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BMJ Open 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 6 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 2 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 8 weeks of twice-weekly supervised CR exercise training commencing at either 2 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 (inpatient), 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 6 min walk distance. Secondary outcomes will include measures of functional fitness, quality of life and cost-effectiveness.

Ethics and dissemination Recruitment commenced on 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 NCT03223558; Pre-results.

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

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 multicentre design.

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 patients² 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 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 3 weeks of total inactivity had a more profound impact on exercise capacity than 30 years of ageing.^{14 15} Cardiac muscle mass has also been shown to decrease by 8% after 6 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 1 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 inpatient 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 postdischarge.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 2 kg 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 dumb bell 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 poststernotomy.

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 postcardiac 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 postsurgical 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 6-week wait post-surgery, and safety does not appear to be compromised by earlier CR. While 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 policy-makers 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 exercise training commenced at 2 weeks (early CR) with exercise training commenced at 6 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 with 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 and (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 8 weeks of CR exercise training commencing at either 2 weeks (early CR) or 6 weeks (usual care CR) post-surgery. Outcomes will be measured at baseline (within 7 days of surgery), start of CR (2 or 6 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 guidelines.²⁶

SETTING

The SCAR trial will be conducted at two cardiac rehabilitation venues provided by University Hospitals

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Coronary artery bypass graft and mitral/aortic valve replacement patients recovering from sternotomy and eligible for cardiac rehabilitation exercise training in accordance with UK standards²⁷; ▶ Able to provide written informed consent; ▶ Male or female; ▶ 18–90 years of age. 	<ul style="list-style-type: none"> ▶ Serious cardiac arrhythmias; ▶ Current neurological disorders or previous cerebral vascular accident with residual neurological deficit significant enough to limit exercise; ▶ Unable to enrol for the full study duration; ▶ Inability to comply with guidelines for participation in exercise training^{53 54}; ▶ Significant limiting comorbidities that would prevent full participation.

Coventry and Warwickshire (UHCW) National Health Service (NHS) Trust, (1) Atrium Health, Centre for Exercise and 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 forty patients will be recruited over a 2-year period, commencing 15 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](#).

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 preoperative assessment clinic appointment (approximately 2 weeks prior to surgery) or on admission for surgery. For emergency admissions, patients will be informed of the study early in the postoperative period if it is inappropriate for the study to be discussed presurgery. 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 inpatient 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 postoperative period. Baseline data collection will include clinical examination, 6 min 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 social care use, will also be administered. Subsequently, participants will be randomised to twice weekly CR exercise training, commencing at either 2 weeks post-surgery (early CR) or 6 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 postsurgical Driving and Vehicle Licensing Agency restrictions.

INTERVENTIONS

Participants in both groups will attend 8 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 1 hour. The usual care CR group will adhere to current UK standards (BACPR/ACPICR, Association of Chartered Physiotherapists in Cardiac Rehabilitation),²⁷ commencing exercise training at 6 weeks post-surgery. In brief, a 15 min 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 min of moderate intensity interval training (1–2 min intervals), progressing to 20–40 min of continuous cardiovascular exercise at 40%–70% HRR. After a 10 min cool down, a full programme of functional muscular strength, flexibility and proprioception exercises will be undertaken (eg, resistance machines, free weights, multiplane 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 from the 6-MWT. Duration and workload will be increased, as tolerated, based on heart rate and patient reported rating of perceived exertion. Written home exercise guidance will be provided for the 6 weeks preceding CR enrolment. This guidance has been produced locally and recommends short bouts (5 min) 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 postexercise fatigue.

