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# PREhabilitation for improving QUality of recovery after ELective cardiac surgery (PREQUEL) study: protocol of a randomised controlled trial

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## ABSTRACT

**Introduction** Frailty is a multidimensional syndrome in which multiple small physiological deficits accumulate gradually, resulting in a loss of physiological reserve and adaptability, putting a patient that is exposed to a stressor at a higher risk of adverse outcomes. Both pre-frailty and frailty are associated with poor patient outcomes and higher healthcare costs. The effect of a prehabilitation programme and standard care on the quality of recovery in pre-frail and frail patients undergoing elective cardiac surgery will be compared.

**Method and analysis** A single-centre, superiority, stratified randomised controlled trial with a blinded outcome assessment and intention-to-treat analysis. Pre-frail and frail patients awaiting elective coronary artery bypass graft, with or without valvular repair/replacement, will be recruited. 164 participants will be randomly assigned to either prehabilitation (intervention) or standard care (no intervention) groups. The prehabilitation group will attend two sessions/week of structured exercise (aerobic and resistance) training, supervised by a physiotherapist, for 6–10 weeks before surgery with early health promotion advice in addition to standard care. The standard care group will receive the usual routine care (no prehabilitation). Frailty will be assessed at baseline, hospital admission and at 1 and 3 months after surgery. The primary outcomes will be participants' perceived quality of recovery (15-item Quality of Recovery questionnaire) after surgery (day 3), days at home within 30 days of surgery and the changes in WHO Disability Assessment Schedule 2.0 score between baseline and at 1 and 3 months after surgery. Secondary outcomes will include major adverse cardiac and cerebrovascular events, psychological distress levels, health-related quality of life and healthcare costs.

**Ethics and dissemination** The Joint CUHK-NTEC Clinical Research Ethics Committee approved the study protocol (CREC Ref. No. 2017.696T). The findings will be presented at scientific meetings, in peer-reviewed journals and to study participants.

**Trial registration number** ChiCTR1800016098; Pre-results.

## Strengths and limitations of this study

- A randomised controlled trial will provide a high-quality assessment of the effect of structured exercise prehabilitation on important patient-centred outcomes, such as quality of recovery, days at home within 30 days of surgery and disability-free survival, after elective cardiac surgery.
- Gain a deeper understanding of how a prehabilitation intervention works by documenting changes in preoperative frailty levels, and the subsequent association of changes in frailty score with postoperative quality of recovery outcome and other major adverse events.
- This study will not include patients who are severely frail and may not be generalizable to other settings with structurally different prehabilitation programmes for cardiac surgery.

## INTRODUCTION

### Frailty

Frailty is a multidimensional syndrome that occurs when multiple small physiological deficits accumulate gradually, eventually resulting in a loss of physiological reserve and adaptability, putting a patient at a higher risk of adverse outcomes.[1] The prevalence of frailty before cardiac surgery varies among studies but generally ranges from 20% to 50%.[2] In older adults undergoing aortic valve replacement, the prevalence of frailty ranged from 26% to 68%, depending on the frailty instruments used and the type of surgical approach used in a multicentre study of 1020 patients from 2012 to 2016.[3] In another study, pre-frailty (Clinical Frailty Scale [CFS] score of 4)[1] was present in 60% of patients undergoing elective coronary artery bypass grafting with or without valve replacement.[4] These results suggest that frailty is becoming a progressively important public health problem. Despite increasing recognition that frail individuals are more vulnerable to sudden changes in health status (stressors),[5 6] most clinicians can identify frailty before surgery but often ignore it.[7]

Preoperative frailty is associated with poorer clinical outcomes and higher healthcare costs in patients undergoing cardiac

surgery. Even adjusting for routine risk scoring systems in cardiac surgery, frailty was associated with a twofold to sixfold increased risk of major adverse cardiac and cerebrovascular events (MACCEs), prolonged hospital stay, in-hospital mortality and 1-year mortality in two systematic reviews.[8 9] In another study, frailty was also associated with a threefold to eightfold increased risk of postoperative delirium.[10] Not surprisingly, the total cost of hospitalisation associated with frailty was high after adjusting for age, gender, predicted risk of mortality and type of cardiac procedure (adjusted additional cost in Canadian dollars: $21 245, 95% CI $12 418 to $30 073; p<0.001).[11]

Vulnerable (pre-frail) patients may also be at risk of poor patient outcomes after cardiac surgery. Compared with non-frail patients, pre-frail patients (CFS of 4) had a longer intensive care unit (ICU) stay (mean difference 2.0 days, 95% CI 1.7 to 2.3), a longer hospital stay (mean difference 3.0 days, 95% CI 1.8 to 4.2), a higher risk of postoperative stroke (HR 1.8, 95% CI 1.3 to 2.5) and a higher risk of in-hospital mortality (HR 1.8, 95% CI 1.5 to 2.3).[4] In patients undergoing transcatheter aortic valve replacement, the cumulative short-term mortality and long-term mortality was higher in the pre-frail group than in the non-frail group (30 days: 1.8% vs 1.3%, 1 year: 8.6% vs 7.2%).[12]

