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PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL)

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Abstract

Introduction

Prehabilitation prior to surgery has been shown to reduce postoperative complications, reduce length of hospital stay, and improve quality of life after cancer and limb reconstruction surgery. However, there is minimal data on the impact of prehabilitation in patients undergoing cardiac surgery, despite the fact these patients are generally older and have more comorbidities and frailty. This trial will assess the feasibility and impact of a prehabilitation intervention consisting of exercise and inspiratory muscle training on pre-operative functional exercise capacity in adult patients awaiting elective cardiac surgery, and determine any impact on clinical outcomes after surgery.

Methods and Analysis

PrEPS is a randomised controlled single-centre trial recruiting 180 participants undergoing elective cardiac surgery. Participants will be randomised in a 1:1 ratio to standard pre-surgical care or standard care plus a prehabilitation intervention. The primary outcome will be change in functional exercise capacity measured as change in the 6 minute walk test distance from baseline. Secondary outcomes will evaluate the impact of prehabilitation on pre-operative and post-operative outcomes including; respiratory function, health related quality of life, anxiety and depression, frailty, and post-operative complications and resource use. This trial will evaluate if a prehabilitation intervention can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery in elective patients awaiting cardiac surgery, and impact post-operative outcomes.

Ethics and Dissemination

A favourable opinion was given by the Sheffield Research Ethics Committee in 2019. Trial findings will be disseminated to patients, clinicians, commissioning groups and through peer reviewed publication.

Trial registration

International Standard Randomised Controlled Trial Number 13860094. Registered on 24 October 2019

PROTOCOL V6.0 24 February 2022

Article Summary

Strengths and Limitations of this study

1. Largest pragmatic trial combining exercise and IMT for the first time in this population
2. Will establish if a prehab intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery
3. Robust assessment of fidelity of the intervention and compliance
4. Important accelerometer sub study to explore change in activity levels and qualitative sub study to explore views and experiences of patients and staff
5. Limited to single centre but will provide critical safety data essential for wider implementation

Keywords

Cardiac Surgery, Prehabilitation, Exercise, High-intensity Inspiratory Muscle Training (IMT)

Introduction

Over 35,000 patients undergo cardiac surgery every year in the UK alone(1). Over the last decade the average age of these patients has increased worldwide, as has the prevalence of patients with multiple comorbidities having cardiac surgery(2). This has the potential to increase mortality, morbidity and resource use resulting from increasing rates of post-operative complications and associated prolonged use of hospital resources.

Prehabilitation programmes are fast becoming a method of being pro-active prior to surgery with the aim of reducing post-operative complications and mortality, giving patients themselves a method of managing their fitness pre-surgery; ultimately with the aim of speeding up recovery and return to normal function after surgery. A BMJ editorial in September 2017(3) highlighted the urgent need to recognise that the drive to improve outcomes after surgery must include optimising patients' health prior to surgery with evidence based prehabilitation programmes. It recognised that programs would have to be tailored for patients and specific interventions.

In cardiac surgery however, there have been few trials investigating the impact of prehabilitation. Primarily, concerns around safety due to delaying intervention to allow prehabiliation to occur and the impact of exercise as part of the intervention has contributed to a lack of trial data. This is despite evidence that exercise interventions can improve

cardiovascular function and fitness; an important predictor of mortality in older patients(4). Poor cardiovascular fitness is known to be associated with higher all-cause mortality(5).

In patients awaiting cardiac surgery, the concern has been that severe coronary and valvular lesions e.g. severe aortic stenosis, cause symptoms with exercise and may precipitate complications. Furthermore patients are frequently told by their clinicians not to exercise whilst they wait for surgery. Moreover, severe aortic stenosis, left main stem stenosis, unstable angina, aortic aneurysms, and other cardiac condition are all contraindicated in most exercise and rehabilitation protocols currently used in the UK(6).

There is emerging evidence that patients with severe cardiac conditions can undergo exercise safely. The 6MWT was shown to be safe in a feasibility study of 244 patients with chronic lung or heart disease with no instances of adverse events(7). A trial in which low risk patients awaiting electives coronary artery bypass surgery underwent high-intensity treadmill training reported no significant adverse effects(8). However, neither of these trials included patients with severe cardiac conditions awaiting surgical intervention. A recent trial in patients with large abdominal aortic aneurysms awaiting repair has showed that even High Intensity Interval Training (HIIT) appeared to be safe and beneficial(9). These data have suggested that exercising patients awaiting cardiac surgery may be safe, therefore stimulating further interest in the role of exercise based prehabilitation prior to cardiac surgery.

Inspiratory muscle training (IMT) has the most evidence for improving outcomes after thoracic and cardiac surgery. This is most commonly achieved using inspiratory threshold-loading devices (threshold-IMT) which increase respiratory muscle strength and endurance, in turn improving respiratory volume and sputum clearance(10), thereby reducing postoperative pulmonary complications (PPCs). In cardiac surgery, preoperative IMT has been shown to reduce PPCs and have a modest effect on postoperative length of stay in high risk patients with pre-existing COPD after surgery(11). This finding has been confirmed in a number of systematic reviews and meta-analyses(12-14). A large multicentre trial funded by the NIHR (The INSPIRE Trial) to provide definitive evidence of benefit of IMT is currently ongoing.

To date no RCT has combined IMT with exercise in a prehabilitation intervention to determine the impact in patients undergoing cardiac surgery.

A trial is urgently needed to determine if patients with severe cardiac conditions can undergo prehabilitation safely prior to cardiac surgery. This was corroborated by a priority setting exercise conducted by The James Lind Alliance in the UK in 2019, to identify the top 10 research priorities for adult cardiac surgery research. In this Delphi style consensus exercise involving nearly 1000 patients and stakeholders, research to determine if prehabilitation benefited patients prior to cardiac surgery was the 4th most important of the ten priority research areas(15).

The PREPs trial will evaluate if a prehabilitation intervention consisting of exercise and inspiratory muscle training in patients awaiting elective cardiac surgery can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery. Other assessments include the impact of the intervention on post-operative clinical outcomes, speed of return to normal activity, patients' recovery from surgery and quality of life after surgery.

Methods/Analysis

Trial design

A single site prospective, parallel group randomised controlled trial will be conducted to compare the effect of a prehabilitation intervention on functional, physical and clinical outcomes compared to standard care. Participants will be randomly allocated 1:1 to either standard care or the intervention. Participants allocated to standard care will receive routine pre-operative advice only. Participants allocated to the intervention will receive routine pre-operative advice and a prehabilitation intervention consisting of supervised cardiac exercise sessions, high intensity inspiratory muscle training and a home exercise programme.

Participants will be followed up at routine clinical appointments prior to surgery, during surgical admission, and at 6 and 12 weeks following index surgery (figure 1). After the intervention period all participants will continue with the site's standard pre- and post-operative care.

Objectives

The Primary objective is to assess the impact of a pre-operative rehabilitation intervention (prehabilitation) on pre-operative functional exercise capacity (measured by change in the 6-minute walk test (6MWT)) from baseline in patients awaiting cardiac surgery.

The secondary objectives are to evaluate the impact of prehabilitation on outcomes including; respiratory function (measured by maximal inspiratory pressure (MIP)), health related quality of life (measured by the EQ-5D-5L), anxiety and depression (measured by the Hospital Anxiety and Depression Scale (HADS) and frailty (measured by grip strength) after the prehabilitation intervention.

The tertiary objectives are to evaluate the impact of prehabilitation on post-operative complication rates, including length of hospital stay, PPCs, and health related quality of life up to 12 weeks after surgery.

Two sub studies will also explore: the use of activity monitors to measure change in objectively measured physical activity from baseline to post-intervention, and the experiences of prehabilitation prior to elective cardiac surgery through the opinions of trial participants and the healthcare professionals responsible for prehabilitation delivery.

Eligibility

Patients aged 18 and over listed for elective cardiac surgery under the care of the participating surgeons will be screened for eligibility. The exclusion criteria are: unstable angina leading to the need for urgent surgery, malignant arrhythmias, currently participating in another interventional clinical trial, known pregnancy, contraindications to exercise prehabilitation.

Recruitment

Adults listed for elective cardiac surgery will be screened by the clinical team and given a patient information sheet (PIS) and letter of invitation prior to their routine clinic appointment. Eligibility will be confirmed by a clinician at the time of listing for surgery. Written informed consent will be obtained before any trial procedures are performed.

Baseline Data Collection

Baseline assessments will be performed after consent and prior to randomisation. Women of childbearing potential will perform a pregnancy test to confirm pregnancy status before undertaking any further research activity. The baseline assessments will consist of the 6MWT, MIP, EQ5D5L questionnaire, activity monitoring (optional), HADS, Rockwood frailty score and hand grip strength. Participants' medical notes will be used to collect a full medical history, gender, height and weight, and date of birth/age. Participants consenting to take part in the 7 day activity monitoring sub study will be provided with an accelerometer, instructions on it use, and options for returning the accelerometer.

Randomisation

Participants will be randomised in a 1:1 ratio to either the control arm (standard care only), or the intervention arm (standard care plus the prehabilitation intervention) using a 24-hour, central, secure, web-based system (SealedEnvelope™). Randomisation will be performed using a minimisation scheme that takes into account Rockwood frailty score, 6MWD, age and gender to balance baseline physical fitness between the arms. It will not be possible to conceal the allocation of treatment from the participant, or the team delivering the intervention and measuring the primary outcome. The surgeons performing the participants' cardiac surgery will not be informed of the allocation, however they will not be officially blinded.

Outcome Measures

The primary outcome will be change in exercise capacity measured by the 6-minute walk test from baseline to pre-surgical assessment. This is a self-paced 6-minute walk recording the distance walked in metres around a 25 meter standardised track. All participants will receive standardised instruction and support(16). A pulse oximeter will be attached to the participant during the walk for continuous monitoring of oxygen saturations and heart rate. The test will be performed twice at baseline to account for a learning effect; the distance achieved on the two walks will be recorded and the highest value used for baseline measurement. The 6MWT will be repeated once at 6 and 12 weeks following index surgery to assess the post-operative impact of prehabilitation.

The secondary outcome measures in Table 1. will be collected at baseline, pre-surgical assessment, 6 and 12 weeks following index surgery.

Secondary Outcomes	Measurement
Change in Inspiratory muscle strength	Maximal inspiratory pressure (MIP)

Frailty	Hand Grip strength
Quality of life	EQ-5D-5L
Anxiety and Depression	Hospital Anxiety and Depression Scale (HADS)

Table 1. Secondary outcome measures

Maximal inspiratory pressure (MIP) is used to measure inspiratory muscle strength and will be measured using a hand-held electronic transducer (POWERbreath KH2 (HaB Ltd UK), according to guidelines set out in the ATS/ERS statement of 2002(17).

Hand grip strength will used as an objective measurement of frailty. Participants will be asked to grip a dynamometer (Jamar hydraulic hand dynamometer) as hard as they can using their dominant hand whilst being seated. The highest grip strength of 3 attempts will be recorded.

Two patient reported questionnaires will be collected; the EQ-5D-5L general health questionnaire(18) consists of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a standard vertical 20cm visual analogue scale (EQ-5D VAS) on a scale of 0 to 100 measuring current health-related quality of life. The health state of each participant, will be measured before and after the intervention period and post-surgery to determine any change in their health (gain or loss). The HADS self-reported questionnaire consists of 14 questions (7 for anxiety and 7 for depression) rated on a Likert-type scale from 0 to 3(19) and will be used to evaluate participants' mood.

In addition, surgical and post-operative data will be collected from participants' medical notes including: duration of operation, cardiopulmonary bypass times, time on ICU, and discharge information. Pulmonary and cardiac complications will be documented as outlined in Table 2.

Post-operative cardiac surgery complications	
Renal failure/acute kidney injury, tracheostomy, delirium, TIA, stroke, new atrial fibrillation, RBC transfusion, blood product transfusion, cardiac arrest, myocardial infarction, all-cause mortality, infection (in-hospital only), or sepsis (6- and 12-week follow-up only)	
Pulmonary Complications	
Grade 1	• New onset purulent sputum or change in character of chronic sputum • Fever with no focus outside of the lungs • New rise in c-reactive protein or white blood cell count, positive blood culture • Atelectasis radiological finding or abnormal lung findings requiring non-invasive intervention • Hypoxaemia • Administration of additional post-operative antibiotics • Transtracheal aspirate
Grade 2	• Pleural effusion needing drainage • Lung infection • Pneumothorax • Post-operative reintubation • Clinically significant atelectasis requiring tracheobronchial suction
Grade 3	• Ventilatory failure with postoperative ventilator dependence >8h • Reintubation with a subsequent period of ventilation >48h

Table 2. Pulmonary Cardiac Complications

Sub-studies

Accelerometer Sub-study

Participants in both trial arms will be invited to take part in an accelerometer sub-study. Participants will wear an activity monitor on their non-dominant wrist for a continuous period of 7 days at baseline and after the intervention. Data collected will be used to explore change in activity levels (including time spent in MVPA, light physical activity and sedentary behaviour), change in moderate-to-vigorous physical activity and to compare activity levels between the control and intervention group. The correlation between 7 day activity monitor data and patient reported activity diaries pre and post intervention will also be explored.

