PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PREHABILIATION IN ELECTIVE PATIENTS UNDERGOING CARDIAC SURGERY: A RANDOMISED CONTROL TRIAL (THE PrEPS TRIAL) – A Study Protocol
AUTHORS	Akowuah, Enoch; Mathias, Ayesha; Bardgett, Michelle; Harrison, Samantha; Kasim, Adetayo; Loughran, Kirsti; Ogundimu, Emmanuel; Trevis, Jason; Wagnild, Janelle; Witharana, Pasan; Hancock, Helen; Maier, Rebecca

VERSION 1 – REVIEW

REVIEWER	Rakesh C. Arora University Hospitals, Surgery
REVIEW RETURNED	15-Aug-2022

GENERAL COMMENTS	Summary: Study Setting: Single Centre Study Design: RCT P: Adults undergoing an elective cardiac surgery procedure I: 4 week supervised and 4 week unsupervised, exercise prehabiliation program C: current standard of care (SoC) O (Primary Endpoint - i.e. why are we doing it and was it registered with reported outcome: Improvement in 6 minute walk test (6MWT) Strengths: 1. Important question considering the currently aging cardiac surgery patient population. 2. Inclusion of a detail SPIRIT checklist Comments/Concerns: The following comments/questions are seeking clarification on a few issues (separated by section) to further strengthen the manuscript. GENERAL COMMENTS: Prehabilitation can include different elements to address vulnerability in the older adult. The authors/designers of this trial have selected to focus primarily on the exercise/sacropenia component of frailty (i.e. not inclusive of the cognitive, lifestyle and/or mood aspects). It would be helpful for the authors to provide additional commentary on this design element. METHODS: Please confirm if this is a single centre or multi-centre endeavour. METHODS: The Authors have chosen to examine the impact of Prehab on 6MWT. Can the authors provide some details on the linkage of 6MWT improvements (or declination) on outcomes after

	cardiac surgery? METHODS: The Authors have chosen to include patients 18 years and older. Frailty is less commonly present in the younger patients undergoing cardiac surgery. Can the Authors provide additional details/rationale for this age inclusion criteria? METHODS: Can the Authors provide additional details/definition of certain exclusion criteria (i.e. urgency status, malignant arrhythmias, contra-indications to prehab etc.). These are not adequately described. METHODS: The Authors have stated that they are using the Rockwood frailty scale. Can they clarify if they are using the 9-point Clinical Frailty Scale (CFS) or a full (or modified) Frailty Index. METHODS: Can the Authors provide additional details on the number of patients to be included and process of analysis of accelerometer data? METHODS: Can the Authors provide additional details on how they chose prehab protocol “adherence” for both the supervised and unsupervised components to be 50%? Similarly, how will the investigators objectively track physical activity completion/compliance for the unsupervised, home based component in those without accelerometer data? METHODS: Presumably, patient wait time will be variable. How will the Authors ensure that patients are being scheduled for their surgery following the 4 week home component of their program? Will the SoC patient be held to the same waiting period? STATISTICS: Please provide additional details on how a improvement on the 6MWT of 25m is deemed clinically significant and how (if any) this change is associated with meaningful clinical outcomes in the postoperative cardiac surgery patient. Minor Concerns: 1. Consider inclusion of the below references: Arthur, H. M., Daniels, C., McKelvie, R., Hirsh, J., & Rush, B. (2000). Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Annals of Internal Medicine, 133(4), 253–262. Sawatzky, J.-A. v, Kehler, D. S., Ready, a E., Lerner, N., Boreskie, S., Lamont, D., Luchik, D., Arora, R. C., & Duhamel, T. a. (2014). Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study. Clinical Rehabilitation. Stammers, a. N., Kehler, D. S., Afilalo, J., Avery, L. J., Bagshaw, S. M., Grocott, H. P., Legare, J.-F., Logsetty, S., Metge, C., Nguyen, T., Rockwood, K., Sareen, J., Sawatzky, J. -a., Tangri, N., Giacomantonio, N., Hassan, A., Duhamel, T. a., & Arora, R. C. (2015). Protocol for the PREHAB study--Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. BMJ Open, 5(3), e007250–e007250.

REVIEWER	Ian Waite King's College London, Physiotherapy & Cardiology
REVIEW RETURNED	16-Aug-2022

GENERAL COMMENTS	This is an exciting study which is a step in the right direction in providing valuable outcomes and further insight in to the use of Prehabilitation in the cardiac population. I'm pleased to see the addition of the Qualitative sub-study, as this is something that is currently lacking in this area and will hopefully provide necessary insight in to patient experiences and acceptance of the intervention(s). There are of course limitations within the study, such as the variable amount of overall intervention time, but this is also the reality with surgical patient and the common changes to waiting times. Also, presumably patients with MSK limitations or travel difficulties who would not be able to attend face to face sessions would therefore be ineligible to take part? Does this then mean that those recruited are more physically able and how does this reflect on the whole population of patients awaiting cardiac surgery. I'm sure these limitations and others would be addressed in detail following data collection and in turn help shape the next phase of prehabilitation research in the cardiac population.