## Prehabilitation

Managing pre-frail to moderately frail patients may be an effective way to prevent, delay or even reverse frailty. Physical activity may be an important component of frailty management. In particular, exercise training has been shown to improve various aspects of physical function of the frail elderly (eg, muscle strength, body composition, mobility, functional status and fall prevention) in a recent systematic review of nine randomised controlled trials (RCTs) (n=1067).[13] Tailored exercise training is hence expected to improve physical fitness and increase functional capacity so that patients are better prepared to withstand the consequences of the physical stress of surgery.[14] In a systematic review, prehabilitation in 643 older adults before orthopaedic surgery had beneficial effects (effect size >0.2) in improving strength, flexibility, balance and speed in five of the seven RCTs.[15] In addition to structured exercise training, many 'surgical schools' also incorporate other health promotion activities, such as smoking cessation, nutritional advice and psychological support to reduce preoperative stress.[16] Preliminary evidence suggests that a brief cognitive behavioural intervention with activity and risk factor reduction goals are more than 90% likely to be cost-effective if the cost per quality adjusted life years was less than £30 000.[17]

Physical therapy before cardiac surgery, especially inspiratory muscle training and breathing exercises, reduced the risk of postoperative pneumonia (risk ratio [RR] 0.45, 95% CI 0.24 to 0.83), postoperative atelectasis (RR 0.52, 95% CI 0.32 to 0.87) and shortened the length of postoperative stay in the hospital (mean difference −3.21 days, 95% CI −5.73 to −0.69).[14] However, the systematic review of eight RCTs (n=856)[14] did not address the potential benefits of total body exercise or assess frailty in the included studies. Also, the external generalisability to our setting is questionable as three of the included studies (n=347) had high prevalence of patients with chronic obstructive pulmonary disease (>20%) compared with a substantially lower prevalence in Hong Kong, where a 5% prevalence of patients with a preoperative history of asthma or chronic obstructive pulmonary disease has been reported.[18]

The timing and duration of prehabilitation programmes before elective cardiac surgery appear to be associated with the risk of postoperative outcomes. In 117 patients undergoing cardiac surgery, randomly allocated to either light physical exercise (1 hour, two times per week) and mental stress reduction or standard care within 2 weeks of surgery, there was little or no benefit on improving perioperative quality of life, length of stay in the hospital (p=0.54) or risk of postoperative atrial fibrillation (p=0.71).[19] In another pilot RCT (n=17), prehabilitation exercise and health promotion (medication use, stress, diet and cardiovascular risk factor management) for 1 hour two times per week for at least 4 weeks showed outcome effectiveness using the 6 min walk test as the primary outcome.[20] Patients in the prehabilitation group were able to walk further by 136 m (95% CI 61 to 209) and increase gait speed by 27% before surgery, both clinically meaningful improvements.[20] A larger RCT with 244 pre-frail to moderately frail participants from the same research group is ongoing to assess the effectiveness of prehabilitation on hospital length of stay.[21] Moderate physical exercise (1 hour, two times per week) for 8 weeks in low-risk cardiac surgical patients was associated with shorter ICU stay (median 1.5 hours, 95% CI 0.2 to 4.5), shorter hospital stay (median 1.0 day, 95% CI 0 to 1.0) and improved quality of life up to 6 months after surgery.[22] Notably, only one of these RCTs[20] measured frailty levels by the 5 m gait speed test and reported changes in frailty levels between prehabilitation groups over time.

The effect of self-reported preoperative physical activity on patient outcomes after cardiac surgery was mixed in a recent systematic review of 11 cohort studies (n=5733), partly reflecting the unreliability of self-reported preoperative physical activity questionnaires.[23] Taken together, these findings suggest that prehabilitation for cardiac surgical patients may be an effective intervention if given over 1–2 months before surgery with objective preoperative measures of physical activity. Whether prehabilitation works by improving frailty levels is not well established. This study attempts to address this knowledge gap. The main hypothesis is that prehabilitation improves the level of postoperative recovery and reduces the risk of adverse outcomes following cardiac surgery by improving frailty levels.

We plan to conduct the PREhabilitation for improving QUality of recovery after ELective cardiac Surgery trial. The primary objectives of the study are

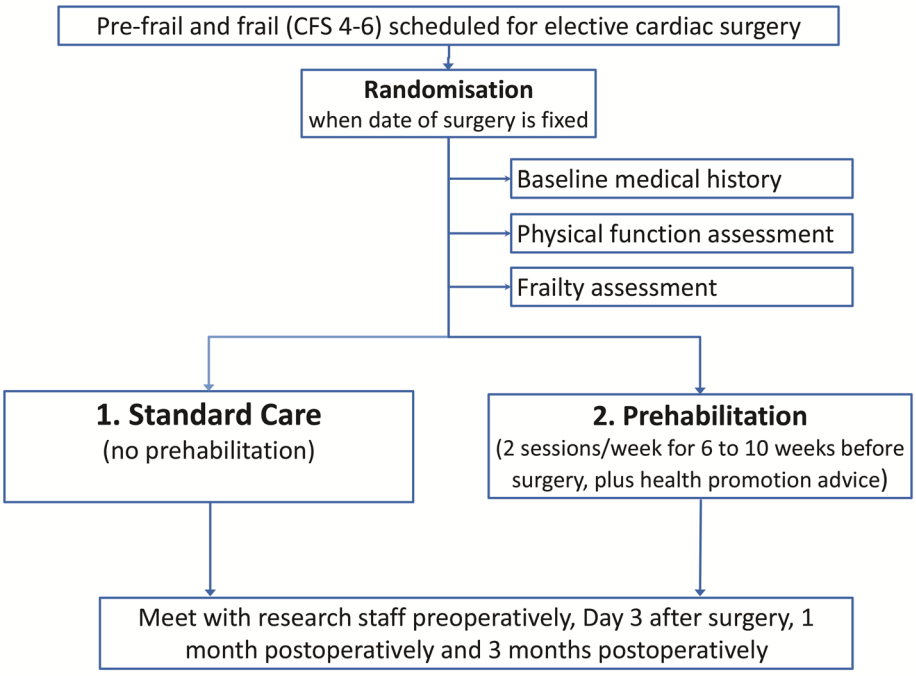


**Figure 1** Patient flow.

1. To examine the effect of prehabilitation on quality of early to short-term recovery after elective cardiac surgery in pre-frail and frail patients.
2. To determine how much the effect of prehabilitation on quality of early to short-term recovery is associated with improved frailty levels.