Qualitative Sub-study

Participants in both arms will offered the opportunity to take part in a focus group exploring their experiences of the taking part in the PrEPS trial. Participants within the intervention and control arms of the trial will attend separate focus groups which will take place after the 12-week post-operative assessment to avoid interference with 12-week patient reported outcomes.

Focus groups will also take place with HCPs involved in the delivery of prehabilitation to explore their experiences of delivering the intervention as part of the PrEPS trial.

Focus group recordings will be transcribed verbatim and analysed using a deductive thematic analysis(20). Themes will be mapped against theoretical constructs of Normalisation Process Theory to highlight relationships and overlap between themes(21).

Standard care

Participants randomised to the standard care group will continue with routine pre-operative care, consisting of specialist nurse review, meeting the surgeon and anaesthetist, and receiving information regarding preparation for surgery. Participants will be provided with a patient diary and asked to document any form of exercise that they carry out independently as well as healthcare visit details to aid collection of adverse events.

Prehabilitation intervention

Participants randomised to the intervention group will receive standard care and a hospital based prehabilitation intervention consisting of an initial fitness assessment, a supervised exercise programme twice a week for 4 weeks, an unsupervised home exercise programme consisting of up to 45 mins of prescribed daily exercise and High Intensity-Inspiratory muscle training (HI-IMT) involving twice daily training for a duration of 4 weeks.

Initial Assessment

At the first cardiac prehabilitation visit, participants will be assessed by a cardiac rehab specialist physiotherapist and nurse to gauge their physical fitness. This involves a subjective and objective assessment; table 3 details these assessments.

Subjective Assessment	
1	General wellbeing
2	Recent health issues and medical history
3	Fitness and activity levels
4	Anxiety levels
5	Social circumstances and support
Objective Assessment	
1	HR and BP measurements
2	ECG if indicated
3	Respiratory function (rate, breathing pattern and auscultation with stethoscope)
4	Musculoskeletal system (joint range and muscle strength)
5	Other physical problems

Table 3. Participant initial assessments to gauge physical fitness

Participants will also be seen by a respiratory physiotherapist and instructed on how to carry out High Intensity-Inspiratory Muscle Training (HI-IMT). Participants will be given their own device (a POWERbreathe medic plus (HaB Ltd UK)) and an instruction leaflet/diary to use at home.

Supervised exercise programme

The maximum HR and target HR will be calculated for each participant. Exercise intensity will be individually prescribed using the combined results of the initial fitness assessment and the baseline 6MWT. The physiotherapist will discuss the principles of the prescribed exercise with the participant and any precautions they should take to mitigate injury and illness. Participants will be encouraged to achieve a predicted target heart rate of 60 – 75% max and a moderate BORG score (12 or 13) during their cardiovascular exercise with actual figure achieved being recorded.

The cardiac prehabilitation exercise sessions will consist of 3 stages listed in table 4.

Stage 1	▪ 15 minutes warm up consisting of preparatory stretches.
Stage 2	▪ Up to 25 minutes of cardiovascular (CV) exercise and resistance-based training with active recovery (AR).
Stage 3	▪ 15 minute cool down period including maintenance stretches

Table 4. Stages of Cardiac Prehabilitation Programme

Home exercise programme

Participants will be asked to perform up to 45 minutes of exercise at home (unsupervised) up to 7 times a week during the 4-week intervention period. This exercise will be tailored to the individual participant's ability based upon their physical fitness assessment and their baseline 6MWT results. Progress will be discussed with the participant once a week during the prehabilitation classes. As this is unsupervised, the intensity will be lower than that prescribed for the supervised classes. Participants will be set achievable targets and have their exercise progressed if they have managed comfortably during the week as measured by their self-reported Borg scores and diaries.

High Intensity-Inspiratory Muscle Training (HI-IMT)

Participants will be asked to perform HI-IMT twice a day for 4 weeks at home starting from their first supervised exercise session. Using their device, participants will be asked to breathe in as forcefully as possible before slowly breathing out 6 times, then rest, before performing another set of 6 breaths. There will be 6 sets of 6 breaths in each HI-IMT training session. The resting time between the sets starts at 60 seconds and decreases by 15 seconds after each set, ending with a rest period of five seconds before the final set.

The device will be set at 50% of their MIP. Participants will be shown how to increase or decrease the resistance on their device to train with a difficulty level of "somewhat hard", which is equivalent to a Borg score of 12 to 13. This will be highlighted in the instruction booklet/diary. Participants will have their HI-IMT technique checked once a week during their prehabilitation classes to ensure they are training effectively.

End of Intervention

The end of the intervention is the final prehabilitation class. On completion of the 4-week intervention period participants will be encouraged to continue with home exercise and IMT independently until their day of surgery and document any activity in their patient diary.

Fidelity of the intervention

The five domains of the treatment fidelity framework, provided by the National Institutes of Health's Behavioral Change Consort will be assessed to ensure fidelity of the prehabilitation intervention throughout the trial(22). Table 5 details these domains.

1	Study design issues will ensure the "treatment dose" in each condition is fixed
2	Monitoring and improving the intervention will involve standardising the process by providing interventionists with a protocol
3	Fidelity of intervention delivery will involve a single observation of an exercise class to ensure delivery is per-protocol. A checklist will then be completed at 6 monthly intervals to ensure consistency in delivery
4	Receipt of treatment by patients (did they understand how to undergo the exercises)

5	Enactment of treatment skills by patients (e.g. did they engage in a home exercise program) will be assessed during focus groups conducted within the qualitative sub-study

Table 5. 5 Domains of the treatment fidelity framework in line with assessments to record fidelity

In addition to the above, self-monitoring data will be collected via exercise diaries.

Assessment of Compliance

Self-reported patient diaries and prehabilitation attendance records will be used to measure adherence to the intervention. Participants will be considered to have adhered to the intervention if they attend ≥50% of the prehabilitation classes (at least 4 out of 8).

Patient Public Involvement (PPI)

Patients and members of the public were involved in identifying prehabilitation in this population as a research priority and in design of the trial. Cardiac rehabilitation patients were consulted in the development of the prehabiliation intervention and relevant trial documentation. A patient representative is a member of the Trial Oversight Committee (TOC) to ensure PPI input throughout the entirety of the trial. Findings will also be disseminated to participants and relevant patient groups.

End of trial

The end of the clinical trial is defined as the 12 week follow up of the last participant. Data queries will be addressed for a period of up to 3 months following this. Participants may choose to withdraw from the trial at any time. Clinicians may also choose to withdraw participants at any time for reasons including non-compliance, adverse events and pregnancy.

Safety reporting

The safety of delivering a prehabilitation intervention a key outcome of the trial. Although there is now some evidence of a low risk to patient safety from studies where physical activity has been assessed in patients with cardiac and/or pulmonary conditions, there is no such evidence in patients with severe cardiac conditions awaiting cardiac surgery.

To mitigate any safety concerns of participants, clinician and other stakeholders, the trial is designed so that the most intensive exercise intervention will be carried out within a hospital setting. Lower intensity exercise will be prescribed at home after assessment each week by the trial team.

Adverse events and serious adverse events will be collected and monitored throughout the trial. Due to the nature of the study population identified expected adverse events including; angina, breathlessness, light-headedness, arrhythmia and fatigue.

The relationship between the intervention (prehabilitation) and the occurrence of each AE will be assessed and categorised by the Chief Investigator (or delegate). Serious events that are unexpected and related, will be reported to the REC committee within 15 days of notification.

It is crucial that safety is monitored throughout the trial so that any findings may be used in future trials, particularly when considering if this practice can be circulated across the wider community and out of hospitals settings.

Statistical analysis

Primary and secondary outcomes will be analysed following the intention-to-treat principle, with patients analysed according to randomisation regardless of whether they actually received or adhered to the allocated treatment. Per-protocol and as-treated analyses may be conducted as sensitivity and exploratory analyses. A full statistical analysis plan will be developed and agreed with the Trial Oversight Committee before data collection is completed. Data will be analysed at the end of the study; no interim outcome analyses are planned.

The primary analysis testing the impact of the cardiac prehabilitation programme on pre-operative functional exercise capacity (measured by 6MWD) will be based on a linear mixed-effects model accounting for baseline randomisation factors, except for baseline 6MWD which is explicitly incorporated in the model to calculate change from baseline. The model will account for intra-patient correlation using a random intercept model. Subgroup analyses conducted for the primary outcome will be pre-specified in the analysis plan. All continuous secondary outcomes will be analysed using the same approach as used for the primary outcome. All non-continuous data will be analysed in the same way, but with a generalised linear model using the appropriate distributional assumptions and link function. Descriptive analysis will be used to explore outcomes related to the feasibility of the trial. Analyses will be conducted using R statistical software.

Sample size

The sample size is based on detecting a significant improvement in 6MWD after the prehabilitation program compared with the 6MWD at baseline. We have assumed a minimal clinically important difference in 6MWD of 25m with a standard deviation of 56.5m for pre-operative participants(23). Based on detecting a medium effect size of 0.44, 164 participants (82 in each group) will provide 80% power to detect a difference of 25 metres in the 6MWD. Adjusting for 10% missing data, 180 participants will be recruited for the trial.

Data

Data will be entered at site onto an electronic case report form for each participant. The database will be hosted by Sealed Envelope© who abide by GDPR and are responsible for the security of the data contained within the database.

Data will be used according to the provision of GDPR, and applicable new regulations, and individuals will not be identifiable through any reports or publications that result from the trial. Quality control measures will ensure that all

data are reliable and have been processed accurately at every stage of the study. Source Data Validations (SDV) will be undertaken by the Trial Management staff to optimise data quality for key data including primary/secondary outcome variables and SAE data.

Trial Oversight Committee

An independent Trial Oversight Committee (TOC) will monitor data completion rates and safety reporting throughout the duration of the trial. Data collected in the trial will be used to support other research in the future, and may be shared anonymously with other researchers.

Ethics and Dissemination

The PrEPS trial was granted a favourable opinion by the Yorkshire and Humber, Sheffield Research Ethics Committee on the 25/10/2019 (19/YH/0317). Trial findings will be disseminated to patients using patients focused literature, visual aids and animated films via patient charities like Heart Valve Voice and the British Heart Foundation national PPI group. Dissemination to clinicians and professional stakeholders like commissioners will be through peer reviewed publication and conferences. Any changes to the protocol will be communicated to all relevant parties as per the HREC requirements.

Discussion

Prehabilitation in cardiac surgery has lagged behind that for other specialties, especially cancer surgery, abdominal general surgery and limb reconstruction surgery in the UK(24). This is despite the fact that large numbers of patients undergo cardiac surgery in the UK every year (around 35,000). Moreover, cardiac surgery patients in particular stand to benefit from a prehabilitation interventions because they tend to be older, mean age 67 years and increasing(1) and have a higher co-morbid burden (average Charlson score 2.1 vs 1.7) (GIRFT Programme National Specialty Report). In particular, they suffer from high levels of obesity, diabetes, coexisting lung disease and reduced mobility. The chronic nature of most cardiac conditions prior to reaching the point of surgical intervention and the fact that the cardiac disease process itself usually limits physical activity, means that patients awaiting cardiac surgery usually exhibit a high prevalence of frailty and loss of muscle mass and function, a condition usually referred to as sarcopenia(25-27).

In 2019 our group published a review of 483 publications, of which 10 (including 4 metanalysis and 6 RCTs) represented the best evidence to answer the clinical question ‘does pre-habilitation improve outcomes in cardiac surgical patients?”(28). The RCTs were limited by small sample sizes (the smallest had a sample size of 15) and no trial combined physical activity and IMT (the 2 interventions with the largest evidence base of impact for outcomes) as components in the intervention. A subsequent systematic review which explored associations between objectively

measured physical activity during the prehabilitation period and health-related outcomes across surgery types reported significant beneficial associations(29).

The significant benefit of prehabilitation in other therapeutic areas and the scarcity of high quality evidence in cardiac surgery patients identifies an urgent need to provide further data in this area.

Anticipated Impact

This will be the largest ever RCT investigating the impact of a prehabilitation intervention composed of exercise and IMT in patients with severe cardiac disease awaiting elective cardiac surgery. The findings will establish if such an intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery. It will also indicate if there are any impacts on clinical outcome after surgery.