Currently, there are no specific exercise prescription guidelines for outpatient CR in patients who have

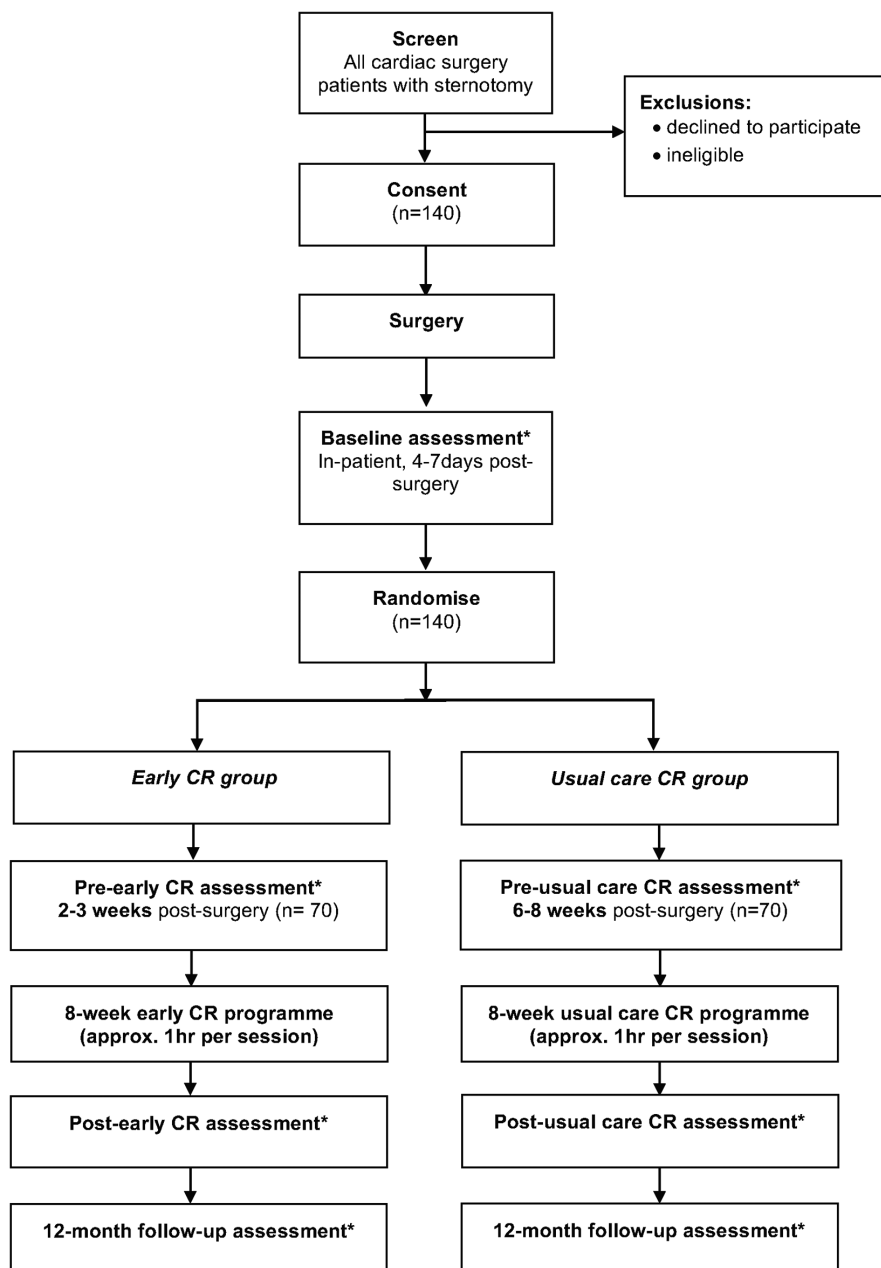


Figure 1 Trial flow chart—University Hospitals Coventry and Warwickshire. *Assessment to include: 6 min walk, five times sit-to-stand, grip strength, isometric leg strength, Generalised Anxiety Disorder assessment, Patient Health Questionnaire, 12-Item Short Form Survey, 5-Item EuroQol, Client Service Receipt Inventory. CR, cardiac rehabilitation.

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 work⁷ 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. **Box 1** provides an overview of the early CR exercise intervention.

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 min continuous cardiovascular exercise achieved by week 4 of the CR programme.

Box 1 General principles of exercise training for early cardiac rehabilitation (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 cardiovascular exercise (excluding rowing machine and arm ergometer for 2 weeks) that is, treadmill, cycle ergometer, step-ups.
- ▶ Seated exercise where necessary.

