship will be agreed based on international recommendations (ICMJE). The trial is anticipated to influence the direction of future research into CR in sternotomy patients. It is also expected that results from this trial will influence national CR guidelines. As such, findings, relating to both scientific outcomes and CR service provision will be disseminated amongst national governing bodies, and associated organisations, via newsletters and conferences.

Figure 1. Trial flow chart

UHCW, University Hospitals Coventry & Warwickshire; CR, cardiac rehabilitation; *Assessment to include six-minute walk, five times sit-to-stand, grip strength, isometric leg strength, Generalised Anxiety Disorder assessment (GAD-7), Patient Health Questionnaire (PHQ-9), 12-Item Short Form Survey (SF-12), 5-Item EuroQol (EQ-5D), client service receipt inventory (CSRI).

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Contributions: SE is the Chief Investigator for the trial, leading on protocol development and the research ethics application. SE, GL, SW, TB, GM, PK, AK, RP and PB all contributed fully to the study design. TB (cardiothoracic surgery) PK (statistics), AK (health economics), provided discipline specific expertise and authored the relevant sections of the protocol and manuscript. GM prepared the manuscript which was edited by SE, TB, PK and AK. All authors read and approved the final version of the manuscript.

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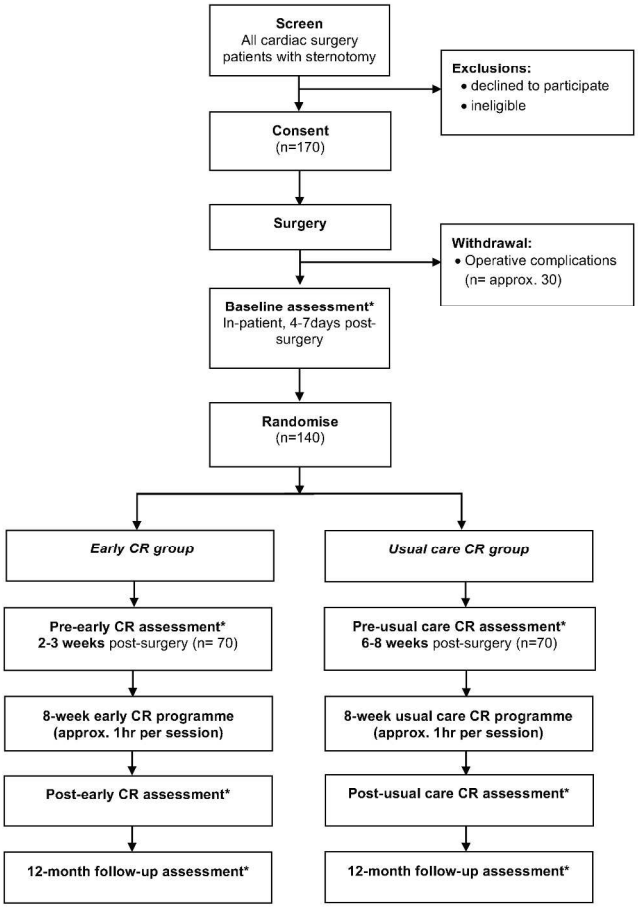
Figure 1. Trial flow chart



210x297mm (300 x 300 DPI)

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	throughout
Protocol version	3	Date and version identifier	all
Funding	4	Sources and types of financial, material, and other support	n/a
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	3
	5b	Name and contact information for the trial sponsor	4
	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	n/a
	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)	24-26

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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	12-16
	6b	Explanation for choice of comparators	12-16
Objectives	7	Specific objectives or hypotheses	13
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)	4
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	18
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)	18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
	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)	16,22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	17-21
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)	6

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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	23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	12
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	19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19
	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	20
	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	22

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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	24
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	22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22
	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)	22
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	N/A
	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	N/A
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	26
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24-25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
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)	X

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	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	24-26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
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	26
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	ethics
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	ethics
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Site file/ethics
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	N/A

*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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Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Manuscripts

Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): study protocol for a randomised controlled trial and economic evaluation.