Trial status

The PrEPS trial opened to recruitment in November 2019, just prior to the start of the global pandemic. The restrictions imposed by the COVID-19 pandemic has had a significant impact on recruitment, elective cardiac surgery and the ability to deliver the prehabilitation intervention. Despite these challenges PrEPS continues to recruit patients and is projected complete follow up data collection by early 2023.

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Author contributions

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICMJE). SPIRITreporting guidelines have been used when compiling this report(30).

Declaration of Competing Interests

There are no competing interests to declare.

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Figure 1. Consort Diagram to show research activity in the PrEPS trial – this consort diagram depicts the stages throughout the trial from screening, randomisation, intervention and through the various follow up stages. A summary of what assessments are conducted is provided at each stage.

PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL)

Figures

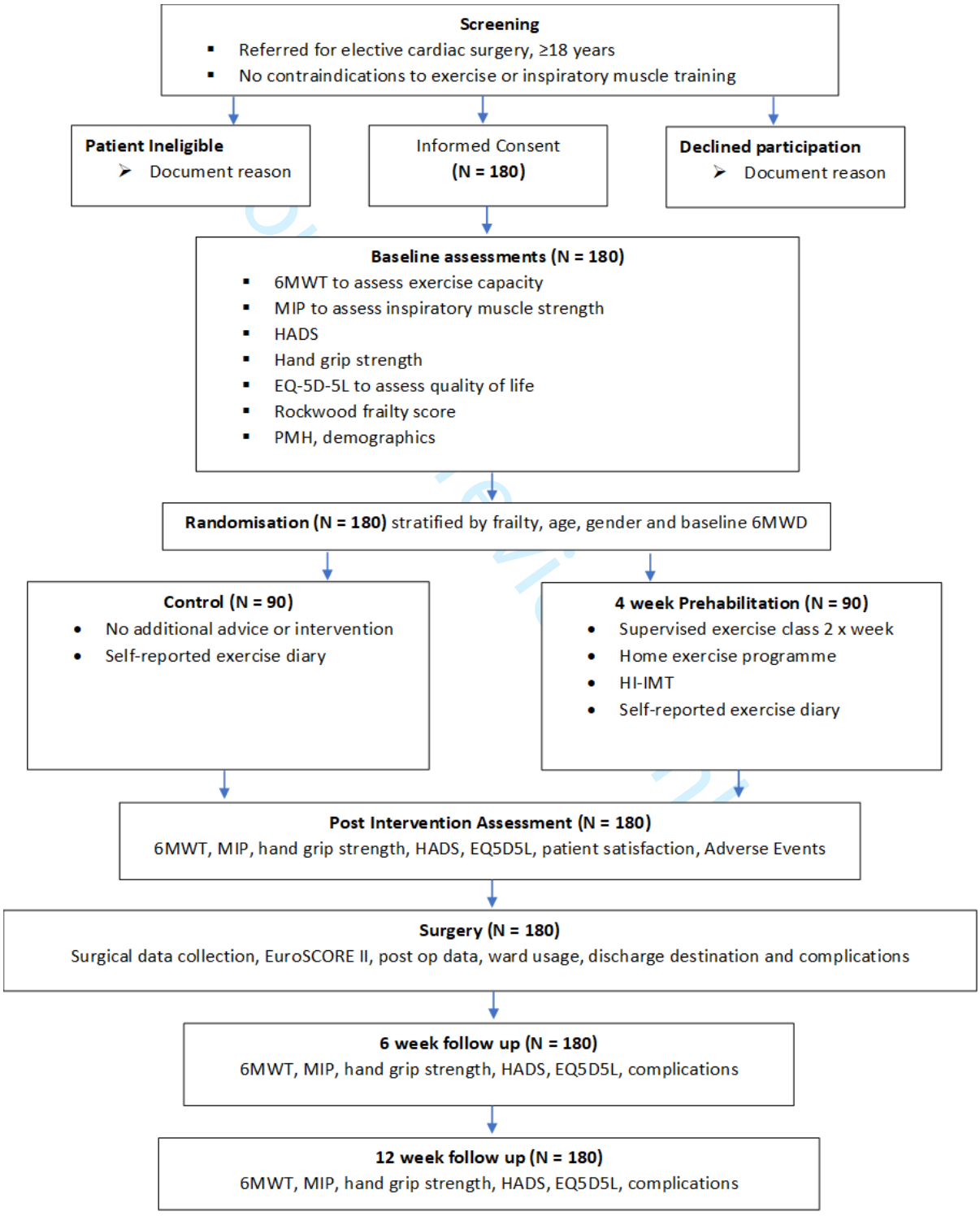

Figure 1. Consort Diagram to show research activity in the PrEPS trial

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Met across various pages within manuscript.
Protocol version	#3	Date and version identifier	Page 2
Funding	#4	Sources and types of financial, material, and other support	Page 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
Roles and responsibilities: sponsor and funder	#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	Not included due to word limit – within protocol itself

Roles and responsibilities: committees	#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)	Page 10
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	Page 3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 3-4
Objectives	#7	Specific objectives or hypotheses	Page 5
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, non-inferiority, exploratory)	Page 4-5
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	Page 4-5
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)	Page 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 8-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 8-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8-10

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 5
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	Page 12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5
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	Page 11-12
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	Page 11-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#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 plan	#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	Page 12
Data collection plan: retention	#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	In protocol – not included in paper due to word limit
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	Page 12

Statistics: outcomes	#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	Page 11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7-8
Statistics: analysis population and missing data	#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)	Page 11
Methods: Monitoring			
Data monitoring: formal committee	#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 – Single Trial Oversight Committee in place – explanation in protocol
Data monitoring: interim analysis	#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	Page 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 12
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)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5-6
Consent or assent: ancillary studies	#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	Page 12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 12
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	Details in protocol – not in paper due to word count
Dissemination policy: trial results	#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	Page 10 and 12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 13

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
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

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PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL)

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PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL) – A Study Protocol

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Abstract

Introduction

Prehabilitation prior to surgery has been shown to reduce postoperative complications, reduce length of hospital stay, and improve quality of life after cancer and limb reconstruction surgery. However, there is minimal data on the impact of prehabilitation in patients undergoing cardiac surgery, despite the fact these patients are generally older and have more comorbidities and frailty. This trial will assess the feasibility and impact of a prehabilitation intervention consisting of exercise and inspiratory muscle training on pre-operative functional exercise capacity in adult patients awaiting elective cardiac surgery, and determine any impact on clinical outcomes after surgery.

Methods and Analysis

PrEPS is a randomised controlled single-centre trial recruiting 180 participants undergoing elective cardiac surgery. Participants will be randomised in a 1:1 ratio to standard pre-surgical care or standard care plus a prehabilitation intervention. The primary outcome will be change in functional exercise capacity measured as change in the 6 minute walk test distance from baseline. Secondary outcomes will evaluate the impact of prehabilitation on pre-operative and post-operative outcomes including; respiratory function, health related quality of life, anxiety and depression, frailty, and post-operative complications and resource use. This trial will evaluate if a prehabilitation intervention can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery in elective patients awaiting cardiac surgery, and impact post-operative outcomes.

Ethics and Dissemination

A favourable opinion was given by the Sheffield Research Ethics Committee in 2019. Trial findings will be disseminated to patients, clinicians, commissioning groups and through peer reviewed publication.

Trial registration

International Standard Randomised Controlled Trial Number 13860094. Registered on 24 October 2019

PROTOCOL V7.0 20 June 2022

Article Summary

Strengths and Limitations of this study

1. Largest pragmatic trial combining exercise and IMT for the first time in this population
2. Will establish if a prehab intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery
3. Robust assessment of fidelity of the intervention and compliance
4. Important accelerometer sub study to explore change in activity levels and qualitative sub study to explore views and experiences of patients and staff
5. Limited to single centre but will provide critical safety data essential for wider implementation

Keywords

Cardiac Surgery, Prehabilitation, Exercise, High-intensity Inspiratory Muscle Training (IMT)

Introduction

Over 35,000 patients undergo cardiac surgery every year in the UK alone(1). Over the last decade the average age of these patients has increased worldwide, as has the prevalence of patients with multiple comorbidities having cardiac surgery(2). This has the potential to increase mortality, morbidity and resource use resulting from increasing rates of post-operative complications and associated prolonged use of hospital resources.

Prehabilitation programmes are fast becoming a method of being pro-active prior to surgery with the aim of reducing post-operative complications and mortality, giving patients themselves a method of managing their fitness pre-surgery; ultimately with the aim of speeding up recovery and return to normal function after surgery. A BMJ editorial in September 2017(3) highlighted the urgent need to recognise that the drive to improve outcomes after surgery must include optimising patients' health prior to surgery with evidence based prehabilitation programmes. It recognised that programs would have to be tailored for patients and specific interventions.

In cardiac surgery however, there have been few trials investigating the impact of prehabilitation. Primarily, concerns around safety due to delaying intervention to allow prehabiliation to occur and the impact of exercise as part of the intervention has contributed to a lack of trial data. This is despite evidence that exercise interventions can improve

cardiovascular function and fitness; an important predictor of mortality in older patients(4). Poor cardiovascular fitness is known to be associated with higher all-cause mortality(5).

In patients awaiting cardiac surgery, the concern has been that severe coronary and valvular lesions e.g. severe aortic stenosis, cause symptoms with exercise and may precipitate complications. Furthermore patients are frequently told by their clinicians not to exercise whilst they wait for surgery. Moreover, severe aortic stenosis, left main stem stenosis, unstable angina, aortic aneurysms, and other cardiac condition are all contraindicated in most exercise and rehabilitation protocols currently used in the UK(6).

There is emerging evidence that patients with severe cardiac conditions can undergo exercise safely. The 6MWT was shown to be safe in a feasibility study of 244 patients with chronic lung or heart disease with no instances of adverse events(7). A trial in which low risk patients awaiting electives coronary artery bypass surgery underwent high-intensity treadmill training reported no significant adverse effects(8). However, neither of these trials included patients with severe cardiac conditions awaiting surgical intervention. A recent trial in patients with large abdominal aortic aneurysms awaiting repair has showed that even High Intensity Interval Training (HIIT) appeared to be safe and beneficial(9). These data have suggested that exercising patients awaiting cardiac surgery may be safe, therefore stimulating further interest in the role of exercise based prehabilitation prior to cardiac surgery.

Inspiratory muscle training (IMT) has the most evidence for improving outcomes after thoracic and cardiac surgery. This is most commonly achieved using inspiratory threshold-loading devices (threshold-IMT) which increase respiratory muscle strength and endurance, in turn improving respiratory volume and sputum clearance(10), thereby reducing postoperative pulmonary complications (PPCs). In cardiac surgery, preoperative IMT has been shown to reduce PPCs and have a modest effect on postoperative length of stay in high risk patients with pre-existing COPD after surgery(11). This finding has been confirmed in a number of systematic reviews and meta-analyses(12-14). A large multicentre trial funded by the NIHR (The INSPIRE Trial) to provide definitive evidence of benefit of IMT is currently ongoing.

To date no RCT has combined IMT with exercise in a prehabilitation intervention to determine the impact in patients undergoing cardiac surgery.

A trial is urgently needed to determine if patients with severe cardiac conditions can undergo prehabilitation safely prior to cardiac surgery. This was corroborated by a priority setting exercise conducted by The James Lind Alliance in the UK in 2019, to identify the top 10 research priorities for adult cardiac surgery research. In this Delphi style consensus exercise involving nearly 1000 patients and stakeholders, research to determine if prehabilitation benefited patients prior to cardiac surgery was the 4th most important of the ten priority research areas(15).

The PREPs trial will evaluate if a prehabilitation intervention consisting of exercise and inspiratory muscle training in patients awaiting elective cardiac surgery can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery. Other assessments include the impact of the intervention on post-operative clinical outcomes, speed of return to normal activity, patients' recovery from surgery and quality of life after surgery.

Methods/Analysis

Trial design

A single centre prospective, parallel group randomised controlled trial will be conducted to compare the effect of a prehabilitation intervention on functional, physical and clinical outcomes compared to standard care. Participants will be randomly allocated 1:1 to either standard care or the intervention. Participants allocated to standard care will receive routine pre-operative advice only. Participants allocated to the intervention will receive routine pre-operative advice and a prehabilitation intervention consisting of supervised cardiac exercise sessions, high intensity inspiratory muscle training and a home exercise programme.

Participants will be followed up at routine clinical appointments prior to surgery, during surgical admission, and at 6 and 12 weeks following index surgery (figure 1). After the intervention period all participants will continue with the site's standard pre- and post-operative care.

Objectives

The Primary objective is to assess the impact of a pre-operative rehabilitation intervention (prehabilitation) on pre-operative functional exercise capacity (measured by change in the 6-minute walk test (6MWT)) from baseline in patients awaiting cardiac surgery.