A secondary objective of the study is to determine if prehabilitation in pre-frail and frail patients is a cost-effective intervention for elective cardiac surgery.

## METHOD AND ANALYSIS

### Trial design

The study design is a single-centre, single-blinded, two-group, parallel, superiority, stratified RCT of 164 adults undergoing general anaesthesia for elective primary cardiac surgery (coronary artery bypass graft, valve replacement or both). The study was developed according to the Consolidated Standards of Reporting Trials statement,[24] and reported with reference to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[25] and its Patient-Reported Outcome Extension (SPIRIT-PRO)[26] statements. The trial has been registered on the Chinese Clinical Trials Registry. An overview of the study design is provided in figure 1. Neither were the patients involved in commenting on the study design nor did they contribute to the editing of this document for readability or accuracy.

### Study setting and population

The study will be conducted at the Prince of Wales Hospital, a university teaching hospital with 1650 beds in Hong Kong. All elective cardiac surgical patients are admitted to our 23-bed ICU for early postoperative care and monitoring with 1:1 nursing at all times, with an expectation of discharge from ICU to a high-dependency cardiac ward within 24 hours after surgery. Currently, 25–30 adults undergo elective coronary artery bypass and/or valvular surgery per month.

### Randomisation and allocation concealment

The stratified randomisation will be a 1:1 allocation according to a computer-generated sequence, using WINPEPI software V.11.65, performed by the one of the investigators (AL) who is not involved in screening, patient recruitment, clinical care or data collection. We will stratify the randomisation into three surgical groups (coronary artery bypass graft with or without valve repair/replacement, isolated valve repair/replacement and transcatheter aortic valve implantation), which have different cardiopulmonary bypass times and recovery profiles, based on case-mix prevalence in order to balance the groups. The treatment allocation will be concealed in consecutively numbered sealed opaque envelopes.

### Eligibility criteria

We will use inclusion and exclusion criteria similar to those used by others.[21] The inclusion criteria are

1. Adults (no age restriction) undergoing elective primary isolated coronary artery bypass grafting, aortic valve repair/replacement, mitral valve repair/replacement or combined coronary artery bypass/valve procedures.
2. Pre-frail to moderately frail patients with a CFS of 4–6 at the time of accepting surgery at the outpatient cardiothoracic surgical clinic.

3. Patients with an estimated 8 or more weeks of surgical waiting list time. One of the coinvestigators (MJU) will ensure that the clinically appropriate listed surgery date is compatible with an optimal prehabilitation time of 6–10 weeks.

The exclusion criteria are

1. Patients with unstable or recently unstable cardiac syndrome (New York Heart Association Class IV, critical left main coronary disease, hospitalisation for arrhythmias, congestive heart failure or acute coronary syndrome before randomisation).
2. Patients with severe left ventricular obstructive disease (severe aortic or mitral stenosis and dynamic left ventricular outflow obstruction).
3. Redo cardiac surgery.
4. Contraindications for prehabilitation, such as those with cognitive deficits who are unable to comply with study procedures, physical limitations that would preclude rehabilitation and inability to regularly attend outpatient prehabilitation sessions, such as those patients who are severely frail (CFS 7–9).

### Participant screening and frailty assessments

For the purposes of this study, we will use three frailty tools to encompass the various domains of the frailty syndrome since there is no 'gold standard' definition for frailty. These domains include physical activity, mobility, energy, strength, cognition, independence and nutritional status.[3] First, the use of the CFS is becoming widespread in the cardiac surgery and ICU settings as it is a simple, quick and highly predictive semiquantitative tool that can be used by nongeriatricians.[3 12 27] The CFS ranges from 1 (very fit) to 9 (terminally ill), with common cut-off categories classified as non-frail (scores 1–3), vulnerable/pre-frail (score 4) and frailty (scores 5–9).[1] Second, the 5 m gait speed has been used as a screening tool for frailty in the Society of Thoracic Surgeons database to predict all-cause mortality and morbidity during the first 30 days after cardiac surgery.[28] Finally, the Essential Frailty Toolset (EFT) is a score from 0 (least frail) to 5 (most frail) derived from the time taken for five chair rises, mini-mental state examination and haemoglobin and serum albumin concentrations.[3] The EFT test had marginally higher discrimination properties for 30-day mortality and worsening disability at 1 year, as well as for mortality at 1 year than the CFS (area under the receiver operating characteristic curve 0.78 vs 0.74).[3] We have chosen these measures based on the need for benchmarking and good diagnostic accuracy properties.