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Key words: Coronary heart disease, coronary artery bypass graft, valve replacement, muscle atrophy, cardiovascular fitness

Word count: 3684

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Abstract

Introduction: Current guidelines recommend abstinence from supervised cardiac rehabilitation (CR) exercise training for six weeks post-sternotomy. This practice is not based on empirical evidence, thus imposing potentially unnecessary activity restrictions. Delayed participation in CR exercise training promotes muscle atrophy, reduces cardiovascular fitness, and prolongs recovery. Limited data suggest no detrimental effect of beginning CR exercise training as early as two weeks post-surgery, but randomised controlled trials are yet to confirm this. The purpose of this trial is to compare CR exercise training commenced early (2 weeks post-surgery) with current usual care (6 weeks post-surgery) with a view to informing future CR guidelines for patients recovering from sternotomy.

Methods and analysis: In this assessor-blind randomised controlled trial, 140 cardiac surgery patients, recovering from sternotomy, will be assigned to eight weeks of twice weekly supervised CR exercise training commencing at either two weeks (early CR) or 6 weeks (usual care CR) post-surgery. Usual care exercise training will adhere to current UK recommendations. Participants in the early CR group will undertake a highly individualised 2-3 week programme of functional mobility, strength and cardiovascular exercise before progressing to a usual care CR programme. Outcomes will be assessed at baseline (in-patient), pre-CR (2 or 6 weeks post-surgery), post CR (10 or 14 weeks post-surgery) and 12 months. The primary outcome will be change in six-minute walk distance. Secondary outcomes will include measures of functional fitness, quality of life and cost effectiveness.

Ethics and dissemination: The study protocol v.1.0, dated 25th January 2017 was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee (17/WM/0057). Recruitment commenced July 2017 and will complete by December 2019. Results will be disseminated via national governing bodies, scientific meetings and peer-reviewed journals.

Trial registration number: This study is registered with ClinicalTrials.gov: NCT03223558

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Strengths and limitations of this study:

- This trial will be conducted in a 'real world' community cardiac rehabilitation environment, ensuring a high degree of ecological validity.
- Randomisation and blinding will minimise any potential bias.
- As a limitation, this trial will only be performed in a single centre, thus potentially reducing external validity. Future trials should consider a multi-centre design.

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Introduction

Every year approximately 35,000 patients undergo coronary artery bypass graft (CABG) or aortic/mitral valve replacement surgery in the UK (1). Functional limitation is common and persistent after surgery, mediated by chest wall pain, respiratory complications, fatigue, and anxiety concerning the resumption of daily activities (2-4). At 12 months, previous studies have reported sternal wound pain in nearly 50% of patients (2), and 'unsatisfactory' functional status and quality of life in a third of patients (5). These issues can delay return to work, particularly for those with physically demanding jobs, and the financial consequences can be significant (6, 7).

The benefits of cardiac rehabilitation (CR) exercise training after sternotomy are well documented. A recent Cochrane review reported reduced cardiovascular mortality and hospital readmissions, in addition to improved quality of life (8). Higher fitness levels following CR exercise training also predict better outcomes and lower mortality rates (9). Historically, supervised CR exercise training does not commence until 42 days (6 weeks) after surgery, during which time functional capacity can deteriorate rapidly (8). This guideline emanates from concerns that exercise may slow healing or increase the likelihood of sternal instability and infection (6). These concerns may be justified given that serious complications, such as mediastinitis, are associated with significant mortality (10, 11). To date, however, there is no evidence directly linking early post-operative physical activity to an increased risk of sternal complications (6).

Existing sternal precautions are likely the product of expert opinion and anecdotal evidence. Consequently, practice varies considerably in hospitals and CR centres around the world (7). Sternal precautions, which often lack individualisation, may be overly

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restrictive, reinforcing fear of activity, and delaying recovery (12, 13). Indeed, long periods of inactivity, particularly in the elderly, can slow healing and promote muscle atrophy. The Dallas bed rest studies demonstrated that three weeks of total inactivity had a more profound impact on exercise capacity than 30 years of aging (14, 15). Cardiac muscle mass has also been shown to decrease by 8% after six weeks of bed rest (15). Additionally, inactivity of 10-12 days is sufficient to lead to a loss of skeletal muscle mass of 0.5-0.6% per day (16). This avoidable muscle wasting is likely to be accelerated in elderly patients, with potentially significant consequences. The increased risk of falls associated with muscle atrophy can lead to hip or pelvic fractures, for which the one year mortality rate can be as high as 40% (17).