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 6-MWT 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 2** outlines the full schedule of outcome assessments.

PRIMARY OUTCOME

The 6-MWT is a general measure of functional capacity and an important prognostic indicator in cardiac surgery populations.^{28–30} Tests will be conducted in accordance with American Thoracic Society guidelines.³¹ Participants will be instructed to walk as far as possible along a 30 m, flat, obstacle-free corridor, turning 180° every 30 m, in the allotted time of 6 min.

FUNCTIONAL FITNESS

The FTSTS test is often used in clinical and research settings³² 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 possible without using their arms for assistance. To ensure good

Table 2 Outcome measures and schedule of assessments

Measure	Instrument	Assessment time point
Primary outcome		
Walking distance	6 min 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; CSRI, Client Service Receipt Inventory.; EQ-5D, 5-Item EuroQol; GAD-7, Generalised Anxiety Disorder assessment; HR-QoL, health-related quality of life; PHQ-9, Patient Health Questionnaire; SF-12, 12-Item Short Form Survey.

test–retest reliability,³³ standardised foot placement and chair height will be required for each participant. A Jamar hand dynamometer (Sammons Preston, Bollingbrook, Illinois, USA) 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,³⁴ and participants will be instructed to maintain maximal grip contraction for 2–5 s. Isometric quadriceps strength will be assessed using a handheld dynamometer (MicroFET2 Torque/Force indicator, Hoggan Health Industries, Utah, USA).³⁵ While sitting in an elevated chair, with hips and knees aligned at 90° 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 and nine-item Patient Health Questionnaire are well validated for the assessment of anxiety and depression.^{36 37} 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 NACR.³⁸ The 12-Item Short Form Survey (SF-12) will be used to evaluate HR-QoL.³⁹ The 12 items of the questionnaire are summarised in two weighted summary scales; mental health score and physical health score, 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 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 dropout will be recorded where the participant is happy to provide this information.

ECONOMIC EVALUATION

The 5-Item EuroQol (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 Dolan⁴⁰ is recommended by National Institute for Health and Care Excellence for use in its health technology appraisal process.⁴¹ An adapted Client Service Receipt Inventory (CSRI), based on examples in the Database of Instruments for Resource Use Measurement (DIRUM) database⁴² 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 (ie, 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, the nature and severity of the event, in addition to its potential association with study participation, will be recorded.⁴³ 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.

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,⁴⁴ we assume a SD 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 with 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.^{45–47} Early CR will be concluded non-inferior to usual care CR if the lower bound of the 95% CI for the mean difference of changes at the end of CR is less than 35m. If the lower bound of the 95% CI 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% CI 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 guideline.⁴⁸

ECONOMIC EVALUATION

Economic evaluation will complement the trial'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 with usual CR (eg, 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 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 2, and economic resource use, listed in table 3, will

Table 3 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
Healthcare 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

A&E, accident and emergency; CR, cardiac rehabilitation; CSRI, Client Service Receipt Inventory.

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 version 15 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 metres 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 statement for the reporting of published economic evaluations.⁵²

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 coinvestigator, 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.

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 among national governing bodies and associated organisations, via newsletters and conferences.

Contributors SE is the chief investigator for the trial, leading on protocol development and the research ethics application. SE, GL, SW, TB, GM, PKK, AJK, RP and PB all contributed fully to the study design. TB (cardiothoracic surgery), PKK (statistics) and AJK (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, PKK and AJK. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Obtained.