VERSION 1 – AUTHOR RESPONSE

Comment 1: Prehabilitation can include different elements to address vulnerability in the older adult. The authors/designers of this trial have selected to focus primarily on the exercise/sacropenia component of frailty (i.e. not inclusive of the cognitive, lifestyle and/or mood aspects). It would be helpful for the authors to provide additional commentary on this design element.

Response: Prior to designing the study, we performed a systematic review of data on prehabilitation in forms of surgery. We found evidence for the effectiveness of exercise and inspiratory muscle training, especially after abdominal and orthopaedic surgery. We found inconsistent evidence of the effectiveness of psychological interventions. Life-style modifications like weight loss and smoking cessation were outside the scope of prehabilitation interventions which could be delivered in patients awaiting urgent surgery. Given these uncertainties, we decided not to include these elements in this study.
Outcome: No changes required

Comment 2: Please confirm if this is a single centre or multi-centre endeavour.

Response: This is a single centre trial.

Outcome: This has been updated in the manuscript to ensure consistency (page 4).

Comment 3: The Authors have chosen to examine the impact of Prehab on 6MWT. Can the authors provide some details on the linkage of 6MWT improvements (or declination) on outcomes after cardiac surgery?

Response: Preoperative 6MWT distance has an association with moderate and severe complications after inpatient cardiac surgery (16) and non-cardiac surgery(17). The 6MWT has been validated as an indicator of recovery after cardiac surgery(18) and for this reason is widely used both clinically in cardiac rehabilitation and as an outcome measure in clinical trials. We chose this as an outcome

measure because it is routinely performed in post cardiac surgery rehabilitation and because the intensity and distance is determined by the patients (unlike the incremental shuttle walk test for example) we felt it would be a safe test to administer in this high risk patient population.

Outcome: Additional explanation and the following references included in the manuscript (page 7);

Comment 4: The Authors have chosen to include patients 18 years and older. Frailty is less commonly present in the younger patients undergoing cardiac surgery. Can the Authors provide additional details/rationale for this age inclusion criteria?

Response: We agree that it may be more clinically effective to target prehab to patients with pre-op evidence of frailty, however this study seeks to answer a slightly different question i.e. the feasibility of delivering a pre-hab intervention and if that intervention can improve physical function in patients with significant cardiac disease requiring surgery. If the study is positive, then a follow on study looking at the clinical efficacy of such an intervention is warranted. In that larger study of clinical efficacy it may be reasonable to understand if the intervention specifically benefits clinically frail patients, as it may have the most impact

Outcome: No changes made to manuscript but his could be added to the discussion if required

Comment 5: Can the Authors provide additional details/definition of certain exclusion criteria (i.e. urgency status, malignant arrhythmias, contra-indications to prehab etc.). These are not adequately described.

Response: The details regarding the exclusion criteria were summarised in the manuscript due to restricted word count.

Outcome: Due to the word count we have included a table in the manuscript to provide additional details for the exclusion criteria (page 5-6). If there is scope to increase the word count we can add this as text if preferred.

Exclusion Criteria
Unstable angina/indication for urgent surgery
Malignant Arrhythmias
Currently Participating in another interventional clinical trial
Known Pregnancy
Contraindications to known cardiac rehabilitations:
o Acute systemic illness or fever
o Uncontrolled atrial or ventricular arrhythmias
o Uncontrolled sinus tachycardia (HR>120 bpm)
o Aortic stenosis with pre-syncope/syncope
o Acute pericarditis or myocarditis
o Uncompensated HF
o Third degree (complete) atrioventricular (AV) block without pacemaker
o Recent embolism
o Severe Musculoskeletal conditions that would prohibit exercise
Contraindications to inspiratory muscle training:
o History of spontaneous pneumothorax/ incomplete recovery following traumatic pneumothorax
o Asthma patients who suffer from frequent, severe exacerbations
o Recently perforated ear drum (within last 3 months)
o Large Bullae
Table 1 Exclusion Criteria

Comment 6: The Authors have stated that they are using the Rockwood frailty scale. Can they clarify if they are using the 9-point Clinical Frailty Scale (CFS) or a full (or modified) Frailty Index.

Response: We are using the 9-point Clinical Frailty Scale (CFS).

Outcome: Details have been added to the manuscript (page 6)

Comment 7: Can the Authors provide additional details on the number of patients to be included and process of analysis of accelerometer data?

Response: Participants in both trial arms will be invited to take part in the optional 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 be asked to wear an activity monitor on their non-dominant wrist for a continuous period of 7 days at baseline and after the intervention period. Data will be processed using the GGIR package in R(23) to explore change in activity levels (including time spent in moderate-to-vigorous physical activity, light physical activity and sedentary behaviour) from baseline to post intervention 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.