Evidence for the safety of earlier CR (<6 weeks post-surgery) exercise training in sternotomy patients is accumulating (18). Studies have shown that in-patient walking and cycling, 1-7 days post-surgery, is safe and effective (19, 20). Further, no difference was found in hospital readmissions, infection rates or sternal instability between patients who started CR exercise training 10 days or 4-7 weeks post-discharge (21). Consequently, current post-sternotomy activity restrictions may be overly cautious. On the grounds of safety, surgical patients are commonly advised to avoid lifting more than 5 lbs for 12 weeks after surgery. Adams and colleagues, however, reported that the forces generated by sneezing and coughing (commonly endured without incident) far exceed that of upper-body dumbbell exercise and other restricted daily activities such as lifting a coffee pot and pushing a lawn mower (7, 12). There is little empirical evidence to support universal restriction of such activities for 12 weeks post sternotomy.

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A number of studies have highlighted the detrimental effects of delayed enrolment on CR programmes following cardiac surgery. In the UK, the National Audit for Cardiac Rehabilitation (NACR), recently reported that, for every 1-day increase in CR wait time, patients were 1% less likely to improve across all fitness-related measures (22). This finding is supported by Canadian data which, in an analysis of 6497 CABG patients, found that longer wait times before CR initiation were associated with lesser improvement in cardiovascular fitness (23). Attendance on CR programmes is also negatively impacted by extended waits. Studies have consistently determined that patients are less likely to attend and adhere to CR, the longer they are required to wait post-cardiac event (24, 25)

Evidence to support the earlier initiation of post-sternotomy CR exercise training is, therefore, apparent in a number of areas. Muscle mass and cardiovascular fitness decline rapidly with post-surgical inactivity, and when CR programme initiation is delayed, attendance is lower, and the benefits of exercise training are reduced. Moreover, there is insufficient evidence to support the current guideline of a six week wait post-surgery, and safety does not appear to be compromised by earlier CR. Whilst the growing evidence base for earlier post-sternotomy CR exercise training is relatively compelling, good quality prospective trials have not been performed. As such, randomised controlled trials are required to confirm benefit, safety and cost effectiveness. Results of such studies are essential before national guidelines can be established, allowing policymakers and clinicians to be confident in altering practice.

The early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR) trial is a single-centre randomised controlled trial, and economic evaluation, comparing supervised

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exercise training commenced at two weeks (early CR) with exercise training commenced at six weeks (usual care CR) post-sternotomy. The main objectives of the trial are:

1. To assess the effect of early CR on functional fitness.
2. To assess the effect of early CR on anxiety, depression and health related quality of life (HR-QoL).
3. To assess compliance and adherence to early CR.
4. To conduct a cost-effectiveness analysis of early CR compared to usual care CR.
5. To assess the safety of early CR

In cardiac surgery patients recovering from sternotomy, our primary hypothesis is that early CR will improve walking distance to the same extent as usual care CR. With limited data on early CR in this population, particularly in the UK, we propose a holistic investigation including the following secondary hypotheses: early CR will 1) be as effective as usual care CR in improving functional fitness; 2) be as effective as usual care CR in improving anxiety and depression; 3) be as effective as usual care CR in improving HR-QoL; 4) demonstrate equivalent adherence and compliance to usual care CR; 5) be as cost effective as usual care CR; 6) be as safe as usual care CR.

Methods and analysis

The SCAR study is an assessor-blind parallel group, randomised controlled trial and economic evaluation. Participants will be randomly allocated to eight weeks of CR exercise training commencing at either two weeks (early CR) or six weeks (usual care CR) post-surgery. Outcomes will be measured at baseline (within 7 days of surgery), start of CR (2 or 6

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weeks), end of CR (10 or 14 weeks), and at 12 months. Assessors will be blinded to group allocation. The trial protocol adheres to the Standard Protocol Items: Recommendations for Clinical Trials (SPIRIT) guidelines (26).