The secondary objectives are to evaluate the impact of prehabilitation on outcomes including; respiratory function (measured by maximal inspiratory pressure (MIP)), health related quality of life (measured by the EQ-5D-5L), anxiety and depression (measured by the Hospital Anxiety and Depression Scale (HADS) and frailty (measured by grip strength) after the prehabilitation intervention.

The tertiary objectives are to evaluate the impact of prehabilitation on post-operative complication rates, including length of hospital stay, PPCs, and health related quality of life up to 12 weeks after surgery.

Two sub studies will also explore: the use of activity monitors to measure change in objectively measured physical activity from baseline to post-intervention, and the experiences of prehabilitation prior to elective cardiac surgery through the opinions of trial participants and the healthcare professionals responsible for prehabilitation delivery.

Eligibility

Patients aged 18 and over listed for elective cardiac surgery under the care of the participating surgeons will be screened for eligibility.

Table 1 describes the exclusion criteria in detail specific to the trial.

Exclusion Criteria
Unstable angina/indication for urgent surgery
Malignant Arrhythmias
Currently Participating in another interventional clinical trial
Known Pregnancy
Contraindications to known cardiac rehabilitations: ○ Acute systemic illness or fever ○ Uncontrolled atrial or ventricular arrhythmias ○ Uncontrolled sinus tachycardia (HR>120 bpm) ○ Aortic stenosis with pre-syncope/syncope ○ Acute pericarditis or myocarditis ○ Uncompensated HF ○ Third degree (complete) atrioventricular (AV) block without pacemaker ○ Recent embolism ○ Severe Musculoskeletal conditions that would prohibit exercise
Contraindications to inspiratory muscle training: ○ History of spontaneous pneumothorax/ incomplete recovery following traumatic pneumothorax ○ Asthma patients who suffer from frequent, severe exacerbations ○ Recently perforated ear drum (within last 3 months) ○ Large Bullae

Table 1 Exclusion Criteria

Recruitment

Adults listed for elective cardiac surgery will be screened by the clinical team and given a patient information sheet (PIS) and letter of invitation prior to their routine clinic appointment. Eligibility will be confirmed by a clinician at the time of listing for surgery. Written informed consent will be obtained before any trial procedures are performed.

Baseline Data Collection

Baseline assessments will be performed after consent and prior to randomisation. Women of childbearing potential will perform a pregnancy test to confirm pregnancy status before undertaking any further research activity. The baseline assessments will consist of the 6MWT, MIP, EQ5D5L questionnaire, activity monitoring (optional), HADS, Rockwood frailty score (9 point Clinical Frailty Scale (CFS)) and hand grip strength. Participants' medical notes will be used to collect a full medical history, gender, height and weight, and date of birth/age. Participants consenting to take part in the 7 day activity monitoring sub study will be provided with an accelerometer, instructions on it use, and options for returning the accelerometer.

Randomisation

Participants will be randomised in a 1:1 ratio to either the control arm (standard care only), or the intervention arm (standard care plus the prehabilitation intervention) using a 24-hour, central, secure, web-based system (SealedEnvelope™). Randomisation will be performed using a minimisation scheme that takes into account Rockwood frailty score, 6MWD, age and gender to balance baseline physical fitness between the arms. It will not be possible to conceal the allocation of treatment from the participant, or the team delivering the intervention and measuring the primary outcome. The surgeons performing the participants' cardiac surgery will not be informed of the allocation, however they will not be officially blinded.

Outcome Measures

The primary outcome will be change in exercise capacity measured by the 6-minute walk test from baseline to pre-surgical assessment. This is a self-paced 6-minute walk recording the distance walked in metres around a 25 meter standardised track.

This outcome was chosen because preoperative 6MWT distance is associated with moderate or severe complications after both non-cardiac surgery(16) and cardiac surgery(17). It has also been validated as an indicator of recovery y in patients undergoing cardiac surgery(18).

All participants will receive standardised instruction and support(19). A pulse oximeter will be attached to the participant during the walk for continuous monitoring of oxygen saturations and heart rate. The test will be performed twice at baseline to account for a learning effect; the distance achieved on the two walks will be recorded and the highest value used for baseline measurement. The 6MWT will be repeated once at 6 and 12 weeks following index surgery to assess the post-operative impact of prehabilitation.

The secondary outcome measures in Table 2. will be collected at baseline, pre-surgical assessment, 6 and 12 weeks following index surgery.

Secondary Outcomes	Measurement
Change in Inspiratory muscle strength	Maximal inspiratory pressure (MIP)
Frailty	Hand Grip strength
Quality of life	EQ-5D-5L
Anxiety and Depression	Hospital Anxiety and Depression Scale (HADS)

Table 2. Secondary outcome measures

Maximal inspiratory pressure (MIP) is used to measure inspiratory muscle strength and will be measured using a hand-held electronic transducer (POWERbreath KH2 (HaB Ltd UK), according to guidelines set out in the ATS/ERS statement of 2002(20).

Hand grip strength will used as an objective measurement of frailty. Participants will be asked to grip a dynamometer (Jamar hydraulic hand dynamometer) as hard as they can using their dominant hand whilst being seated. The highest grip strength of 3 attempts will be recorded.

Two patient reported questionnaires will be collected; the EQ-5D-5L general health questionnaire(21) consists of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a standard vertical 20cm visual analogue scale (EQ-5D VAS) on a scale of 0 to 100 measuring current health-related quality of life. The health state of each participant, will be measured before and after the intervention period and post-surgery to determine any change in their health (gain or loss). The HADS self-reported questionnaire consists of 14 questions (7 for anxiety and 7 for depression) rated on a Likert-type scale from 0 to 3(22) and will be used to evaluate participants' mood.

In addition, surgical and post-operative data will be collected from participants' medical notes including: duration of operation, cardiopulmonary bypass times, time on ICU, and discharge information. Pulmonary and cardiac complications will be documented as outlined in Table 3.

Post-operative cardiac surgery complications	
Renal failure/acute kidney injury, tracheostomy, delirium, TIA, stroke, new atrial fibrillation, RBC transfusion, blood product transfusion, cardiac arrest, myocardial infarction, all-cause mortality, infection (in-hospital only), or sepsis (6- and 12-week follow-up only)	
Pulmonary Complications	
Grade 1	• New onset purulent sputum or change in character of chronic sputum • Fever with no focus outside of the lungs • New rise in c-reactive protein or white blood cell count, positive blood culture • Atelectasis radiological finding or abnormal lung findings requiring non-invasive intervention • Hypoxaemia • Administration of additional post-operative antibiotics • Transtracheal aspirate
Grade 2	• Pleural effusion needing drainage • Lung infection • Pneumothorax • Post-operative reintubation • Clinically significant atelectasis requiring tracheobronchial suction
Grade 3	• Ventilatory failure with postoperative ventilator dependence >8h • Reintubation with a subsequent period of ventilation >48h

Table 3. Pulmonary Cardiac Complications

Sub-studies

Accelerometer Sub-study

Participants in both trial arms will be invited to take part in an accelerometer sub-study. We anticipate that 50-60% of the trial cohort will take part in the sub-study however this trial is ongoing and therefore this data is not yet available.

Participants will wear an activity monitor on their non-dominant wrist for a continuous period of 7 days at baseline and after the intervention period. Data collected will be processed using the GGIR package in R(23) to explore change in activity levels (including time spent in MVPA, light physical activity and sedentary behaviour), change in moderate-to-vigorous physical activity and between the control and intervention group. The correlation between 7 day activity monitor data and patient reported activity diaries pre and post intervention will also be explored.

Qualitative Sub-study

Participants in both arms will offered the opportunity to take part in a focus group exploring their experiences of the taking part in the PrEPS trial. Participants within the intervention and control arms of the trial will attend separate focus groups which will take place after the 12-week post-operative assessment to avoid interference with 12-week patient reported outcomes.

Focus groups will also take place with HCPs involved in the delivery of prehabilitation to explore their experiences of delivering the intervention as part of the PrEPS trial.

Focus group recordings will be transcribed verbatim and analysed using a deductive thematic analysis(24). Themes will be mapped against theoretical constructs of Normalisation Process Theory to highlight relationships and overlap between themes(25).

Standard care

Participants randomised to the standard care group will continue with routine pre-operative care, consisting of specialist nurse review, meeting the surgeon and anaesthetist, and receiving information regarding preparation for surgery. Participants will be provided with a patient diary and asked to document any form of exercise that they carry out independently as well as healthcare visit details to aid collection of adverse events.

Prehabilitation intervention

Participants randomised to the intervention group will receive standard care and a hospital based prehabilitation intervention consisting of an initial fitness assessment, a supervised exercise programme twice a week for 4 weeks, an unsupervised home exercise programme consisting of up to 45 mins of prescribed daily exercise and High Intensity-Inspiratory muscle training (HI-IMT) involving twice daily training for a duration of 4 weeks.

Initial Assessment

At the first cardiac prehabilitation visit, participants will be assessed by a cardiac rehab specialist physiotherapist and nurse to gauge their physical fitness. This involves a subjective and objective assessment; table 4 details these assessments.

	Subjective Assessment
1	General wellbeing

2	Recent health issues and medical history
3	Fitness and activity levels
4	Anxiety levels
5	Social circumstances and support
Objective Assessment	
1	HR and BP measurements
2	ECG if indicated
3	Respiratory function (rate, breathing pattern and auscultation with stethoscope)
4	Musculoskeletal system (joint range and muscle strength)
5	Other physical problems

Table 4. Participant initial assessments to gauge physical fitness

Participants will also be seen by a respiratory physiotherapist and instructed on how to carry out High Intensity-Inspiratory Muscle Training (HI-IMT). Participants will be given their own device (a POWERbreathe medic plus (HaB Ltd UK)) and an instruction leaflet/diary to use at home.

Supervised exercise programme

The maximum HR and target HR will be calculated for each participant. Exercise intensity will be individually prescribed using the combined results of the initial fitness assessment and the baseline 6MWT. The physiotherapist will discuss the principles of the prescribed exercise with the participant and any precautions they should take to mitigate injury and illness. Participants will be encouraged to achieve a predicted target heart rate of 60 – 75% max and a moderate BORG score (12 or 13) during their cardiovascular exercise with actual figure achieved being recorded.

The cardiac prehabilitation exercise sessions will consist of 3 stages listed in table 5.

Stage 1	▪ 15 minutes warm up consisting of preparatory stretches.
Stage 2	▪ Up to 25 minutes of cardiovascular (CV) exercise and resistance-based training with active recovery (AR).
Stage 3	▪ 15 minute cool down period including maintenance stretches

Table 5. Stages of Cardiac Prehabilitation Programme

Home exercise programme

Participants will be asked to perform up to 45 minutes of exercise at home (unsupervised) up to 7 times a week during the 4-week intervention period. This exercise will be tailored to the individual participant's ability based upon their physical fitness assessment and their baseline 6MWT results. Progress will be discussed with the participant once a week during the prehabilitation classes. As this is unsupervised, the intensity will be lower than that prescribed for the supervised classes. Participants will be set achievable targets and have their exercise progressed if they have managed comfortably during the week as measured by their self-reported Borg scores and diaries.

High Intensity-Inspiratory Muscle Training (HI-IMT)

Participants will be asked to perform HI-IMT twice a day for 4 weeks at home starting from their first supervised exercise session. Using their device, participants will be asked to breathe in as forcefully as possible before slowly breathing out 6 times, then rest, before performing another set of 6 breaths. There will be 6 sets of 6 breaths in each HI-IMT training session. The resting time between the sets starts at 60 seconds and decreases by 15 seconds after each set, ending with a rest period of five seconds before the final set.

The device will be set at 50% of their MIP. Participants will be shown how to increase or decrease the resistance on their device to train with a difficulty level of "somewhat hard", which is equivalent to a Borg score of 12 to 13. This will be highlighted in the instruction booklet/diary. Participants will have their HI-IMT technique checked once a week during their prehabilitation classes to ensure they are training effectively.

End of Intervention

The end of the intervention is the final prehabilitation class. On completion of the 4-week intervention period participants will be encouraged to continue with home exercise and IMT independently until their day of surgery and document any activity in their patient diary.

Fidelity of the intervention

The five domains of the treatment fidelity framework, provided by the National Institutes of Health's Behavioral Change Consort will be assessed to ensure fidelity of the prehabilitation intervention throughout the trial(26). Table 6 details these domains.

1	Study design issues will ensure the "treatment dose" in each condition is fixed
2	Monitoring and improving the intervention will involve standardising the process by providing interventionists with a protocol
3	Fidelity of intervention delivery will involve a single observation of an exercise class to ensure delivery is per-protocol. A checklist will then be completed at 6 monthly intervals to ensure consistency in delivery
4	Receipt of treatment by patients (did they understand how to undergo the exercises)
5	Enactment of treatment skills by patients (e.g. did they engage in a home exercise program) will be assessed during focus groups conducted within the qualitative sub-study

Table 6. 5 Domains of the treatment fidelity framework in line with assessments to record fidelity

In addition to the above, self-monitoring data will be collected via exercise diaries.