A physiotherapist will first screen patients for their eligibility to participate in the study. Consecutive eligible patients with a scheduled operation date will be recruited into the study. The sealed opaque envelope will be opened after obtaining written informed consent. All patients will have a thorough evaluation of medical history, physical function (6 min walk test [6MWT] for cardiorespiratory fitness testing, 5 m gait speed test as one of the screening tool for frailty and 30 s chair stand test for lower limb muscular strength and endurance testing), recent cardiovascular tests and procedures, current medications (β-blockers, calcium channel blockers, ACE inhibitors/angiotensin receptor blockers, nitrates, aspirin and antiplatelets) and other identifiable cardiovascular risk factors.

### Blinding

A research nurse, collecting the postoperative outcomes (via face-to-face interview and telephone follow-up), will be blinded to treatment allocation to reduce measurement bias. Due to the nature of the intervention and the requirements of informed consent, trial participants may not be blinded to the treatment allocated with certainty. The physiotherapist, cardiothoracic surgeons, ICU and ward staff will not be blinded to intervention allocation because they have access to the patient's electronic record of prehabilitation visits using the Hospital Authority Clinical Management System.

### Interventions

All patients will receive standardised surgical processes and perioperative care under existing protocols for preoperative patient education, standardised anaesthesia,[29] postoperative ICU sedation, analgesia and weaning from mechanical ventilation, perioperative physiotherapy, and early mobilisation. Participants assigned to the control arm of the study (table 1) will be given current usual care without a structured exercise and preoperative health promotion/patient education programme (no prehabilitation).

In contrast, participants randomised to the intervention arm (table 1) will be given prehabilitation (two times per week, supervised by a physiotherapist) in addition to current usual care. Patients will undergo a structured 6–10 weeks of preoperative exercise training to optimise the physical and psychosocial fitness of patients with underlying frailty syndrome before surgery in a dedicated room with gymnasium equipment at the Day Surgery Centre, Prince of Wales Hospital. The result of the submaximal exercise test from the 6MWT will be used as an estimation of individual peak oxygen uptake and hence oxygen uptake reserve ($VO_2R$) for exercise prescription.[30] Individual heart rate performance and subjective perceived exertion will be monitored continuously throughout exercise. Each patient's prehabilitation programme will be individualised and symptom limited, in which exercise prescription and progression will be based on the results of the exercise test, individual health status, exercise performance and training response.

Based on the American College of Sport Medicine guidelines on exercise prescription,[30] the exercise protocol will include 5–10 min warm-up and cool-down activities, 20–60 min of aerobic exercises (with training intensity between 40% and 80% of $VO_2R$), and resistance training using cuff weight, which began with very light-to-light intensity (40%–50% of one repetition maximum), for 10–15 repetitions per major muscle groups of upper

Table 1 Comparison of control and intervention care

| Control group | Treatment group |
|---|---|
| *Standard care*:<br>► Standardised surgical processes and perioperative care under existing protocols for preoperative patient education.<br>► Standardised anaesthesia.<br>► Postoperative intensive care unit sedation, analgesia and weaning from mechanical ventilation.<br>► Perioperative physiotherapy and early mobilisation according to existing protocols. | *Standard care+prehabilitation programme*:<br>► As in control group.<br>► Warm-up activities (5–10 min).<br>► Aerobic exercises in the form of walking/running, stepping, arm cycling and leg cycling (with training intensity between 40% and 80% of oxygen uptake reserve [20–60 min]).<br>► Resistance training (10–15 repetitions:major muscle groups of upper and lower limbs [eg, shoulder overhead press, biceps curl, knee lift and quadriceps extension in sitting and hamstrings curl exercises], one to three sets each).<br>► Cool down activities (5–10 min).<br>► Home exercise programme encouraged.<br>► Preoperative health promotion/patient education.<br>► Education on breathing techniques and daily activities.<br>► Advice on nutrition, smoking cessation and positive psychology support. |

and lower limbs with one to three sets, depending on individual tolerance and performance. A home exercise programme will be encouraged with individualised exercise prescription, monitoring advice and recording sheet so that patients can perform 3–5 days of aerobic exercise per week in total (in the form of walking/running and stepping mainly) and 2–3 days of resistance exercise (same exercises prescribed during supervised sessions). Additional education on breathing techniques and daily activities will be given by a physiotherapist supervising the prehabilitation programme for all participants for consistency. Verbal and written advice on nutrition, smoking cessation and positive psychology support will be given to patients during the prehabilitation programme. Prehabilitation will be offered to those who have completed the whole series of training in order to improve the adherence and compliance at no cost.

## Data collection

The physiotherapist will collect frailty measures (CFS, 5 m gait speed and EFT) before prehabilitation begins in both groups (table 2) and will collect patient's compliance with attendance at prehabilitation visits in order to examine any dose–response effects. The research nurse will collect the following demographic data: age, gender, education level, American Society of Anesthesiologists' Physical Status, predicted mortality using the logistic European System for Cardiac Operative Risk Evaluation (EuroScore), details of surgical procedures, duration of anaesthesia, duration of cardiopulmonary bypass time, ICU admission severity of illness score (APACHE III), duration of mechanical ventilation, ICU length of stay, duration of the hospital stay, discharge destination (home, hospital or nursing aged-care facility), 30-day mortality and 90-day mortality status from the patient's medical record. To reduce detection bias, the research nurse, a blinded outcome assessor, will perform frailty tests at hospital admission and collect CFS scores after surgery in both groups (table 2). Frailty will be a mediator in the causal model relationship between prehabilitation and overall quality of recovery.