Setting

The SCAR trial will be conducted at two cardiac rehabilitation venues provided by University Hospitals Coventry & Warwickshire (UHCW) NHS Trust, 1) Atrium Health, Centre for Exercise & Health, Coventry, and 2) Hospital of St. Cross, Rugby. Both CR programmes are certified by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR), thus, providing the necessary infrastructure and expertise for the delivery of the SCAR intervention. All cardiac surgery will be performed at University Hospital, Coventry, a national specialist tertiary cardiac centre. One hundred and seventy patients will be recruited over a two-year period, commencing 15th July 2017.

Participants

All patients who are to undergo elective or emergency sternotomy for coronary artery bypass graft surgery or mitral/aortic valve replacement will be screened for eligibility. Inclusion and exclusion criteria are summarised in table 1.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria
▪ Coronary artery bypass graft and mitral/aortic valve replacement patients recovering from sternotomy, and eligible for cardiac rehabilitation exercise training in accordance with UK standards (27)	▪ Serious cardiac arrhythmias ▪ Current neurological disorders or previous cerebral vascular accident with residual neurological deficit significant enough to limit exercise
▪ Able to provide written informed consent	▪ Unable to enrol for the full study duration ▪ Inability to comply with guidelines for participation in exercise training (28, 29)
▪ Male or female	▪ Significant limiting comorbidities that would prevent full participation
▪ 18-90 years of age	

Study Procedures

The participant study pathway is illustrated in figure 1. All cardiac surgery patients will be screened and assessed for eligibility by the research team in consultation with the trial clinical lead. Patients meeting the inclusion criteria will be informed of the study at the first available opportunity. For elective patients, this will take place at either the pre-operative assessment clinic appointment (approximately two weeks prior to surgery), or on admission for surgery. For emergency admissions, patients will be informed of the study early in the post-operative period if it is inappropriate for the study to be discussed pre-surgery. Those who may be interested in participating will be given the patient information leaflet and permitted a minimum of 24 hours to consider their involvement prior to a follow-up phone call or in-patient visit from the research team. Non-English speaking patients will have access to translation services. Informed consent will be obtained on admission for surgery or early in the post-operative period. Baseline data collection will include clinical examination, 6-minute walk test (6-MWT), five times sit-to-stand test (FTSTS), hand grip strength, and isometric leg muscle strength. Instruments to assess anxiety and depression, HR-QoL, and health and

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social care use, will also be administered. Subsequently, participants will be randomised to twice weekly CR exercise training, commencing at either two weeks post-surgery (early CR) or six weeks post-surgery (usual care CR). All measures will be repeated immediately prior to starting CR (2 or 6 weeks post-surgery), on completion of 8 weeks of CR exercise training (10 or 14 weeks post-surgery), and at 12 months follow-up. Transport to and from the CR venues will be offered to patients who are not permitted to drive due to post-surgical Driving and Vehicle Licencing Agency (DVLA) restrictions.

Interventions

Participants in both groups will attend eight weeks of twice-weekly supervised CR exercise training. Both groups will exercise at the same time, in the same facility, with equal levels of supervision, and each session will last approximately one hour. The usual care CR group will adhere to current UK standards (BACPR/ACPICR) (27), commencing exercise training at six weeks post-surgery. In brief, a 15-minute warm-up will incorporate light cardiovascular and mobility exercises (<40% heart rate reserve, HRR). The subsequent cardiovascular exercise component (cycle ergometer, rowing ergometer, treadmill, arm ergometer, cross trainer) will involve 20 minutes of moderate intensity interval training (1-2 minute intervals), progressing to 20-40 minutes of continuous cardiovascular exercise at 40-70% HRR. After a 10-minute cool-down, a full programme of functional muscular strength, flexibility and proprioception exercises will be undertaken (e.g. resistance machines, free weights, multi-plane functional daily living exercise). Care will be taken to ensure upper body exercises are performed in such a way to avoid sternal and leg wound pain/complications. Exercise intensity will be prescribed using estimated metabolic equivalents (METs) from the six-minute walk test (6-MWT). Duration and workload will be increased, as tolerated, based on heart rate and patient reported rating of perceived exertion (RPE). Written home exercise guidance will be

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provided for the six weeks preceding CR enrolment. This guidance has been produced locally and recommends short bouts (5 minutes) of light-moderate intensity walking, progressing in duration each week after surgery. In addition, a series of shoulder mobility exercises will be completed, with the advice to avoid pain and/or undue post-exercise fatigue.