Assessment of Compliance

Self-reported patient diaries and prehabilitation attendance records will be used to measure adherence to the intervention. Adherence was defined as completing 50% of the supervised exercise classes (4 out if 8 sessions) in-line

with documented adherence rates to cardiac rehabilitation(27-29). Exercise diaries will capture the physical activity completion for the unsupervised component.

Patient Public Involvement (PPI)

Patients and members of the public were involved in identifying prehabilitation in this population as a research priority and in design of the trial. Cardiac rehabilitation patients were consulted in the development of the prehabiliation intervention and relevant trial documentation. A patient representative is a member of the Trial Oversight Committee (TOC) to ensure PPI input throughout the entirety of the trial. Findings will also be disseminated to participants and relevant patient groups.

End of trial

The end of the clinical trial is defined as the 12 week follow up of the last participant. Data queries will be addressed for a period of up to 3 months following this. Participants may choose to withdraw from the trial at any time. Clinicians may also choose to withdraw participants at any time for reasons including non-compliance, adverse events and pregnancy.

Safety reporting

The safety of delivering a prehabilitation intervention a key outcome of the trial. Although there is now some evidence of a low risk to patient safety from studies where physical activity has been assessed in patients with cardiac and/or pulmonary conditions, there is no such evidence in patients with severe cardiac conditions awaiting cardiac surgery.

To mitigate any safety concerns of participants, clinician and other stakeholders, the trial is designed so that the most intensive exercise intervention will be carried out within a hospital setting. Lower intensity exercise will be prescribed at home after assessment each week by the trial team.

Adverse events and serious adverse events will be collected and monitored throughout the trial. Due to the nature of the study population identified expected adverse events including; angina, breathlessness, light-headedness, arrhythmia and fatigue.

The relationship between the intervention (prehabilitation) and the occurrence of each AE will be assessed and categorised by the Chief Investigator (or delegate). Serious events that are unexpected and related, will be reported to the REC committee within 15 days of notification.

It is crucial that safety is monitored throughout the trial so that any findings may be used in future trials, particularly when considering if this practice can be circulated across the wider community and out of hospitals settings.

Statistical analysis

Primary and secondary outcomes will be analysed following the intention-to-treat principle, with patients analysed according to randomisation regardless of whether they actually received or adhered to the allocated treatment. Per-protocol and as-treated analyses may be conducted as sensitivity and exploratory analyses. A full statistical analysis plan will be developed and agreed with the Trial Oversight Committee before data collection is completed. Data will be analysed at the end of the study; no interim outcome analyses are planned.

The primary analysis testing the impact of the cardiac prehabilitation programme on pre-operative functional exercise capacity (measured by 6MWD) will be based on a linear mixed-effects model accounting for baseline randomisation factors, except for baseline 6MWD which is explicitly incorporated in the model to calculate change from baseline. The model will account for intra-patient correlation using a random intercept model. Subgroup analyses conducted for the primary outcome will be pre-specified in the analysis plan. All continuous secondary outcomes will be analysed using the same approach as used for the primary outcome. All non-continuous data will be analysed in the same way, but with a generalised linear model using the appropriate distributional assumptions and link function. Descriptive analysis will be used to explore outcomes related to the feasibility of the trial. Analyses will be conducted using R statistical software.

Sample size

The sample size is based on detecting a significant improvement in 6MWD after the prehabilitation program compared with the 6MWD at baseline. We have assumed a minimal clinically important difference in 6MWD of 25m with a standard deviation of 56.5m for pre-operative participants(30). Based on detecting a medium effect size of 0.44, 164 participants (82 in each group) will provide 80% power to detect a difference of 25 metres in the 6MWD. Adjusting for 10% missing data, 180 participants will be recruited for the trial.

Data

Data will be entered at site onto an electronic case report form for each participant. The database will be hosted by Sealed Envelope© who abide by GDPR and are responsible for the security of the data contained within the database.

Data will be used according to the provision of GDPR, and applicable new regulations, and individuals will not be identifiable through any reports or publications that result from the trial. Quality control measures will ensure that all data are reliable and have been processed accurately at every stage of the study. Source Data Validations (SDV) will be undertaken by the Trial Management staff to optimise data quality for key data including primary/secondary outcome variables and SAE data.

Trial Oversight Committee

An independent Trial Oversight Committee (TOC) will monitor data completion rates and safety reporting throughout the duration of the trial. Data collected in the trial will be used to support other research in the future, and may be shared anonymously with other researchers.

Ethics and Dissemination

The PrEPS trial was granted a favourable opinion by the Yorkshire and Humber, Sheffield Research Ethics Committee on the 25/10/2019 (19/YH/0317). Trial findings will be disseminated to patients using patients focused literature, visual aids and animated films via patient charities like Heart Valve Voice and the British Heart Foundation national PPI group. Dissemination to clinicians and professional stakeholders like commissioners will be through peer reviewed publication and conferences. Any changes to the protocol will be communicated to all relevant parties as per the HREC requirements.

Discussion

Prehabilitation in cardiac surgery has lagged behind that for other specialties, especially cancer surgery, abdominal general surgery and limb reconstruction surgery in the UK(31). This is despite the fact that large numbers of patients undergo cardiac surgery in the UK every year (around 35,000). Moreover, cardiac surgery patients in particular stand to benefit from a prehabilitation interventions because they tend to be older, mean age 67 years and increasing(1) and have a higher co-morbid burden (average Charlson score 2.1 vs 1.7) (GIRFT Programme National Specialty Report). In particular, they suffer from high levels of obesity, diabetes, coexisting lung disease and reduced mobility. The chronic nature of most cardiac conditions prior to reaching the point of surgical intervention and the fact that the cardiac disease process itself usually limits physical activity, means that patients awaiting cardiac surgery usually exhibit a high prevalence of frailty and loss of muscle mass and function, a condition usually referred to as sarcopenia(32-34).

In 2019 our group published a review of 483 publications, of which 10 (including 4 metanalysis and 6 RCTs) represented the best evidence to answer the clinical question ‘does pre-habilitation improve outcomes in cardiac surgical patients?”(35). The RCTs were limited by small sample sizes (the smallest had a sample size of 15) and no trial combined physical activity and IMT (the 2 interventions with the largest evidence base of impact for outcomes) as components in the intervention. A subsequent systematic review which explored associations between objectively measured physical activity during the prehabilitation period and health-related outcomes across surgery types reported significant beneficial associations(36).

The significant benefit of prehabilitation in other therapeutic areas and the scarcity of high quality evidence in cardiac surgery patients identifies an urgent need to provide further data in this area.

Anticipated Impact

This will be the largest ever RCT investigating the impact of a prehabilitation intervention composed of exercise and IMT in patients with severe cardiac disease awaiting elective cardiac surgery. The findings will establish if such an intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery. It will also indicate if there are any impacts on clinical outcome after surgery.

Trial status

The PrEPS trial opened to recruitment in November 2019, just prior to the start of the global pandemic. The restrictions imposed by the COVID-19 pandemic has had a significant impact on recruitment, elective cardiac surgery and the ability to deliver the prehabilitation intervention. Despite these challenges PrEPS continues to recruit patients and is projected complete follow up data collection by early 2023.

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Author contributions

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICMJE).

1. Enoch Akowuah - devised the clinical question, applied for funding, Chief investigator with overall responsibility for the trial, reviewed and contributed to all areas of the manuscript
2. Ayesha Mathias - Trial manager with day to day responsibility for delivery of the trial, drafted all areas of the manuscript and contributed to all areas
3. Michelle Bardgett - Senior trial manager, author of the trial protocol, governance oversite, contributed to all areas of manuscript
4. Samantha Harrison - Contributed specifically to the Qualitative Sub-Study and Intervention Design and Delivery sections within the manuscript
5. Adetayo Kasim - General oversight of the Statistical Analysis section of the manuscript and overall review of whole manuscript
6. Kirsti Loughran - Contributed specifically to the Qualitative Sub-Study section within the manuscript

7. Emmanuel Ogundimu - Statistical oversight and contributed specifically to the Statistical Analysis
8. Jason Trevis - Contributed specifically to the Qualitative Sub-Study section within the manuscript
9. Janelle Wagnild - Drafted and contributed specifically to the Statistical Analysis and accelerometer sub-study sections of the manuscript
10. Pasan Witharana - Contributed specifically to the Qualitative Sub-Study section within the manuscript
11. Helen Hancock - Co-Applicant, Protocol Author, general overview and contribution to all areas within manuscript
12. Rebecca Maier - Co-Applicant, Protocol Author, general overview and contribution to all areas within manuscript

Several reviews of the manuscript took place prior to a final draft with all authors reviewing the final draft once complete prior to submission. All authors are informed of any revisions that may need to take place following editorial review and confirm these changes are acceptable prior to re-submission.

Declaration of Competing Interests

There are no competing interests to declare.

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Figure 1. Consort Diagram to show research activity in the PrEPS trial – this consort diagram depicts the stages throughout the trial from screening, randomisation, intervention and through the various follow up stages. A summary of what assessments are conducted is provided at each stage.

PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL)

Figures

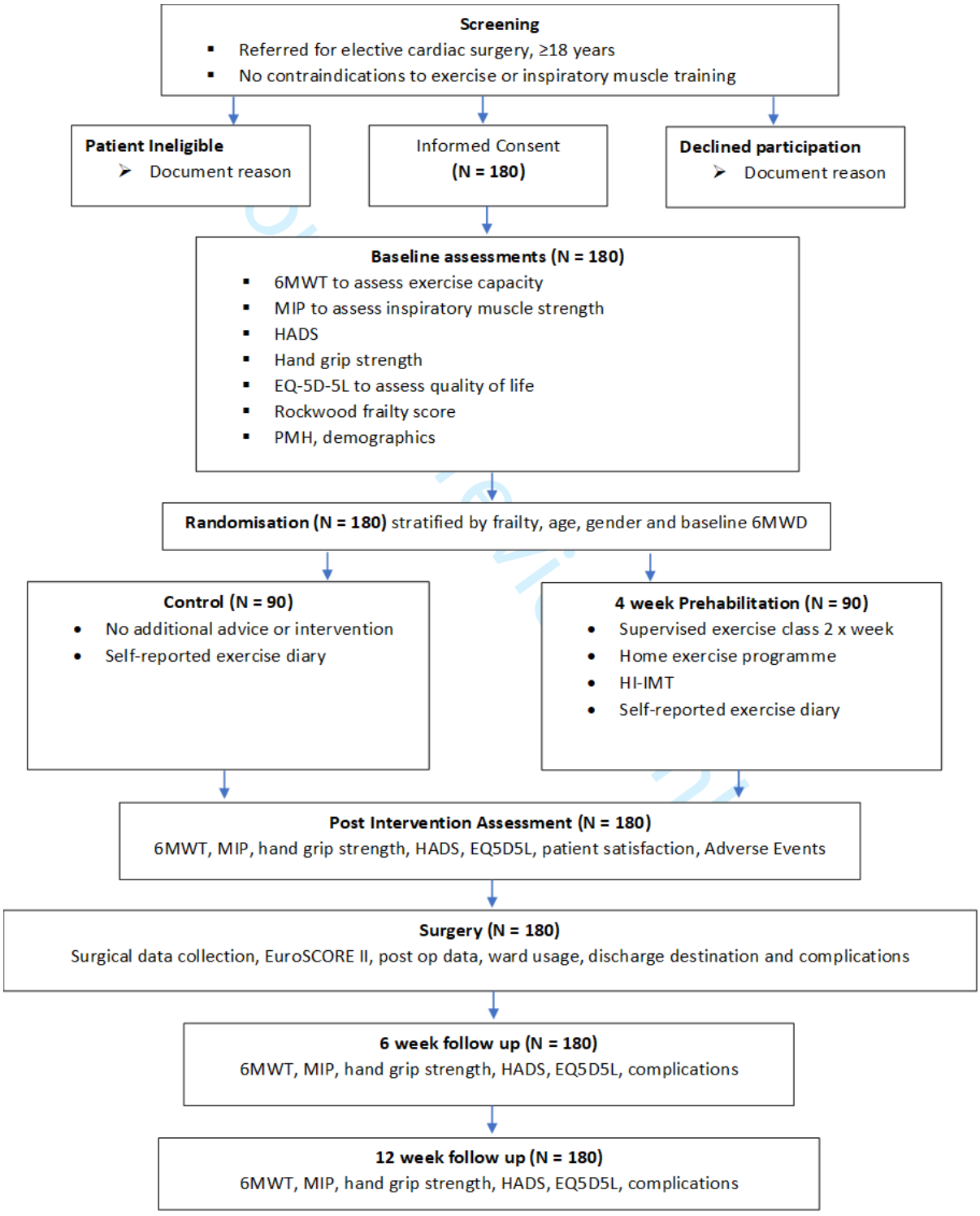

Figure 1. Consort Diagram to show research activity in the PrEPS trial

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Met across various pages within manuscript.
Protocol version	#3	Date and version identifier	Page 2
Funding	#4	Sources and types of financial, material, and other support	Page 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
Roles and responsibilities: sponsor and funder	#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	Not included due to word limit – within protocol itself