## Outcome measures

### Primary outcomes

The patient-centred primary outcomes of recovery will be measured in the early postoperative period, at 1 and 3 months after cardiac surgery (table 2). These include the following:

#### *Quality of recovery*

The Chinese version of the 15-item Quality of Recovery (QoR-15) score will be used on postoperative day 3 after cardiac surgery. It has been recommended as one of the standardised outcomes for assessing patient comfort after surgery.[31] The QoR-15 score includes the items measuring pain, physical comfort, physical independence, psychological support and emotional state.[32] The QoR-15 score ranges from 0 to 150 and takes about 3 min to complete.[32] The validity (convergent, construct, and discriminant), reliability (internal consistency, split-half and test–retest), responsiveness, acceptability and feasibility properties have been well established.[32]

#### *Days (alive and) at home within 30 days of surgery*

The days at home within 30 days of surgery ($DAH_{30}$), which is a patient-centred, generic outcome measure, will be used to measure the patient's overall recovery profile.[33] $DAH_{30}$ is a composite measure that incorporates the details on postoperative hospital length of stay, discharge to rehabilitation centre or nursing home, hospital readmissions, and postoperative deaths.[33] Construct validity has been established with this objective measure in perioperative studies involving cardiac surgical patients.[33] Half-a-day difference is considered clinically meaningful.[33]

#### *Disability-free survival*

The purpose of measuring disability, defined as difficulty or dependency in carrying out the activities of daily living, is that frailty is often a precursor or a coexisting factor

Table 2 Assessments overview*

| Assessment | Baseline (day 0) | Prehospital period | Admission before surgery | POD3/postop ward | POM1 | POM3 |
|---|---|---|---|---|---|---|
| Enrolment | | | | | | |
| Eligibility screen | X | | | | | |
| Informed consent | X | | | | | |
| Demographic data | X | | | | | |
| Comorbidity data | X | | | | | |
| Randomisation | X | | | | | |
| Physical function test (6MWT and chair stand test) | X | | X | | | |
| Intervention | | | | | | |
| Prehabilitation if randomised to the intervention group | | X | | | | |
| Clinical Frailty Scale | X | | X | | X | X |
| Other frailty measures (gait speed and EFT) | X | | X | | X | |
| Outcomes | | | | | | |
| *Primary* | | | | | | |
| Quality of recovery | | | | X | | |
| $DAH_{30}$ | | | | | X | |
| WHODAS | X | | | | X | X |
| *Secondary* | | | | | | |
| MACCE | | | | X | | |
| HADS | X | | X | | X | X |
| EQ-5D | X | | X | | X | X |
| Costs | | X | ---------- | ---------- | ---------- | X |

*Physiotherapist collects baseline and prehospital data, while the research nurse collects all other subsequent data.
$DAH_{30}$, days at home within 30 days of surgery; EFT, Essential Frailty Toolset; EQ-5D, EuroQol EQ-5D Questionnaire; HADS, Hospital Anxiety and Depression Score; MACCE, major adverse cardiac and cerebrovascular event; POD3, postoperative day 3; POM1, postoperative 1 month; POM3, postoperative 3 months; WHODAS, WHO Disability Assessment Schedule; 6MWT, 6 min walk test.

for disability.[2] New or residual disability after surgery is of particular concern to patients and healthcare professionals.[34] In this study, the changes in disability-free survival (baseline and postoperative 1 and 3 months) will be measured using the Chinese (Hong Kong) version of the 12-item WHO Disability Assessment Schedule (WHODAS) 2.0 score that has been validated in surgical patients.[34] It takes about 5 min to complete.[34] The psychometric properties of the WHODAS in postoperative patients include good clinical acceptability, excellent discriminatory validity, moderate convergent validity with EuroQol EQ-5D Questionnaire (EQ-5D), excellent reliability and responsiveness.[34]

Patients will be asked to rate the difficulty in carrying out 12 specified activities on a 5-point Likert scale (0=none to 4=extreme) in the past 30 days. The total score is converted to a scale from 0% (no disability) to 100% (maximum disability), with the following subcategories: none (0%–4%), mild (5%–24%), moderate (25%–49%), severe (50%–95%) and complete (96%–100%) disability.[34] We will use the 25% threshold to define disability and an increase in the WHODAS score of ≥8% from their baseline assessment to define new disability.[34]

## Secondary Outcomes

### *MACCEs during hospitalisation*

MACCEs during hospitalisation (eg, myocardial infarction, delirium, stroke, renal failure, reoperation and mortality) will be collected from the Division of Cardiothoracic Surgery quality-assurance database, which is identical to the dataset of the Society for Cardiothoracic Surgery in Great Britain and Ireland. ICU delirium, defined by a three-times-per-day routine bedside Confusion Assessment Method for the Intensive Care Unit assessments will also be included in the composite outcome. The type of ICU delirium will be further classified as hypoactive, hyperactive or mixed using Richmond Agitation Sedation Scale scores as in our previous study.[35]

### *Psychological distress*

We will use the Chinese (Hong Kong) version of the Hospital Anxiety and Depression Scale (HADS).[36] HADS

is a valid and reliable tool with seven questions relating to anxiety and seven questions relating to depression. For each subscale, the score ranges from 0 to 21, with higher scores indicating a greater severity of disorder. HADS will be measured at baseline, on hospital admission, and at the first and third months after surgery (table 2).