Currently there are no specific exercise prescription guidelines for outpatient CR in patients who have undergone recent sternotomy (<6 weeks). In the first 2-3 weeks of early CR, participants will follow a highly individualised exercise programme dictated by their current level of fitness and post-surgery symptoms/limitations. General guidance will be taken from previous exploratory work (7) aimed at maintaining and increasing mobility and functional strength. Shoulder and chest mobility/strength exercises will be performed when they can be completed with minimal discomfort, and moderate intensity cardiovascular interval training will be gradually introduced. By weeks 2-3 of early CR, participants will progress towards achieving current UK standards as above (BACPR/ACPICR) (27). Initially, warm-up and cool-down will be specifically tailored to the planned exercises, without adhering to current guidelines. Table 2 provides an overview of the early CR exercise intervention.

Table 2. General principles of exercise training for early CR (first 2-3 weeks of CR)

- Highly individualised programme based on current limitations, mobility, fitness and symptoms
- Shortened warm-up and cool down where required, appropriate to the main exercise component
- Focus on improvement of posture, mobility, proprioception and functional strength
- Range of movement dictated by sternal and leg wound pain – pain free exercise advised
- Low-moderate intensity CV exercise (excluding rowing machine and arm ergometer for 2 weeks) i.e treadmill, cycle ergometer, step-ups
- Seated exercise where necessary

Extension of the CR programme beyond 8 weeks will be permitted in both groups

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where two or more consecutive exercise sessions are missed. This is in keeping with standard practice in UK cardiac rehabilitation programmes, and the pragmatic nature of the trial. Sufficient adherence to the study protocol will be determined by the following criteria:

- A minimum of 66% of sessions completed (12 of 18).
- 20 minutes continuous cardiovascular exercise achieved by week four of the CR programme.

Randomisation and blinding:

Trial participants will be allocated to early CR or usual care CR, on a 1:1 basis, via block randomisation. The random allocation sequence will be generated by the trial statistician, implemented by an independent CR team member, and compliance will be ensured by UHCW NHS Trust R&D department. Randomisation requests will only be submitted further to completion of all baseline assessments, thus ensuring allocation concealment. At all time points, outcome assessors will be blinded to group allocation, as will the cardiac surgeons. Due to the nature of the trial, it will not be possible to blind the CR staff involved in the delivery of the exercise training interventions. Likewise, participants cannot be blinded.

Study outcome measures:

The primary outcome measure is the change in six-minute walk distance at the end of the CR exercise training programme. Secondary outcomes will include measures of 1) functional fitness; 2) anxiety and depression; 3) HR-QoL; 4) compliance and adherence; 5) cost effectiveness, and 6) safety. Table 3 outlines the full schedule of outcome assessments.

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Table 3. Outcome measures and schedule of assessments

Measure	Instrument	Assessment time point
Primary outcome		
Walking distance	Six-minute walk test	Baseline, start CR, end CR, 12 months
Secondary outcomes		
Functional fitness	Five times sit-to-stand	Baseline, start CR, end CR, 12 months
	Handgrip strength	Baseline, start CR, end CR, 12 months
	Isometric leg strength	Baseline, start CR, end CR, 12 months
Anxiety and depression	GAD-7	Baseline, start CR, end CR, 12 months
	PHQ-9	Baseline, start CR, end CR, 12 months
HR-QOL	SF-12	Baseline, start CR, end CR, 12 months
Compliance, adherence	Compliance/adherence/drop-out rates	Continuous
Cost effectiveness	EQ-5D	Baseline, start CR, end CR, 12 months
	CSRI	Start CR, end CR, 12 months
Safety	Adverse event monitoring	Continuous

CR, cardiac rehabilitation; GAD-7, Generalised Anxiety Disorder assessment; PHQ-9, Patient Health Questionnaire; HR-QoL, health related quality of life; SF-12; 12-Item Short Form Survey; EQ-5D, 5-Item EuroQol; CSRI, client service receipt inventory.

