THE PREHAB STUDY

CLINICAL STUDY PROTOCOL

The PREHAB Study - Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery. A three center prospective, randomized, open, blinded endpoint (PROBE) controlled trial using assessor blinding and intention-to-treat analysis.

Study Synopsis

Title:	**The PREHAB Study** - Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery.	
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Study Design:	A five centre prospective, randomized, open, blinded endpoint (PROBE) controlled trial using assessor blinding and intention-to-treat analysis.	
Expected number of participants:	244 individuals (122 in each arm) split up evenly between five study sites.	
Intervention:	Patients in the *Prehab* group will receive, in addition to the standard of care, a	

	four to eight-week comprehensive exercise therapy and education program at a community-based *CR* facility (see details in appendix). Patients will be asked to complete at least two sessions of supervised, structured exercise class plus have the option to attend one additional exercise class per week for a minimum of four weeks up to the time of their surgery, with progression to a moderate to high-intensity interval program based on the supervised assessment of the patient's capabilities. *Prehab* participants will also attend four education sessions on topics such as risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, exercise, and stress management and promotion of self-managed care.
Duration per participant:	~ 4-8 weeks
Inclusion criteria *(all need to be fulfilled for eligibility):*	1. Patients, aged 60 years or older, undergoing elective isolated coronary artery bypass grafting (*CABG*), aortic valve repair/replacement for moderate aortic stenosis or severe regurgitation, mitral valve repair/replacement for moderate stenosis or severe regurgitation or combined *CABG*/valve procedures. 2. Patients with Clinical Frailty Score (*CFS*) ≥3 (managing well) and < 7 (8 = very severely frail, approaching end-of-life or 9 = terminally ill) at time of acceptance for cardiac surgery. 3. Patients with an estimated ≥ 4 week wait time.
Exclusion criteria *(any of the following factors will result in ineligibility):*	1. Patients who have unstable or recent unstable cardiac syndrome as defined by: • Severe heart failure (*NYHA* IV) or angina (*CCS* class IV) symptoms. • Critical left main (LM) coronary disease. Hospitalization for arrhythmias • *CHF* or acute coronary syndrome prior to randomization. 2. Patients who have severe left ventricular obstructive disease (defined by): • Severe aortic or mitral stenosis (aortic or mitral valve area <1.0cm2 or mean gradient > 40 mmHg or > 10mmHg respectively) • Dynamic left ventricular (*LV*) outflow obstruction. 3. Patients who have demonstrated exercise induced ventricular arrhythmias or have experienced a recent hospitalization for arrhythmias; 4. Patients who have cognitive deficits that would preclude rehabilitation; 5. Patients who have physical limitations that would preclude rehabilitation; 6. Patients who are unable to attend the *Prehab* program.
Primary outcomes:	Proportion of patients with hospital length of stay >7 days
Secondary outcomes:	(1) pre-operative frailty, (2) exercise capacity, (3) physical activity behavior, (4) in-hospital outcomes, (5) 1-year clinical outcomes, (6) 1-year health-related quality of life, (7) cost-analysis.
Safety:	Safety data including new hospitalization, worsening angina or heart failure and arrhythmias will be captured and all adverse events will be reportable to the

	study Data Safety Monitoring Board (*DSMB*). Safety Monitoring: Clinical stability during the pre-habilitation period is to be evaluated twice per week by the *CR* team using clinical questioning in comparison to their baseline stress test. All cases will be reviewed in conjunction with the attending physician.
Statistical methods and sample size calculation:	The sample size calculation was based on the primary objective – determining the effect of *Prehab* on rates of prolonged hospital length of stay > 7 days. Our preliminary data, demonstrated the proportion of frail patients in the Control group with a hospital length of stay > 7 days to be 58.3%. For the *Prehab* group, based on improvements in functional capacity in our pilot RCT and the work by Arthur et al.14, we believe an absolute 20% reduction in proportion of patients that require prolonged hospital length of stay of greater than 7 days, is feasible. A sample size of 194 individuals (97 in each group) will be required for a two-tailed test at an alpha of 0.05 and power of 80%. All patients assigned to the pilot *Prehab* group completed the intervention, however, we are mindful that we will be recruiting frail, elderly patients who may have a higher dropout rate. Hence, we are estimating a 20% dropout rate and plan to recruit 244 individuals (122 in each study arm) to achieve an eventual sample size of 194 after dropout.
Time schedule:	Planned start of study: April 2014 Planned end of study: May 2017 **Planned duration: 3.5 years**