### *Health-related quality of life*

The changes (baseline, hospital admission, and postoperative 1 and 3 months) in health-related quality of life (table 2) will be measured using the Chinese (Hong Kong) version of the EuroQoL EQ-5D.[37] Patients will be asked to rate their mobility, self-care, usual activities, pain/discomfort and anxiety/depression on five levels (no problems, slight problems, moderate problems, severe problems and extreme problems) and to rate their health state from 0 (worst imaginable) to 100 (best imaginable).[37] The descriptive responses will be used to estimate the EQ-5D utilities by applying a set of Hong Kong reference weights.[38] Quality-adjusted life year (QALY) needed for cost-effectiveness analysis will be estimated from multiplying the duration of time spent in a health state by EQ-5D utility.

### *Costs*

The costs of outpatient prehabilitation sessions, ICU and hospital stays, postoperative outpatient visits and readmissions within 3 months will be estimated from the perspective of the Hospital Authority. The physiotherapist staff salary, obtained from the personnel department, will be based on the midpoint of the relevant pay scale. Prices will be based on 2020 costs in Hong Kong dollars.

## Sample size calculation

Group sample sizes of 56 (intervention arm) and 56 (control arm) will achieve 80% power to reject the null hypothesis of equal means when the mean difference is 0.92 (minimal clinically important difference)[39] with a SD of 1.72 for both groups taken from our previous study involving cardiac surgical patients[18] with the nine-item Quality of Recovery (QoR) questionnaire and with a significance level of 0.05 using a 2-sided two-sample equal-variance t-test. Thus, we wish to detect a medium standardised effect size. To incorporate an expected correlation of 0.5 between prehabilitation and frailty for mediation analysis[40] and 10% lost to follow-up, a total sample size of 164 will be needed (82 per group). Our expected correlation of 0.5 is within the results reporting the association between prehabilitation and frailty (r=0.72, 95% CI 0.42 to 0.88).[41] We will be using the QoR-15 tool[32] as a primary outcome and expect it to perform as well as the nine-item QoR tool we had previously used since equivalence has been established.[39] Thus, a clinical meaningful difference of 8.0 with the QoR-15 scale that ranges from 0 to 150 will be expected with the proposed 164 patients.[39] This sample size will also have 80% power to detect a probability of 0.626 that prehabilitation has one more $DAH_{30}$ day (SD 2.2) more than the control group using a Mann-Whitney rank-sum test with a 0.05 two-sided significance level from PASS 14 software (NCSS, Kaysville, UT, USA).

## Statistical methods

Missing data will be checked and imputed using the most common category value for categorical variables or median for continuous variables if there is less than 10% missing data. Otherwise, multiple imputation techniques will be used. The Shapiro-Wilk test will be used to check data for normality. Appropriate multivariate tests, with adjustment to type of surgery (covariate used for stratified randomisation), will be used for group comparisons at baseline. All statistical tests will be performed using Stata V.15 with a two-sided significance level set at $p<0.05$. We will use intention-to-treat analysis for primary analysis, with a per-protocol analysis for sensitivity analysis.

Generalised estimating equation (GEE) models with a Gaussian distribution, identity-link function, unstructured correlation, and robust variance or quantile regression[33] will be used to obtain mean differences in primary outcomes between groups after adjusting for covariates (such as type of surgery, age, gender, physical fitness from the 6MWT and comorbidities) based on clinical relevance and adjustments for a directed acyclic graph[42] to answer the first study objective. Time-varying confounders may include HADS scores, albumin and haemoglobin concentrations. A GEE model with Poisson distribution and log-link function will be used to obtain a common relative risk of MACCE associated with prehabilitation to help answer the first objective. There is no gold standard for defining frailty, and the relative diagnostic ability of individual scores has not been robustly assessed. While acknowledging this limitation, in order to best answer the second objective, frailty measures will be considered as a mediator variable in the causal model relationship between prehabilitation and recovery measures in the above analyses using techniques outlined by VanderWeele.[43] A subgroup analysis between pre-frail (CFS 4) and frail patients (CFS 5 and 6) is also planned to examine if the magnitudes of the association between prehabilitation and quality of recovery differ. To answer another secondary objective, a cost-effectiveness acceptability curve will be drawn to detect differences in the joint cost-effects ($DAH_{30}$ or QALY) relationships between groups using the net-benefit framework.[44] Prehabilitation will be considered as cost-effective if there is a reduction in the overall perioperative treatment cost per gain in $DAH_{30}$ and/or QALYs.

## Patient and public involvement

Patients and the public were not involved in the development of the research question or in the design of the study. Study participants will receive a one-page plain language summary of the results on completion of the study as part of the knowledge translation approach.

## DISCUSSION

The time period before elective cardiac surgery presents opportunities for interventions that may improve postoperative outcomes, and also provides a 'teachable moment' for behavioural and risk factor modification. Lack of physical activity is common (67%) in patients awaiting cardiac surgery,[45] and a decline in functional status has been shown to occur in elderly patients waiting for more than 6 weeks for transcatheter aortic valve implantation.[46] There is a paucity of studies that have examined progression in frailty before surgery, and whether a preoperative structured exercise training combined with nutritional and smoking cessation advice and cognitive/psychological support (prehabilitation programme) can improve the level of frailty in cardiac surgical patients is currently unclear. A home-based exercise programme in a small cohort of cardiac surgical patients (n=20) showed that there was a 12% improvement in CFS scores.[41] Our proposed prehabilitation programme (consisting of aerobic exercise and resistance training, and preoperative health promotion and education) aims at optimising the preoperative well-being of those pre-frail and frail cardiac surgical patients by enhancing their physical and functional statuses and alleviating psychological distress. A physiotherapist-supervised programme can ensure the exercise prescription is individualised, with safety and progression being monitored based on individual performance and tolerance.