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Primary outcome

The six-minute walk test (6-MWT) is a general measure of functional capacity, and an important prognostic indicator in cardiac surgery populations (30-32). Tests will be conducted in accordance with American Thoracic Society (ATS) guidelines (33). Participants will be instructed to walk as far as possible along a 30m, flat, obstacle free corridor, turning 180 degrees every 30m, in the allotted time of six minutes.

Functional fitness

The five times sit-to-stand test is often used in clinical and research settings (34) for the measurement of functional lower-extremity muscular strength and power. To complete the FTSTS, the participant will be instructed to stand up and sit down five times as quickly as

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possible without using their arms for assistance. To ensure good test-retest reliability (35), standardised foot placement and chair height will be required for each participant. A Jamar hand dynamometer (Sammons Preston Inc; Bollingbrook, Illinois) will be used to evaluate hand grip strength in the dominant hand. The position of the participant's arm will adhere to American Society of Hand Therapists recommendations (36) and participants will be instructed to maintain maximal grip contraction for 2-5 seconds. Isometric quadriceps strength will be assessed using a hand held dynamometer (MicroFET2 Torque/Force indicator, Hoggan Health Industries, Utah, US) (37). Whilst sitting in an elevated chair, with hips and knees aligned at 90 degrees and the lower leg vertical, participants will exert maximal force against equal and opposite resistance provided by the assessor.

Anxiety, depression and HR-QoL

The seven item Generalised Anxiety Disorder assessment (GAD-7) and nine-item Patient Health Questionnaire (PHQ-9) are well validated for the assessment of anxiety and depression (38, 39). Both are widely used as brief diagnostic tools, and measures of severity. Furthermore, they are routinely recorded in the CR population as part of standard clinical practice with the results reported in the National Audit of Cardiac Rehabilitation (NACR) (40). The 12-Item Short Form Survey (SF-12) will be used to evaluate HR-QoL (41). The 12 items of the questionnaire are summarised in two weighted summary scales; mental health score (MCS) and physical health score (PCS), where lower scores indicate more severe disability.

Compliance and adherence

Compliance and adherence is an important outcome in patients commencing CR exercise training early post-surgery. Attendance at CR exercise sessions will be closely monitored

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along with compliance to the prescribed exercise regimen. The number of sessions attended will be documented, as will the number of sessions successfully completed. Detailed reasons for incomplete sessions, and drop out, will be recorded where the participant is happy to provide this information.

Economic evaluation

The EQ-5D questionnaire is a commonly used generic measure of health status. A key feature is the availability of 'value sets' to weight the EQ-5D health states reported by participants and populations. The UK value set reported by Dolan (1997) (42) is recommended by NICE for use in its health technology appraisal process (43). An adapted client service receipt inventory (CSRI), based on examples in the DIRUM database (44) will be administered at each time point to capture participant health and social care service use since the last time point. The cost of delivering early CR and usual care CR (i.e. staff, equipment, facility) will be recorded throughout the CR programme.

Safety

To verify the safety of early CR exercise training, all adverse and serious adverse events will be carefully monitored, recorded and reported. In line with the principles of Good Clinical Practice (GCP), the nature and severity of the event, in addition to its potential association with study participation, will be recorded (45). As with current usual care, the local CR team, in conjunction with the trial clinician, will decide if participants with sternal instability or wound infection should be delayed or withdrawn.

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Sample size

The sample size calculation is based on the primary analysis of change in 6-MWT distance post-CR from baseline. Based on a recent systematic review and meta-analysis of CR patients (46), we assume a standard deviation of 65m. Assuming that mean changes in 6-MWT distances at the end of CR sessions for both early CR and usual care CR are equal, 60 patients are required in each group (120 in total) to conclude non-inferiority (non-inferiority margin of 35) with 90% power. To allow for approximate dropout rate of 15%, 70 patients will need to be randomised to each group (140 in total).

Data collection and management

Data will be collected by research staff on case report forms at four time points; baseline, pre-CR, post-CR and 12 months follow up. Local policy and national data protection guidance will be followed with study data anonymously recorded on a bespoke trial database using unique study identification numbers.