Roles and responsibilities: committees	#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)	Page 10
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	Page 3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 3-4
Objectives	#7	Specific objectives or hypotheses	Page 5
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, non-inferiority, exploratory)	Page 4-5
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	Page 4-5
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)	Page 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 8-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 8-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8-10

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 5
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	Page 12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5
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	Page 11-12
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	Page 11-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#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 plan	#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	Page 12
Data collection plan: retention	#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	In protocol – not included in paper due to word limit
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	Page 12

Statistics: outcomes	#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	Page 11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7-8
Statistics: analysis population and missing data	#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)	Page 11
Methods: Monitoring			
Data monitoring: formal committee	#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 – Single Trial Oversight Committee in place – explanation in protocol
Data monitoring: interim analysis	#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	Page 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 12
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)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5-6
Consent or assent: ancillary studies	#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	Page 12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 12
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	Details in protocol – not in paper due to word count
Dissemination policy: trial results	#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	Page 10 and 12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 13

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
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

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PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL) – A Study Protocol

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PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL) – A Study Protocol

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Abstract

Introduction

Prehabilitation prior to surgery has been shown to reduce postoperative complications, reduce length of hospital stay, and improve quality of life after cancer and limb reconstruction surgery. However, there is minimal data on the impact of prehabilitation in patients undergoing cardiac surgery, despite the fact these patients are generally older and have more comorbidities and frailty. This trial will assess the feasibility and impact of a prehabilitation intervention consisting of exercise and inspiratory muscle training on pre-operative functional exercise capacity in adult patients awaiting elective cardiac surgery, and determine any impact on clinical outcomes after surgery.

Methods and Analysis

PrEPS is a randomised controlled single-centre trial recruiting 180 participants undergoing elective cardiac surgery. Participants will be randomised in a 1:1 ratio to standard pre-surgical care or standard care plus a prehabilitation intervention. The primary outcome will be change in functional exercise capacity measured as change in the 6 minute walk test distance from baseline. Secondary outcomes will evaluate the impact of prehabilitation on pre-operative and post-operative outcomes including; respiratory function, health related quality of life, anxiety and depression, frailty, and post-operative complications and resource use. This trial will evaluate if a prehabilitation intervention can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery in elective patients awaiting cardiac surgery, and impact post-operative outcomes.

Ethics and Dissemination

A favourable opinion was given by the Sheffield Research Ethics Committee in 2019. Trial findings will be disseminated to patients, clinicians, commissioning groups and through peer reviewed publication.

Trial registration

International Standard Randomised Controlled Trial Number 13860094. Registered on 24 October 2019

PROTOCOL V7.0 20 June 2022

Article Summary

Strengths and Limitations of this study

1. Largest pragmatic trial combining exercise and IMT for the first time in this population
2. Will establish if a prehab intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery
3. Robust assessment of fidelity of the intervention and compliance
4. Important accelerometer sub study to explore change in activity levels and qualitative sub study to explore views and experiences of patients and staff
5. Limited to single centre but will provide critical safety data essential for wider implementation

Keywords

Cardiac Surgery, Prehabilitation, Exercise, High-intensity Inspiratory Muscle Training (IMT)

Introduction

Over 35,000 patients undergo cardiac surgery every year in the UK alone(1). Over the last decade the average age of these patients has increased worldwide, as has the prevalence of patients with multiple comorbidities having cardiac surgery(2). This has the potential to increase mortality, morbidity and resource use resulting from increasing rates of post-operative complications and associated prolonged use of hospital resources.

Prehabilitation programmes are fast becoming a method of being pro-active prior to surgery with the aim of reducing post-operative complications and mortality, giving patients themselves a method of managing their fitness pre-surgery; ultimately with the aim of speeding up recovery and return to normal function after surgery. A BMJ editorial in September 2017(3) highlighted the urgent need to recognise that the drive to improve outcomes after surgery must include optimising patients' health prior to surgery with evidence based prehabilitation programmes. It recognised that programs would have to be tailored for patients and specific interventions.

In cardiac surgery however, there have been few trials investigating the impact of prehabilitation. Primarily, concerns around safety due to delaying intervention to allow prehabiliation to occur and the impact of exercise as part of the intervention has contributed to a lack of trial data. This is despite evidence that exercise interventions can improve

cardiovascular function and fitness; an important predictor of mortality in older patients(4). Poor cardiovascular fitness is known to be associated with higher all-cause mortality(5).

In patients awaiting cardiac surgery, the concern has been that severe coronary and valvular lesions e.g. severe aortic stenosis, cause symptoms with exercise and may precipitate complications. Furthermore patients are frequently told by their clinicians not to exercise whilst they wait for surgery. Moreover, severe aortic stenosis, left main stem stenosis, unstable angina, aortic aneurysms, and other cardiac condition are all contraindicated in most exercise and rehabilitation protocols currently used in the UK(6).

There is emerging evidence that patients with severe cardiac conditions can undergo exercise safely. The 6MWT was shown to be safe in a feasibility study of 244 patients with chronic lung or heart disease with no instances of adverse events(7). A trial in which low risk patients awaiting electives coronary artery bypass surgery underwent high-intensity treadmill training reported no significant adverse effects(8). However, neither of these trials included patients with severe cardiac conditions awaiting surgical intervention. A recent trial in patients with large abdominal aortic aneurysms awaiting repair has showed that even High Intensity Interval Training (HIIT) appeared to be safe and beneficial(9). These data have suggested that exercising patients awaiting cardiac surgery may be safe, therefore stimulating further interest in the role of exercise based prehabilitation prior to cardiac surgery.

Inspiratory muscle training (IMT) has the most evidence for improving outcomes after thoracic and cardiac surgery. This is most commonly achieved using inspiratory threshold-loading devices (threshold-IMT) which increase respiratory muscle strength and endurance, in turn improving respiratory volume and sputum clearance(10), thereby reducing postoperative pulmonary complications (PPCs). In cardiac surgery, preoperative IMT has been shown to reduce PPCs and have a modest effect on postoperative length of stay in high risk patients with pre-existing COPD after surgery(11). This finding has been confirmed in a number of systematic reviews and meta-analyses(12-14). A large multicentre trial funded by the NIHR (The INSPIRE Trial) to provide definitive evidence of benefit of IMT is currently ongoing.

To date no RCT has combined IMT with exercise in a prehabilitation intervention to determine the impact in patients undergoing cardiac surgery.

A trial is urgently needed to determine if patients with severe cardiac conditions can undergo prehabilitation safely prior to cardiac surgery. This was corroborated by a priority setting exercise conducted by The James Lind Alliance in the UK in 2019, to identify the top 10 research priorities for adult cardiac surgery research. In this Delphi style consensus exercise involving nearly 1000 patients and stakeholders, research to determine if prehabilitation benefited patients prior to cardiac surgery was the 4th most important of the ten priority research areas(15).

The PREPs trial will evaluate if a prehabilitation intervention consisting of exercise and inspiratory muscle training in patients awaiting elective cardiac surgery can improve pre-operative physical function, inspiratory muscle function, frailty, and quality of life prior to surgery. Other assessments include the impact of the intervention on post-operative clinical outcomes, speed of return to normal activity, patients' recovery from surgery and quality of life after surgery.

Methods/Analysis

Trial design

A single centre prospective, parallel group randomised controlled trial will be conducted to compare the effect of a prehabilitation intervention on functional, physical and clinical outcomes compared to standard care. Participants will be randomly allocated 1:1 to either standard care or the intervention. Participants allocated to standard care will receive routine pre-operative advice only. Participants allocated to the intervention will receive routine pre-operative advice and a prehabilitation intervention consisting of supervised cardiac exercise sessions, high intensity inspiratory muscle training and a home exercise programme.

Participants will be followed up at routine clinical appointments prior to surgery, during surgical admission, and at 6 and 12 weeks following index surgery (figure 1). After the intervention period all participants will continue with the site's standard pre- and post-operative care.

Objectives

The Primary objective is to assess the impact of a pre-operative rehabilitation intervention (prehabilitation) on pre-operative functional exercise capacity (measured by change in the 6-minute walk test (6MWT)) from baseline in patients awaiting cardiac surgery.

The secondary objectives are to evaluate the impact of prehabilitation on outcomes including; respiratory function (measured by maximal inspiratory pressure (MIP)), health related quality of life (measured by the EQ-5D-5L), anxiety and depression (measured by the Hospital Anxiety and Depression Scale (HADS) and frailty (measured by grip strength) after the prehabilitation intervention.

The tertiary objectives are to evaluate the impact of prehabilitation on post-operative complication rates, including length of hospital stay, PPCs, and health related quality of life up to 12 weeks after surgery.

Two sub studies will also explore: the use of activity monitors to measure change in objectively measured physical activity from baseline to post-intervention, and the experiences of prehabilitation prior to elective cardiac surgery through the opinions of trial participants and the healthcare professionals responsible for prehabilitation delivery.

Eligibility

Patients aged 18 and over listed for elective cardiac surgery under the care of the participating surgeons will be screened for eligibility.

Table 1 describes the exclusion criteria in detail specific to the trial.

Exclusion Criteria
Unstable angina/indication for urgent surgery

Malignant Arrhythmias
Currently Participating in another interventional clinical trial
Known Pregnancy
Contraindications to known cardiac rehabilitations: ○ Acute systemic illness or fever ○ Uncontrolled atrial or ventricular arrhythmias ○ Uncontrolled sinus tachycardia (HR>120 bpm) ○ Aortic stenosis with pre-syncope/syncope ○ Acute pericarditis or myocarditis ○ Uncompensated HF ○ Third degree (complete) atrioventricular (AV) block without pacemaker ○ Recent embolism ○ Severe Musculoskeletal conditions that would prohibit exercise
Contraindications to inspiratory muscle training: ○ History of spontaneous pneumothorax/ incomplete recovery following traumatic pneumothorax ○ Asthma patients who suffer from frequent, severe exacerbations ○ Recently perforated ear drum (within last 3 months) ○ Large Bullae

Table 1 Exclusion Criteria

Recruitment

Adults listed for elective cardiac surgery will be screened by the clinical team and given a patient information sheet (PIS) and letter of invitation prior to their routine clinic appointment. Eligibility will be confirmed by a clinician at the time of listing for surgery. Written informed consent (see supplementary material consent form v4.0) will be obtained before any trial procedures are performed.

Baseline Data Collection

Baseline assessments will be performed after consent and prior to randomisation. Women of childbearing potential will perform a pregnancy test to confirm pregnancy status before undertaking any further research activity. The baseline assessments will consist of the 6MWT, MIP, EQ5D5L questionnaire, activity monitoring (optional), HADS, Rockwood frailty score (9 point Clinical Frailty Scale (CFS)) and hand grip strength. Participants' medical notes will be used to collect a full medical history, gender, height and weight, and date of birth/age. Participants consenting to take part in the 7 day activity monitoring sub study will be provided with an accelerometer, instructions on it use, and options for returning the accelerometer.

Randomisation

Participants will be randomised in a 1:1 ratio to either the control arm (standard care only), or the intervention arm (standard care plus the prehabilitation intervention) using a 24-hour, central, secure, web-based system (SealedEnvelope™). Randomisation will be performed using a minimisation scheme that takes into account Rockwood frailty score, 6MWD, age and gender to balance baseline physical fitness between the arms. It will not be possible to conceal the allocation of treatment from the participant, or the team delivering the intervention and measuring the primary outcome. The surgeons performing the participants' cardiac surgery will not be informed of the allocation, however they will not be officially blinded.

Outcome Measures

The primary outcome will be change in exercise capacity measured by the 6-minute walk test from baseline to pre-surgical assessment. This is a self-paced 6-minute walk recording the distance walked in metres around a 25 meter standardised track.

This outcome was chosen because preoperative 6MWT distance is associated with moderate or severe complications after both non-cardiac surgery(16) and cardiac surgery(17). It has also been validated as an indicator of recovery in patients undergoing cardiac surgery(18).

All participants will receive standardised instruction and support(19). A pulse oximeter will be attached to the participant during the walk for continuous monitoring of oxygen saturations and heart rate. The test will be performed twice at baseline to account for a learning effect; the distance achieved on the two walks will be recorded and the highest value used for baseline measurement. The 6MWT will be repeated once at 6 and 12 weeks following index surgery to assess the post-operative impact of prehabilitation.

The secondary outcome measures in Table 2. will be collected at baseline, pre-surgical assessment, 6 and 12 weeks following index surgery.