It is recognised that both pre-frailty and frailty are associated with poorer patient outcomes. This study will provide important information that will potentially confirm the efficacy of preoperative rehabilitation in order to improve postoperative outcomes for patients undergoing elective cardiac surgery who are pre-frail and frail. The findings will identify those vulnerable and frail patients scheduled for cardiac surgery, quantify its impact on postoperative recovery and determine how much, if any, can be modified by a prehabilitation intervention. A better estimation of the risk of adverse postoperative outcomes and projected health-related quality of life will facilitate decision-making on surgical management and the setting of realistic goals.

A limitation of the study is that only patients who are pre-frail and moderately frail will be recruited. Patients who are severely frail (CFS of 7–9) will be excluded as it is likely that these highly dependent patients will not be able to attend a regular structured outpatient training programme. Second, there is no high-quality diagnostic instrument to define frailty and pre-frailty in cardiac surgical patients apart from the CFS. We will use CFS to screen the patients during recruitment since it is a simple assessment to provide quick and predictive screening in cardiac surgery and ICU settings.[3 12 27] Other frailty assessment tools (5 m gait speed and EFT) will be used in the study to compare and countercheck the frailty status of the participants.

The development and implementation of prehabilitation services are justified if the findings of this study are that prehabilitation can be shown to be effective. In the next decade, there will be greater demands for cardiac surgical services from the expected increase in the ageing population with coronary heart disease,[47] of whom a quarter to half undergoing cardiac surgery will also be frail. If the prehabilitation programme is shown to be effective, those vulnerable and frail patients are likely to benefit by improving their preoperative frailty, enhancing their physical and psychological well-being, and reducing their functional decline, and in turn enhancing their quality of recovery after surgery. The results of the cost-effectiveness analysis will determine if implementation of prehabilitation is worthwhile from the perspective of the hospital system. If favourable results are obtained, prehabilitation may have the potential to be a new standard of care in Hong Kong and internationally.

## ETHICS AND DISSEMINATION

A physiotherapist will explain to the patient the risks and benefits of the study and the time commitment required for the study before surgery is scheduled. Written informed consent will be obtained from the patient. Patients may withdraw from the project without prejudice. Data will be kept confidential in secure offices of the Department of Anaesthesia and Intensive Care. Only group data will be published. Approval for the project has been obtained from The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee. The study will adhere to local laws, Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice and institutional policies.

All adverse events that occur during the waiting list period will be recorded by the research team and reported to the trial management committee. The trial management committee, comprising external and independent clinicians, will review all events within 48 hours and discuss them at regular trial committee meetings. During the prehabilitation sessions, an on-call ICU physician will be available to deal with acute clinical problems.

The results will be disseminated at international conferences and in peer-reviewed journals.

## TRIAL STATUS

The patient recruitment started in July 2018. We expect patient recruitment and 3 months of follow-up to be completed in June 2022.

**Contributors** The protocol was jointly designed and written by DKWY and AL, and was critically reviewed by GMJ, TG, MJU, W-TW and MKHW. All authors approved the final version of the manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee has approved the study protocol on 27 February 2018 (CREC Ref. No.: 2017.696-T).