Statistical analysis

The primary analysis will test non-inferiority of the early CR group compared to usual care CR based on changes in 6-MWT distances. The non-inferiority margin has been set at 35m based on the previously reported minimally important clinical differences (47-49). Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% confidence interval for the mean difference of changes at the end of CR is less than 35m. If the lower bound of the 95% confidence interval for the mean difference in changes at the end of CR is above 0, early CR will be concluded superior to usual care CR. The 95% confidence interval will be based on the t-distribution for the mean difference in changes between early and usual care CR.

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In secondary analysis, a linear mixed model will include all 6-MWT distances taken from each patient at different time points, from baseline (at randomisation) to 14 weeks. Fourteen weeks is the time point at which CR exercise training will be complete in the usual care CR group. The model will include terms for group (early or usual care CR), and time (baseline, pre-CR, post-CR, 12 months). To assess if the trends for early CR and usual care CR are different, an interaction term for group and time will be included in the linear mixed models. All data will be summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (50).

Economic evaluation

Economic evaluation will complement the trail's clinical effectiveness results and inform decision-making on the commissioning of early CR. We will conduct a cost-effectiveness analysis to estimate cost per unit of health gains due to early CR compared to usual CR (e.g. cost per additional distance covered in the 6-MWT). The costs and effects for participants in each group will be compared for the economic evaluation of the intervention. Given that the primary outcome is measured in natural units, and that the trial lasts 12 months, a cost-effectiveness (CE) approach is preferred for the economic evaluation (51). A service provider perspective will be adopted: a client service receipt inventory (CSRI), administered pre-CR, post CR and at 12 months, will collect data for participants' health and social care resource use (direct medical and non-medical resources) since the last data collection point. Health outcome measures for effectiveness, reported in table 3, and economic resource use, listed in table 4, will be measured as per the recommendations of the Expert Delphi Consensus Survey (52). The collected resource use and effects data will be handled with Stata software for statistical analysis of economic evaluation (53). The missing values will be analysed through multiple imputation. The incremental cost and effectiveness ratios will be estimated for early

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CR and obtained by dividing the incremental cost by the incremental gain in meters from the 6-MWT. Incremental cost and effectiveness ratios and Cost-Effectiveness Acceptability Curves will be used to evaluate if the health benefit generated by early CR is worth any additional cost associated with the intervention. A non-parametric bootstrap technique will be employed to report uncertainty around CE measures. The CE analysis will adhere to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of published economic evaluations (54).

Table 4. Resource use and intervention cost measures

Measure	Instrument	Assessment time point
Secondary care		
Number and length of admissions (inpatient stay or day case) Number of outpatient appointments	CSRI	Start CR, end CR, 12 months
Emergency care		
Number of visits to A&E Number of admissions to hospital, after A&E	CSRI	Start CR, end CR, 12 months
Primary care		
Type of professional seen Number and length of visits	CSRI	Start CR, end CR, 12 months
Health care at home		
Type of professional seen Number and length of visits	CSRI	Start CR, end CR, 12 months
Medication Name/class/dose	CSRI	Start CR, end CR, 12 months
Cost of intervention Staff, equipment, facility	Cost diary	Every participant contact

CSRI, client service receipt inventory; CR, cardiac rehabilitation; A&E, accident and emergency

Patient and public involvement

Patient and public involvement (PPI) has shaped the study design. Our patient forum endorsed the acceptability of early CR exercise training after surgery, and stressed the importance of returning to work/activities of daily living as soon as possible. Our PPI co-

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investigator, with lived experience of cardiac surgery, met with several surgical patients, each of whom was sent an overview of the early research protocol. The feedback helped researchers select outcome measures that were relevant to patients' daily experiences and, that crucially, would not unduly inconvenience participants. Multiple, time consuming, invasive outcome measures were considered unethical so early after major surgery.

Ethics

The study protocol v1.0, dated 25th January 2017, was approved by the NHS Health Research Authority, West Midlands - Edgbaston Research Ethics Committee on 24th February 2017 (17/WM/0057).