Outcome: This additional detail has been added to the manuscript (page 8) and additional reference included.

Comment 8: Can the Authors provide additional details on how they chose prehab protocol "adherence" for both the supervised and unsupervised components to be 50%? Similarly, how will the investigators objectively track physical activity completion/compliance for the unsupervised, home based component in those without accelerometer data?

Response: 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.

Outcome: The detail above and references have been added to the manuscript (page 11).

Comment 9: Presumably, patient wait time will be variable. How will the Authors ensure that patients are being scheduled for their surgery following the 4 week home component of their program? Will the SoC patient be held to the same waiting period?

Response: One of the main challenges of this trial has been scheduling surgery to occur in a timely fashion following the prehabilitation intervention. All surgeons have agreed to endeavour to do this wherever possible however the disruption caused by the COVID-19 pandemic will likely have an impact on this. Both arms are subject to the same waiting period and time to surgery will be presented in the analysis. Although timing of surgery is an important consideration, the primary outcome is collected at the pre-op assessment clinic and not at the time of surgery.

A sub-analysis will be performed to understand the impact of waiting times on outcomes according to the per-protocol analysis (pre-specified within the SAP), which has the following timing-related criteria: 1) pre-surgical assessment within 2 weeks of final class (for outcomes measured at pre-surgical assessment, Intervention arm only) and 2) surgery within 2 weeks of pre-surgical assessment for postoperative outcomes (both arms).

Outcome: No change to manuscript

Comment 10- Statistics: Please provide additional details on how an improvement on the 6MWT of 25m is deemed clinically significant and how (if any) this change is associated with meaningful clinical outcomes in the postoperative cardiac surgery patient.

Response: The 6MWT has been validated as an indicator of recovery after cardiac surgery and the clinically significant difference of 25m was identified from existing literature. This is already referenced in the paper therefore no changes have been made

Outcome: Reference already cited on page 13

Minor Concerns:
1. Consider inclusion of the below references:

Arthur, H. M., Daniels, C., McKelvie, R., Hirsh, J., & Rush, B. (2000). Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Annals of Internal Medicine, 133(4), 253–262. (22 years old)

Sawatzky, J.-A. v, Kehler, D. S., Ready, a E., Lerner, N., Boreskie, S., Lamont, D., Luchik, D., Arora, R. C., & Duhamel, T. a. (2014). Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study. Clinical Rehabilitation. (less than 20 patienst)

Stammers, a. N., Kehler, D. S., Afilalo, J., Avery, L. J., Bagshaw, S. M., Grocott, H. P., Legare, J.-F., Logsetty, S., Metge, C., Nguyen, T., Rockwood, K., Sareen, J., Sawatzky, J. -a., Tangri, N., Giacomantonio, N., Hassan, A., Duhamel, T. a., & Arora, R. C. (2015). Protocol for the PREHAB study--Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. BMJ Open, 5(3), e007250–e007250. (protocol paper by the reviwer- trial now abandoned)

Response: We thank the reviewers for highlighting the above references for consideration within the manuscript.

Outcome: We have reviewed each of the papers and have decided not to include these in the protocol manuscript as we did not consider these at the time of protocol development. We will consider these for reference and discussion within the results manuscript.

Reviewer: 2
Dr. Ian Waite, King's College London
Comments to the Author:

This is an exciting study which is a step in the right direction in providing valuable outcomes and further insight in to the use of Prehabilitation in the cardiac population. I'm pleased to see the addition of the Qualitative sub-study, as this is something that is currently lacking in this area and will hopefully provide necessary insight in to patient experiences and acceptance of the intervention(s).

Comments Reviewer 2: There are of course limitations within the study, such as the variable amount of overall intervention time, but this is also the reality with surgical patient and the common changes to waiting times. Also, presumably patients with MSK limitations or travel difficulties who would not be able to attend face to face sessions would therefore be ineligible to take part? Does this then mean

that those recruited are more physically able and how does this reflect on the whole population of patients awaiting cardiac surgery. I'm sure these limitations and others would be addressed in detail following data collection and in turn help shape the next phase of prehabilitation research in the cardiac population.

Response: We would thank you for your positive comments and are pleased that the reviewer recognises the importance of the question and the challenges of designing and delivering a trial to address them.

The individual prehabilition intervention is designed by the prehab delivery team after initial consultation, and where possible modifications are made to take into account individual patient needs. However, patients with significant physical limitations which means they can't exercise may be excluded. This represents a small proportion of the patients having cardiac surgery but will be addressed in further discussion of the results.

VERSION 2 – REVIEW

REVIEWER	Rakesh C. Arora University Hospitals, Surgery
REVIEW RETURNED	22-Nov-2022

GENERAL COMMENTS	The Authors have responded to my previous comments and undertaken substantive changes to their manuscript. I do not have any further comments.