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REFERENCES

1. Page RD MJ, Kinsman S. *econd National Thoracic Surgery Activity & Outcomes Report on behalf of the Society for Cardiothoracic Surgery in Great Britain & Ireland*. Henley-on-Thames: Published by Dendrite Clinical Systems Ltd, 2011. ISBN 978-0-9568154-1-5.
2. King KM, Parry M, Southern D, *et al*. Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. *Heart* 2008;94:493–7.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618–25.
4. Moon MH, Kang JK, Kim HW, *et al*. Pain after median sternotomy: collateral damage or mitigatable byproduct? *Thorac Cardiovasc Surg* 2013;61:194–201.
5. Falcoz PE, Chocron S, Stoica L, *et al*. Open heart surgery: one-year self-assessment of quality of life and functional outcome. *Ann Thorac Surg* 2003;76:1598–604.
6. Cahalin LP, Lapier TK, Shaw DK. Sternal Precautions: Is It Time for Change? Precautions versus Restrictions - A Review of Literature

- and Recommendations for Revision. *Cardiopulm Phys Ther J* 2011;22:5–15.
7. Adams J, Lotshaw A, Exum E, *et al.* An alternative approach to prescribing sternal precautions after median sternotomy, "Keep Your Move in the Tube". *Proc* 2016;29:97–100.
 8. Anderson L, Thompson DR, Oldridge N, *et al.* Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016;1:CD001800.
 9. Barons MJ, Turner S, Parsons N, *et al.* Fitness predicts long-term survival after a cardiovascular event: a prospective cohort study. *BMJ Open* 2015;5:e007772.
 10. Losanoff JE, Richman BW, Jones JW. Disruption and infection of median sternotomy: a comprehensive review. *Eur J Cardiothorac Surg* 2002;21:831–9.
 11. Ridderstolpe L, Gill H, Granfeldt H, *et al.* Superficial and deep sternal wound complications: incidence, risk factors and mortality. *Eur J Cardiothorac Surg* 2001;20:1168–75.
 12. Adams J, Cline MJ, Hubbard M, *et al.* A new paradigm for post-cardiac event resistance exercise guidelines. *Am J Cardiol* 2006;97:281–6.
 13. Parker R, Adams JL, Ogola G, *et al.* Current activity guidelines for CABG patients are too restrictive: comparison of the forces exerted on the median sternotomy during a cough vs. lifting activities combined with valsalva maneuver. *Thorac Cardiovasc Surg* 2008;56:190–4.
 14. McGuire DK, Levine BD, Williamson JW, *et al.* A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. *Circulation* 2001;104:1358–66.
 15. Perhonen MA, Franco F, Lane LD, *et al.* Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol* 2001;91:645–53.
 16. Wall BT, Dirks ML, van Loon LJ. Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia. *Ageing Res Rev* 2013;12:898–906.
 17. Berry SD, Samelson EJ, Bordes M, *et al.* Survival of aged nursing home residents with hip fracture. *J Gerontol A Biol Sci Med Sci* 2009;64:771–7.
 18. Eder B, Hofmann P, von Duvillard SP, *et al.* Early 4-week cardiac rehabilitation exercise training in elderly patients after heart surgery. *J Cardiopulm Rehabil Prev* 2010;30:85–92.
 19. Hirschhorn AD, Richards DA, Mungovan SF, *et al.* Does the mode of exercise influence recovery of functional capacity in the early postoperative period after coronary artery bypass graft surgery? A randomized controlled trial. *Interact Cardiovasc Thorac Surg* 2012;15:995–1003.
 20. Højskov IE, Moons P, Hansen NV, *et al.* Early physical training and psycho-educational intervention for patients undergoing coronary artery bypass grafting. The SheppHeart randomized 2 × 2 factorial clinical pilot trial. *Eur J Cardiovasc Nurs* 2016;15:425–37.
 21. Pack QR, Dudycha KJ, Roschen KP, *et al.* Safety of early enrollment into outpatient cardiac rehabilitation after open heart surgery. *Am J Cardiol* 2015;115:548–52.
 22. Fell J, Dale V, Doherty P. Does the timing of cardiac rehabilitation impact fitness outcomes? An observational analysis. *Open Heart* 2016;3:e000369.
 23. Marzolini S, Blanchard C, Alter DA, *et al.* Delays in Referral and Enrollment Are Associated With Mitigated Benefits of Cardiac Rehabilitation After Coronary Artery Bypass Surgery. *Circ Cardiovasc Qual Outcomes* 2015;8:608–20.