Dissemination and impact

Research findings will be presented at scientific meetings and published in peer-reviewed journals. All authors will approve the prepared manuscripts and authorship will be agreed based on international recommendations (ICMJE). The trial is anticipated to influence the direction of future research into CR in sternotomy patients. It is also expected that results from this trial will influence national CR guidelines. As such, findings, relating to both scientific outcomes and CR service provision will be disseminated amongst national governing bodies, and associated organisations, via newsletters and conferences.

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Figure 1. Trial flow chart

UHCW, University Hospitals Coventry & Warwickshire; CR, cardiac rehabilitation; *Assessment to include six-minute walk, five times sit-to-stand, grip strength, isometric leg strength, Generalised Anxiety Disorder assessment (GAD-7), Patient Health Questionnaire (PHQ-9), 12-Item Short Form Survey (SF-12), 5-Item EuroQol (EQ-5D), client service receipt inventory (CSRI).

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Contributions: SE is the Chief Investigator for the trial, leading on protocol development and the research ethics application. SE, GL, SW, TB, GM, PK, AK, RP and PB all contributed fully to the study design. TB (cardiothoracic surgery) PK (statistics), AK (health economics), provided discipline specific expertise and authored the relevant sections of the protocol and manuscript. GM prepared the manuscript which was edited by SE, TB, PK and AK. All authors read and approved the final version of the manuscript.

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Competing interests: none.

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Figure 1. Trial flow chart

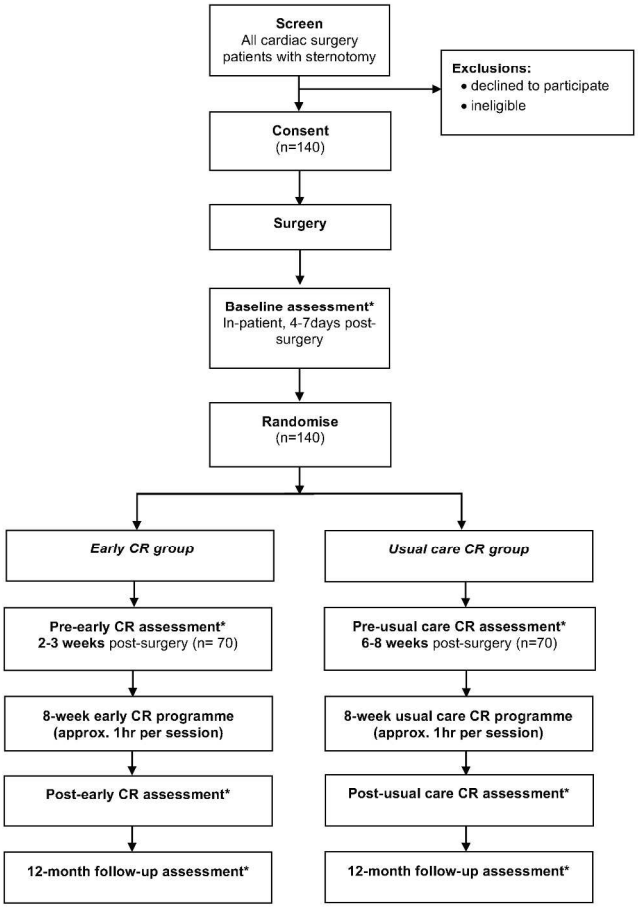

Figure 1. Trial flow chart

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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	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1,4_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	__throughout__
Protocol version	3	Date and version identifier	_____all_____
Funding	4	Sources and types of financial, material, and other support	_____n/a_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____3_____
	5b	Name and contact information for the trial sponsor	_____4_____
	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	_____n/a_____
	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)	_____24-26___

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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	____12-16_____
	6b	Explanation for choice of comparators	___12-16_____
Objectives	7	Specific objectives or hypotheses	_____13_____
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)	_____4_____

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	_____18_____
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)	_____18_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____13_____
	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)	___16,22_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____n/a_____
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	_____17-21____
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)	_____6_____

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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	23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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	12
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	19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19
	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	20
	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	22

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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	24
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	22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22
	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)	22
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	N/A
	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	N/A
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	26
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24-25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
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)	X

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	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	24-26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
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	26
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	ethics
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	ethics
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Site file/ethics
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	N/A

*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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