Secondary Outcomes	Measurement
Change in Inspiratory muscle strength	Maximal inspiratory pressure (MIP)
Frailty	Hand Grip strength
Quality of life	EQ-5D-5L
Anxiety and Depression	Hospital Anxiety and Depression Scale (HADS)

Table 2. Secondary outcome measures

Maximal inspiratory pressure (MIP) is used to measure inspiratory muscle strength and will be measured using a hand-held electronic transducer (POWERbreath KH2 (HaB Ltd UK), according to guidelines set out in the ATS/ERS statement of 2002(20).

Hand grip strength will used as an objective measurement of frailty. Participants will be asked to grip a dynamometer (Jamar hydraulic hand dynamometer) as hard as they can using their dominant hand whilst being seated. The highest grip strength of 3 attempts will be recorded.

Two patient reported questionnaires will be collected; the EQ-5D-5L general health questionnaire(21) consists of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a standard vertical 20cm visual analogue scale (EQ-5D VAS) on a scale of 0 to 100 measuring current health-related quality of life. The health state of each participant, will be measured before and after the intervention period and post-surgery to determine any change in their health (gain or loss). The HADS self-reported questionnaire consists of 14 questions (7 for anxiety and 7 for depression) rated on a Likert-type scale from 0 to 3(22) and will be used to evaluate participants' mood.

In addition, surgical and post-operative data will be collected from participants' medical notes including: duration of operation, cardiopulmonary bypass times, time on ICU, and discharge information. Pulmonary and cardiac complications will be documented as outlined in Table 3.

Post-operative cardiac surgery complications	
Renal failure/acute kidney injury, tracheostomy, delirium, TIA, stroke, new atrial fibrillation, RBC transfusion, blood product transfusion, cardiac arrest, myocardial infarction, all-cause mortality, infection (in-hospital only), or sepsis (6- and 12-week follow-up only)	
Pulmonary Complications	
Grade 1	• New onset purulent sputum or change in character of chronic sputum • Fever with no focus outside of the lungs • New rise in c-reactive protein or white blood cell count, positive blood culture • Atelectasis radiological finding or abnormal lung findings requiring non-invasive intervention • Hypoxaemia • Administration of additional post-operative antibiotics • Transtracheal aspirate
Grade 2	• Pleural effusion needing drainage • Lung infection • Pneumothorax • Post-operative reintubation • Clinically significant atelectasis requiring tracheobronchial suction
Grade 3	• Ventilatory failure with postoperative ventilator dependence >8h • Reintubation with a subsequent period of ventilation >48h

Table 3. Pulmonary Cardiac Complications

Sub-studies

Accelerometer Sub-study

Participants in both trial arms will be invited to take part in an accelerometer sub-study. We anticipate that 50-60% of the trial cohort will take part in the sub-study however this trial is ongoing and therefore this data is not yet available.

Participants will wear an activity monitor on their non-dominant wrist for a continuous period of 7 days at baseline and after the intervention period. Data collected will be processed using the GGIR package in R(23) to explore change in activity levels (including time spent in MVPA, light physical activity and sedentary behaviour), change in moderate-to-vigorous physical activity and between the control and intervention group. The correlation between 7 day activity monitor data and patient reported activity diaries pre and post intervention will also be explored.

Qualitative Sub-study

Participants in both arms will offered the opportunity to take part in a focus group exploring their experiences of the taking part in the PrEPS trial. Written informed consent (see supplementary material qualitative consent v2.0) will be obtained for each participant. Participants within the intervention and control arms of the trial will attend separate focus groups which will take place after the 12-week post-operative assessment to avoid interference with 12-week patient reported outcomes.

Focus groups will also take place with HCPs involved in the delivery of prehabilitation to explore their experiences of delivering the intervention as part of the PrEPS trial.

Focus group recordings will be transcribed verbatim and analysed using a deductive thematic analysis(24). Themes will be mapped against theoretical constructs of Normalisation Process Theory to highlight relationships and overlap between themes(25).

Standard care

Participants randomised to the standard care group will continue with routine pre-operative care, consisting of specialist nurse review, meeting the surgeon and anaesthetist, and receiving information regarding preparation for surgery. Participants will be provided with a patient diary and asked to document any form of exercise that they carry out independently as well as healthcare visit details to aid collection of adverse events.

Prehabilitation intervention

Participants randomised to the intervention group will receive standard care and a hospital based prehabilitation intervention consisting of an initial fitness assessment, a supervised exercise programme twice a week for 4 weeks, an unsupervised home exercise programme consisting of up to 45 mins of prescribed daily exercise and High Intensity-Inspiratory muscle training (HI-IMT) involving twice daily training for a duration of 4 weeks.

Initial Assessment

At the first cardiac prehabilitation visit, participants will be assessed by a cardiac rehab specialist physiotherapist and nurse to gauge their physical fitness. This involves a subjective and objective assessment; table 4 details these assessments.

Subjective Assessment

1	General wellbeing
2	Recent health issues and medical history
3	Fitness and activity levels
4	Anxiety levels
5	Social circumstances and support
Objective Assessment	
1	HR and BP measurements
2	ECG if indicated
3	Respiratory function (rate, breathing pattern and auscultation with stethoscope)
4	Musculoskeletal system (joint range and muscle strength)
5	Other physical problems

Table 4. Participant initial assessments to gauge physical fitness

Participants will also be seen by a respiratory physiotherapist and instructed on how to carry out High Intensity-Inspiratory Muscle Training (HI-IMT). Participants will be given their own device (a POWERbreathe medic plus (HaB Ltd UK)) and an instruction leaflet/diary to use at home.

Supervised exercise programme

The maximum HR and target HR will be calculated for each participant. Exercise intensity will be individually prescribed using the combined results of the initial fitness assessment and the baseline 6MWT. The physiotherapist will discuss the principles of the prescribed exercise with the participant and any precautions they should take to mitigate injury and illness. Participants will be encouraged to achieve a predicted target heart rate of 60 – 75% max and a moderate BORG score (12 or 13) during their cardiovascular exercise with actual figure achieved being recorded.

The cardiac prehabilitation exercise sessions will consist of 3 stages listed in table 5.

Stage 1	▪ 15 minutes warm up consisting of preparatory stretches.
Stage 2	▪ Up to 25 minutes of cardiovascular (CV) exercise and resistance-based training with active recovery (AR).
Stage 3	▪ 15 minute cool down period including maintenance stretches

Table 5. Stages of Cardiac Prehabilitation Programme

Home exercise programme

Participants will be asked to perform up to 45 minutes of exercise at home (unsupervised) up to 7 times a week during the 4-week intervention period. This exercise will be tailored to the individual participant's ability based upon their physical fitness assessment and their baseline 6MWT results. Progress will be discussed with the participant once a week during the prehabilitation classes. As this is unsupervised, the intensity will be lower than that prescribed for the

supervised classes. Participants will be set achievable targets and have their exercise progressed if they have managed comfortably during the week as measured by their self-reported Borg scores and diaries.

High Intensity-Inspiratory Muscle Training (HI-IMT)

Participants will be asked to perform HI-IMT twice a day for 4 weeks at home starting from their first supervised exercise session. Using their device, participants will be asked to breathe in as forcefully as possible before slowly breathing out 6 times, then rest, before performing another set of 6 breaths. There will be 6 sets of 6 breaths in each HI-IMT training session. The resting time between the sets starts at 60 seconds and decreases by 15 seconds after each set, ending with a rest period of five seconds before the final set.

The device will be set at 50% of their MIP. Participants will be shown how to increase or decrease the resistance on their device to train with a difficulty level of "somewhat hard", which is equivalent to a Borg score of 12 to 13. This will be highlighted in the instruction booklet/diary. Participants will have their HI-IMT technique checked once a week during their prehabilitation classes to ensure they are training effectively.

End of Intervention

The end of the intervention is the final prehabilitation class. On completion of the 4-week intervention period participants will be encouraged to continue with home exercise and IMT independently until their day of surgery and document any activity in their patient diary.

Fidelity of the intervention

The five domains of the treatment fidelity framework, provided by the National Institutes of Health's Behavioral Change Consort will be assessed to ensure fidelity of the prehabilitation intervention throughout the trial(26). Table 6 details these domains.

1	Study design issues will ensure the "treatment dose" in each condition is fixed
2	Monitoring and improving the intervention will involve standardising the process by providing interventionists with a protocol
3	Fidelity of intervention delivery will involve a single observation of an exercise class to ensure delivery is per-protocol. A checklist will then be completed at 6 monthly intervals to ensure consistency in delivery
4	Receipt of treatment by patients (did they understand how to undergo the exercises)
5	Enactment of treatment skills by patients (e.g. did they engage in a home exercise program) will be assessed during focus groups conducted within the qualitative sub-study

Table 6. 5 Domains of the treatment fidelity framework in line with assessments to record fidelity

In addition to the above, self-monitoring data will be collected via exercise diaries.

Assessment of Compliance

Self-reported patient diaries and prehabilitation attendance records will be used to measure adherence to the intervention. Adherence was defined as completing 50% of the supervised exercise classes (4 out if 8 sessions) in-line with documented adherence rates to cardiac rehabilitation(27-29). Exercise diaries will capture the physical activity completion for the unsupervised component.

Patient Public Involvement (PPI)

Patients and members of the public were involved in identifying prehabilitation in this population as a research priority and in design of the trial. Cardiac rehabilitation patients were consulted in the development of the prehabiliation intervention and relevant trial documentation. A patient representative is a member of the Trial Oversight Committee (TOC) to ensure PPI input throughout the entirety of the trial. Findings will also be disseminated to participants and relevant patient groups.

End of trial

The end of the clinical trial is defined as the 12 week follow up of the last participant. Data queries will be addressed for a period of up to 3 months following this. Participants may choose to withdraw from the trial at any time. Clinicians may also choose to withdraw participants at any time for reasons including non-compliance, adverse events and pregnancy.

Safety reporting

The safety of delivering a prehabilitation intervention a key outcome of the trial. Although there is now some evidence of a low risk to patient safety from studies where physical activity has been assessed in patients with cardiac and/or pulmonary conditions, there is no such evidence in patients with severe cardiac conditions awaiting cardiac surgery.

To mitigate any safety concerns of participants, clinician and other stakeholders, the trial is designed so that the most intensive exercise intervention will be carried out within a hospital setting. Lower intensity exercise will be prescribed at home after assessment each week by the trial team.

Adverse events and serious adverse events will be collected and monitored throughout the trial. Due to the nature of the study population identified expected adverse events including; angina, breathlessness, light-headedness, arrhythmia and fatigue.

The relationship between the intervention (prehabilitation) and the occurrence of each AE will be assessed and categorised by the Chief Investigator (or delegate). Serious events that are unexpected and related, will be reported to the REC committee within 15 days of notification.

It is crucial that safety is monitored throughout the trial so that any findings may be used in future trials, particularly when considering if this practice can be circulated across the wider community and out of hospitals settings.

Statistical analysis

Primary and secondary outcomes will be analysed following the intention-to-treat principle, with patients analysed according to randomisation regardless of whether they actually received or adhered to the allocated treatment. Per-protocol and as-treated analyses may be conducted as sensitivity and exploratory analyses. A full statistical analysis plan will be developed and agreed with the Trial Oversight Committee before data collection is completed. Data will be analysed at the end of the study; no interim outcome analyses are planned.

The primary analysis testing the impact of the cardiac prehabilitation programme on pre-operative functional exercise capacity (measured by 6MWD) will be based on a linear mixed-effects model accounting for baseline randomisation factors, except for baseline 6MWD which is explicitly incorporated in the model to calculate change from baseline. The model will account for intra-patient correlation using a random intercept model. Subgroup analyses conducted for the primary outcome will be pre-specified in the analysis plan. All continuous secondary outcomes will be analysed using the same approach as used for the primary outcome. All non-continuous data will be analysed in the same way, but with a generalised linear model using the appropriate distributional assumptions and link function. Descriptive analysis will be used to explore outcomes related to the feasibility of the trial. Analyses will be conducted using R statistical software.

Sample size

The sample size is based on detecting a significant improvement in 6MWD after the prehabilitation program compared with the 6MWD at baseline. We have assumed a minimal clinically important difference in 6MWD of 25m with a standard deviation of 56.5m for pre-operative participants(30). Based on detecting a medium effect size of 0.44, 164 participants (82 in each group) will provide 80% power to detect a difference of 25 metres in the 6MWD. Adjusting for 10% missing data, 180 participants will be recruited for the trial.

Data

Data will be entered at site onto an electronic case report form for each participant. The database will be hosted by Sealed Envelope© who abide by GDPR and are responsible for the security of the data contained within the database.