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## REFERENCES

1. Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
2. Graham A, Brown CH. Frailty, aging, and cardiovascular surgery. *Anesth Analg* 2017;124:1053–60.
3. Afilalo J, Lauck S, Kim DH, *et al*. Frailty in older adults undergoing aortic valve replacement: The FRAILTY-AVR study. *J Am Coll Cardiol* 2017;70:689–700.
4. Rodrigues MK, Marques A, Lobo DML, *et al*. Pre-frailty increases the risk of adverse events in older patients undergoing cardiovascular surgery. *Arq Bras Cardiol* 2017;109:299–306.
5. Clegg A, Young J, Iliffe S, *et al*. Frailty in elderly people. *Lancet* 2013;381:752–62.
6. Rodríguez-Mañas L, Féart C, Mann G, *et al*. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci* 2013;68:62–7.
7. Hubbard RE, Story DA. Patient frailty: the elephant in the operating room. *Anaesthesia* 2014;69 Suppl 1:26–34.
8. Sepehri A, Beggs T, Hassan A, *et al*. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014;148:3110–7.
9. Kim DH, Kim CA, Placide S, *et al*. Preoperative frailty assessment and outcomes at 6 months or later in older adults undergoing cardiac surgical procedures: A systematic review. *Ann Intern Med* 2016;165:650.
10. Jung P, Pereira MA, Hiebert B, *et al*. The impact of frailty on postoperative delirium in cardiac surgery patients. *J Thorac Cardiovasc Surg* 2015;149:869–75.
11. Goldfarb M, Bendayan M, Rudski LG, *et al*. Cost of cardiac surgery in frail compared with nonfrail older adults. *Can J Cardiol* 2017;33:1020–6.
12. Shimura T, Yamamoto M, Kano S, *et al*. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation* 2017;135:2013–24.
13. de Labra C, Guimaraes-Pinheiro C, Maseda A, *et al*. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. *BMC Geriatr* 2015;15:154.
14. Hulzebos EH, Smit Y, Helders PP, *et al*. Preoperative physical therapy for elective cardiac surgery patients. *Cochrane Database Syst Rev* 2012;11:CD010118.
15. Halloway S, Buchholz SW, Wilbur J, *et al*. Prehabilitation interventions for older adults: an integrative review. *West J Nurs Res* 2015;37:103–23.
16. Grocott MPW, Plumb JOM, Edwards M, *et al*. Re-designing the pathway to surgery: better care and added value. *Perioper Med* 2017;6:9.
17. Furze G, Dumville JC, Miles JN, *et al*. "Prehabilitation" prior to CABG surgery improves physical functioning and depression. *Int J Cardiol* 2009;132:51–8.
18. Lee A, Chui PT, Chiu CH, *et al*. Risk of perioperative respiratory complications and postoperative morbidity in a cohort of adults exposed to passive smoking. *Ann Surg* 2015;261:297–303.
19. Rosenfeldt F, Braun L, Spitzer O, *et al*. Physical conditioning and mental stress reduction-a randomised trial in patients undergoing cardiac surgery. *BMC Complement Altern Med* 2011;11:20.
20. Sawatzky JA, Kehler DS, Ready AE, *et al*. Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study. *Clin Rehabil* 2014;28:648–57.
21. Stammers AN, Kehler DS, Afilalo J, *et al*. Protocol for the PREHAB study-Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery: a randomised controlled trial. *BMJ Open* 2015;5:e007250.
22. Arthur HM, Daniels C, McKelvie R, *et al*. 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. *Ann Intern Med* 2000;133:253–62.
23. Kehler DS, Stammers AN, Tangri N, *et al*. Systematic review of preoperative physical activity and its impact on postcardiac surgical outcomes. *BMJ Open* 2017;7:e015712.
24. Schulz KF, Altman DG, Moher D. for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332–702.
25. Chan AW, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
26. Calvert M, Kyte D, Mercieca-Bebber R, *et al*. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO extension. *JAMA* 2018;319:483–94.
27. Muscedere J, Waters B, Varambally A, *et al*. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. *Intensive Care Med* 2017;43:1105–22.
28. Afilalo J, Kim S, O'Brien S, *et al*. Gait speed and operative mortality in older adults following cardiac surgery. *JAMA Cardiol* 2016;1:314–21.
29. Zhu F, Gomersall CD, Ng SK, *et al*. A randomized controlled trial of adaptive support ventilation mode to wean patients after fast-track cardiac valvular surgery. *Anesthesiology* 2015;122:832–40.
30. *American College of Sports Medicine, ed. ACSM's guidelines for exercise testing and prescription*. Philadelphia: Wolters Kluwer, 2018.
31. Myles PS, Boney O, Botti M, *et al*. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. *Br J Anaesth* 2018;120:705–11.
32. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332–40.
33. Myles PS, Shulman MA, Heritier S, *et al*. Validation of days at home as an outcome measure after surgery: a prospective cohort study in Australia. *BMJ Open* 2017;7:e015828.
34. Shulman MA, Myles PS, Chan MT, *et al*. Measurement of disability-free survival after surgery. *Anesthesiology* 2015;122:524–36.
35. Lee A, Mu JL, Chiu CH, *et al*. Effect of motor subtypes of delirium in the intensive care unit on fast-track failure after cardiac surgery. *J Thorac Cardiovasc Surg* 2018;155:268–75.
36. Leung CM, Wing YK, Kwong PK, *et al*. Validation of the Chinese-Cantonese version of the Hospital Anxiety and Depression Scale and comparison with the Hamilton Rating Scale of Depression. *Acta Psychiatr Scand* 1999;100:456–61.
37. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. *Dordrecht, Springer Netherlands* 2014.
38. Wong ELY, Ramos-Goñi JM, Cheung AWL, *et al*. Assessing the use of a feedback module to model EQ-5D-5L health states values in Hong Kong. *Patient* 2018;11:235–47.
39. Myles PS, Myles DB, Galagher W, *et al*. Minimal clinically important difference for three quality of recovery scales. *Anesthesiology* 2016;125:39–45.
40. Mascha EJ, Dalton JE, Kurz A, *et al*. Statistical grand rounds: understanding the mechanism: mediation analysis in randomized and nonrandomized studies. *Anesth Analg* 2013;117:980–94.
41. Waite I, Deshpande R, Baghai M, *et al*. Home-based preoperative rehabilitation (prehab) to improve physical function and reduce hospital length of stay for frail patients undergoing coronary artery bypass graft and valve surgery. *J Cardiothorac Surg* 2017;12:91.
42. Attia JR, Oldmeadow C, Holliday EG, *et al*. Deconfounding confounding part 2: using directed acyclic graphs (DAGs). *Med J Aust* 2017;206:480–3.
43. VanderWeele TJ. *Explanation in causal inference: methods for mediation and interaction*. New York, NY: Oxford University Press, 2015.
44. Hoch JS. Improving efficiency and value in palliative care with net benefit regression: an introduction to a simple method for cost-effectiveness analysis with person-level data. *J Pain Symptom Manage* 2009;38:54–61.
45. Nery RM, Barbisan JN. Effect of leisure-time physical activity on the prognosis of coronary artery bypass graft surgery. *Rev Bras Cir Cardiovasc* 2010;25:73–8.
46. Forman JM, Currie LM, Lauck SB, *et al*. Exploring changes in functional status while waiting for transcatheter aortic valve implantation. *Eur J Cardiovasc Nurs* 2015;14:560–9.
47. The Strategic and Planning Division, Hospital Authority. Hospital authority strategic service framework for coronary heart disease. http://www.ha.org.hk/ho/corpcomm/Strategic%20Service%20Framework/Coronary%20Heart%20Disease.pdf (Accessed 11 Jan 2018).