 24. Johnson DA, Sacrinty MT, Gomadam PS, *et al.* Effect of early enrollment on outcomes in cardiac rehabilitation. *Am J Cardiol* 2014;114:1908–11.
 25. Russell KL, Holloway TM, Brum M, *et al.* Cardiac rehabilitation wait times: effect on enrollment. *J Cardiopulm Rehabil Prev* 2011;31:373–7.
 26. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
 27. ACPICR. Standards for physical activity and exercise in the cardiac population. 2015 http://acpicr.com/sites/default/files/ACPICR_Standards_2015_0.pdf
 28. Ross RM, Murthy JN, Wollak ID, *et al.* The six minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulm Med* 2010;10:31.
 29. Opasich C, De Feo S, Pinna GD, *et al.* Distance walked in the 6-minute test soon after cardiac surgery: toward an efficient use in the individual patient. *Chest* 2004;126:1796–801.
 30. Beatty AL, Schiller NB, Whooley MA. Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the heart and soul study. *Arch Intern Med* 2012;172:1096–102.
 31. Holland AE, Spruit MA, Troosters T, *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
 32. Ng S. Balance ability, not muscle strength and exercise endurance, determines the performance of hemiparetic subjects on the timed-sit-to-stand test. *Am J Phys Med Rehabil* 2010;89:497–504.
 33. Bohannon RW. Test-retest reliability of the five-repetition sit-to-stand test: a systematic review of the literature involving adults. *J Strength Cond Res* 2011;25:3205–7.
 34. Fess EE. Grip strength. In: Casanova JS, ed. *Clinical Assessment Recommendations*. 2nd edition. Chicago: American Society of Hand Therapists, 1992:41–5.
 35. Hansen EM, McCartney CN, Sweeney RS, *et al.* Hand-held Dynamometer Positioning Impacts Discomfort During Quadriceps Strength Testing: A Validity and Reliability Study. *Int J Sports Phys Ther* 2015;10:62–8.
 36. Spitzer RL, Kroenke K, Williams JB, *et al.* A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–7.
 37. Kroenke K. Depression screening is not enough. *Ann Intern Med* 2001;134:418–20.
 38. Rehabilitation NAOc. *Annual Report*. York, UK, 2016.
 39. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33.
 40. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.
 41. NICE. *Guide to the methods of technology appraisal*. London: National Institute of Health and Clinical Excellence, 2013.
 42. Ridyard CH, Hughes DA. Methods for the collection of resource use data within clinical trials: a systematic review of studies funded by the UK Health Technology Assessment program. *Value Health* 2010;13:867–72.
 43. ICH Harmonised Tripartite guideline - guideline for good clinical practice E6 (R1). 1996 <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>
 44. Wyrwich KW, Tierney WM, Babu AN, *et al.* A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40:577–92.
 45. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81.
 46. Shoemaker MJ, Curtis AB, Vangsnes E, *et al.* Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulm Phys Ther J* 2013;24:21–9.
 47. Gremeaux V, Troisgros O, Benaïm S, *et al.* Determining the minimal clinically important difference for the six-minute walk test and the 200-meter fast-walk test during cardiac rehabilitation program in coronary artery disease patients after acute coronary syndrome. *Arch Phys Med Rehabil* 2011;92:611–9.
 48. Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
 49. Drummond MF, Sculpher MJ, Claxton K, *et al.* *Methods for the economic evaluation of health care programmes*: Oxford University Press, 2015.
 50. Thorn JC, Brookes ST, Ridyard C, *et al.* Core Items for a Standardized Resource Use Measure (ISRU): Expert Delphi Consensus Survey. *Value in Health* 2017.
 51. Deb P, Norton EC, Manning WG. *Health Econometrics Using Stata*: Stata Press, 2017.
 52. Husereau D, Drummond M, Petrou S, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013;346:f1049.
 53. AACVPR. *Guidelines for cardiac rehabilitation and secondary prevention programs*. 4th Edition. Champaign: IL: Human Kinetics, 2003.
 54. ACSM. *Guidelines for exercise testing and prescription*. 9th ed. Riverwoods: IL: Lippincott Williams & Wilkins, 2014.