Data will be used according to the provision of GDPR, and applicable new regulations, and individuals will not be identifiable through any reports or publications that result from the trial. Quality control measures will ensure that all data are reliable and have been processed accurately at every stage of the study. Source Data Validations (SDV) will be undertaken by the Trial Management staff to optimise data quality for key data including primary/secondary outcome variables and SAE data.

Trial Oversight Committee

An independent Trial Oversight Committee (TOC) will monitor data completion rates and safety reporting throughout the duration of the trial. Data collected in the trial will be used to support other research in the future, and may be shared anonymously with other researchers.

Ethics and Dissemination

The PrEPS trial was granted a favourable opinion by the Yorkshire and Humber, Sheffield Research Ethics Committee on the 25/10/2019 (19/YH/0317). Trial findings will be disseminated to patients using patients focused literature, visual aids and animated films via patient charities like Heart Valve Voice and the British Heart Foundation national PPI group. Dissemination to clinicians and professional stakeholders like commissioners will be through peer reviewed publication and conferences. Any changes to the protocol will be communicated to all relevant parties as per the HREC requirements.

Discussion

Prehabilitation in cardiac surgery has lagged behind that for other specialties, especially cancer surgery, abdominal general surgery and limb reconstruction surgery in the UK(31). This is despite the fact that large numbers of patients undergo cardiac surgery in the UK every year (around 35,000). Moreover, cardiac surgery patients in particular stand to benefit from a prehabilitation interventions because they tend to be older, mean age 67 years and increasing(1) and have a higher co-morbid burden (average Charlson score 2.1 vs 1.7) (GIRFT Programme National Specialty Report). In particular, they suffer from high levels of obesity, diabetes, coexisting lung disease and reduced mobility. The chronic nature of most cardiac conditions prior to reaching the point of surgical intervention and the fact that the cardiac disease process itself usually limits physical activity, means that patients awaiting cardiac surgery usually exhibit a high prevalence of frailty and loss of muscle mass and function, a condition usually referred to as sarcopenia(32-34).

In 2019 our group published a review of 483 publications, of which 10 (including 4 metanalysis and 6 RCTs) represented the best evidence to answer the clinical question ‘does pre-habilitation improve outcomes in cardiac surgical patients?”(35). The RCTs were limited by small sample sizes (the smallest had a sample size of 15) and no trial combined physical activity and IMT (the 2 interventions with the largest evidence base of impact for outcomes) as components in the intervention. A subsequent systematic review which explored associations between objectively measured physical activity during the prehabilitation period and health-related outcomes across surgery types reported significant beneficial associations(36).

The significant benefit of prehabilitation in other therapeutic areas and the scarcity of high quality evidence in cardiac surgery patients identifies an urgent need to provide further data in this area.

Anticipated Impact

This will be the largest ever RCT investigating the impact of a prehabilitation intervention composed of exercise and IMT in patients with severe cardiac disease awaiting elective cardiac surgery. The findings will establish if such an intervention is feasible and if it is effective in improving overall functional exercise capacity prior to surgery. It will also indicate if there are any impacts on clinical outcome after surgery.

Trial status

The PrEPS trial opened to recruitment in November 2019, just prior to the start of the global pandemic. The restrictions imposed by the COVID-19 pandemic has had a significant impact on recruitment, elective cardiac surgery and the ability to deliver the prehabilitation intervention. Despite these challenges PrEPS continues to recruit patients and is projected complete follow up data collection by early 2023.

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Author contributions

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICMJE).

1. Enoch Akowuah - devised the clinical question, applied for funding, Chief investigator with overall responsibility for the trial, reviewed and contributed to all areas of the manuscript
2. Ayesha Mathias - Trial manager with day to day responsibility for delivery of the trial, drafted all areas of the manuscript and contributed to all areas
3. Michelle Bardgett - Senior trial manager, author of the trial protocol, governance oversite, contributed to all areas of manuscript
4. Samantha Harrison - Contributed specifically to the Qualitative Sub-Study and Intervention Design and Delivery sections within the manuscript
5. Adetayo Kasim - General oversight of the Statistical Analysis section of the manuscript and overall review of whole manuscript
6. Kirsti Loughran - Contributed specifically to the Qualitative Sub-Study section within the manuscript

7. Emmanuel Ogundimu - Statistical oversight and contributed specifically to the Statistical Analysis
8. Jason Trevis - Contributed specifically to the Qualitative Sub-Study section within the manuscript
9. Janelle Wagnild - Drafted and contributed specifically to the Statistical Analysis and accelerometer sub-study sections of the manuscript
10. Pasan Witharana - Contributed specifically to the Qualitative Sub-Study section within the manuscript
11. Helen Hancock - Co-Applicant, Protocol Author, general overview and contribution to all areas within manuscript
12. Rebecca Maier - Co-Applicant, Protocol Author, general overview and contribution to all areas within manuscript

Several reviews of the manuscript took place prior to a final draft with all authors reviewing the final draft once complete prior to submission. All authors are informed of any revisions that may need to take place following editorial review and confirm these changes are acceptable prior to re-submission.

Declaration of Competing Interests

There are no competing interests to declare.

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Figure 1. Consort Diagram to show research activity in the PrEPS trial – this consort diagram depicts the stages throughout the trial from screening, randomisation, intervention and through the various follow up stages. A summary of what assessments are conducted is provided at each stage.

PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL)

Figures

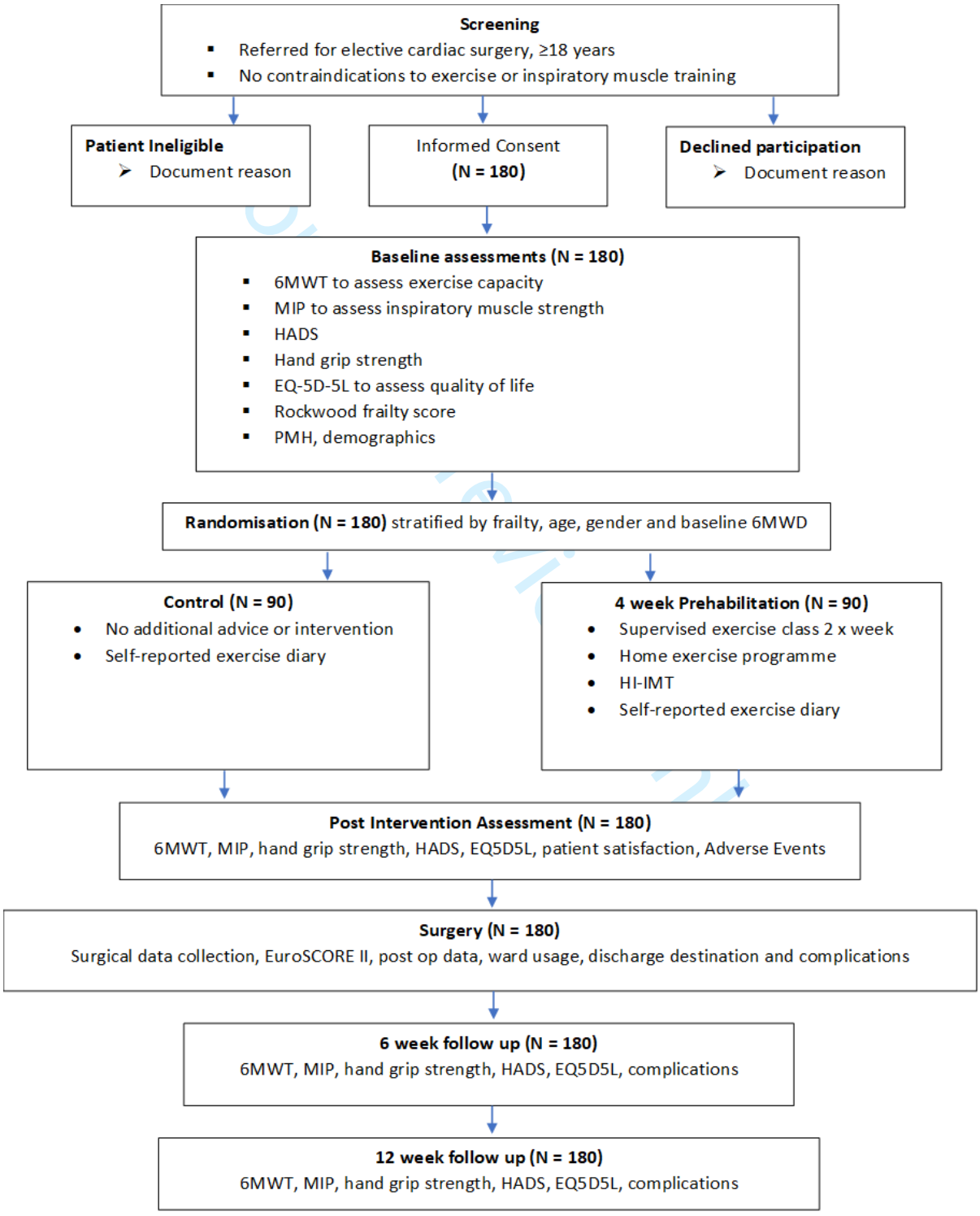

Figure 1. Consort Diagram to show research activity in the PrEPS trial

NHS Recruiting Centre logo

and relevant contact details to be entered

CONSENT FORM

Prehabilitation in Elective Patients Undergoing Cardiac Surgery (PrEPS)

Name of Researcher: [Recruiting Centre PI to be entered]

Participant Identification Number for this trial: __ __ __ __ __

Please INITIAL the box where you agree. Please note that statement 9 is optional:

1. I confirm that I have read the information sheet dated …….. (version ……..) for the above trial. I have has the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Newcastle Clinical Trials Unit, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐

4. I understand that anonymised information about me relevant to the trial will be held on a secure database, which is hosted on an external server and will be transferred to individuals within the research team including members at Newcastle and Durham University for analysis. All data will be anonymised using a participant identification number and stored securely on restricted servers for a period of 7 years after the end of the trial. Any publications resulting from this trial will not include any personal identifiable information ☐

5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers ☐

NHS Recruiting Centre logo

and relevant contact details to be entered

6. I agree to my General Practitioner being informed of my participation in the trial, including any necessary exchange of information about me between my GP and the research team. ☐

7. I understand that if I lose the capacity to decide about my healthcare changes during the trial, ☐

I will not be asked to undertake any further trial activity, however routinely collected information relevant to the trial may be collected.

8. I agree to take part in the above trial. ☐

Optional:

9. I have been offered the opportunity to take part in the trials activity monitor sub study. I have been provided with information and understand what this entails. I agree to take part in the sub study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes

South Tees Hospitals NHS
NHS Foundation Trust

QUALITATIVE CONSENT FORM

Prehabilitation in Elective Patients Undergoing Cardiac Surgery (PrEPS)

Name of Researcher: *Mr Enoch Akowuah*

Participation is entirely optional, and non-participance will have no detrimental affects upon your ongoing care/participation in the primary clinical trial. You are free to withdraw yourself from the sub-study at any point, without any detrimental impact.

Please read the following statements, initial the boxes next to them and sign below.

• I have read the patient/HCP information sheet dated …….. ((Version……) and understand what the PrEPS sub-study entails.	
• I consent to my details being passed to and being contacted by the qualitative research team.	
• I consent to participate in a focus group.	
• I consent to being audio recorded during a focus group.	
• I understand that if participating in an online focus group my email address may be visible to other participants	
• I consent to the audio of my conversation at said focus group being passed to a professional transcription service.	
• I am aware that I may withdraw myself from this sub-study at any time up to and during the focus group and any data already collected will remain in the study.	
• I consent to the data generated being anonymised and published for academic purposes.	

Print name of participant:	Print name of person taking consent:
Signature of participant:	Signature of person taking consent:
Date:	

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Met across various pages within manuscript.
Protocol version	#3	Date and version identifier	Page 2
Funding	#4	Sources and types of financial, material, and other support	Page 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 1
Roles and responsibilities: sponsor and funder	#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	Not included due to word limit – within protocol itself

Roles and responsibilities: committees	#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)	Page 10
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	Page 3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 3-4
Objectives	#7	Specific objectives or hypotheses	Page 5
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, non-inferiority, exploratory)	Page 4-5
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	Page 4-5
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)	Page 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 8-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 8-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8-10

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 5
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	Page 12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5
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	Page 11-12
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	Page 11-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#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 plan	#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	Page 12
Data collection plan: retention	#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	In protocol – not included in paper due to word limit
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	Page 12

Statistics: outcomes	#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	Page 11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7-8
Statistics: analysis population and missing data	#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)	Page 11
Methods: Monitoring			
Data monitoring: formal committee	#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 – Single Trial Oversight Committee in place – explanation in protocol
Data monitoring: interim analysis	#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	Page 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 12
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)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5-6
Consent or assent: ancillary studies	#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	Page 12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 12
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	Details in protocol – not in paper due to word count
Dissemination policy: trial results	#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	Page 10 and 12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 13

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
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