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Terms and Abbreviations

5-GDS	5-point geriatric depression scale. See Appendix II - Five item Geriatric Depression Scale (5-GDS)
6MWT	6 Minute Walking Test. See 3.5.5.4.2 Exercise stress test and 6-minute walk test (6MWT).
ACSM	American College of Sports Medicine. http://www.acsm.org
ADL	Activities of Daily Living. From Older Americans Resources and Services Scale. See http://centerforaging.duke.edu/services/141.
ANOVA	Analysis of Variance
CABG	Coronary Artery Bypass Graft
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit. See http://www.icudelirium.org/docs/CAM_ICU_training.pdf
CCS	Canadian Cardiovascular Society.
CES-D Scale	The two-item Center for Epidemiologic Studies Depression (CES-D) Scale. See http://www.scireproject.com/outcome-measures-new/center-epidemiological-studies-depression-scale-ces-d-and-ces-d-10
CFS	Clinical Frailty Score
Charlson Co-morbidity Index	See http://www.ncbi.nlm.nih.gov/pubmed/3558716?dopt=Abstract
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease.
CR	Cardiac Rehabilitation program. See 3.5.5.3 Core Components of Cardiac Rehabilitation.
CRF	Case Report Form
CVD	Cerebrovascular Disease
DSMB	Data Safety Monitoring Board
EQ-5D	EuroQual-5D (EQ-5D). See http://www.euroqol.org/.
EuroSCORE II	See http://www.euroscore.org/calc.html.
FI	Frailty index.
Functional Co-morbidity Index	See http://www.ncbi.nlm.nih.gov/pubmed/15878473.
GXT	Graded maximal exercise stress test. See 3.5.5.4.2 Exercise stress test and 6-minute walk test (6MWT)
HQP	Highly Qualified Personnel
HREB	Human Research Ethics Board
HRQoL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICU	Intensive Care Unit.
iKT	Integrated Knowledge Translation
IQR	Interquartile Range
LM	Left Main coronary artery
LOS	Length of Stay.
LV	Left Ventrical
MACCE	Major Adverse Cardiac and Cerebral Event
MI	Myocardial Infarction
MoCA	Montreal Cognitive Assessment. See http://www.mocatest.org/.
Modified	See Appendix I - Modified Fried Criteria (1-7)

MVPA	Moderate to Vigorous Physical Activity
NYHA	New York Heart Association. http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp
OARS scale	Older Americans Resources and Services Scale. See http://centerforaging.duke.edu/services/141.
PREHAB	Title of study. "Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery."
Prehab	Refers to the preoperative cardiac pre-habilitation study intervention. For complete definition see section 3.5.5 Prehab Intervention.
PROBE	Rrospective, Randomized, Open, Blinded Endpoint trial.
PVD	Peripheral Vascular Disease.
RASS	Richmond Agitation and Sedation Scale. See http://www.icudelirium.org/docs/RASS.pdf
RCT	Randomized Controlled Trial
REDCap	See http://project-redcap.org/.
ROC analysis	Receiver Operating Curve analysis.
SF-12v2	The Short Form-12 (SF-12v2)
SPPB	Short Physical Performance Battery. See http://www.ndorms.ox.ac.uk/prove/documents/assessors/outcomeMeasures/SPPB_Protocol.pdf
StandC	Standard Care (control group)
STS-PROMM	See http://riskcalc.sts.org/.
TECH VALUE NET	Technology Evaluation in the Elderly Network
TPA	Total Physical Acitivty

Executive Summary

Background: More than half of all cardiac surgeries in Canada are performed on patients aged 65 years and older. Although cardiac surgery is generally safe, there is evidence indicating that elderly patients who are frail prior to surgery have a longer hospital length of stay in addition to higher rates of major complications and mental health disorders after surgery, as compared to non-frail, elderly patients. Therefore, it is critically important for the health care team to identify strategies that will provide improved patient outcomes through appropriate, safe and effective care for frail elderly patients, and furthermore will engage and empower patients in ongoing self-managed care. In Canada, when a patient requires heart surgery, they are placed on a "waiting list". Patients can wait for elective heart surgery for as long as 3-4 months. Fortunately, this waiting system is "safe" and very few patients die while waiting for heart surgery. However, many patients on the waiting list experience feelings of powerlessness and are fearful of "making things worse", which cause them to stop being active and to become even more weakened prior to their operation. A solution to address this problem is to "de-frail" the high-risk patient to ensure that they are better prepared to survive and thrive after cardiac surgery.

Objective: We anticipate that the proposed project will inform clinical practice and facilitate the development of a treatment that will ensure that older patients both survive and thrive after their heart operation.

Methods: We will conduct a clinical trial where frail patients waiting for heart surgery are randomly chosen to either receive the current standard of care or to participate in a 4-8week exercise/education "Pre-habilitation" program at a community-based cardiac rehabilitation facility in one of five cities (Winnipeg, MB; Saint John; NB; Halifax, NS; Montreal, QC; Saint-Foy, QC). Patients who refuse to be randomized or are deemed "unsafe" to participate in the exercise portion of the study but still wish to participate will be enrolled in a follow up registry. We will also plan to work with local health authorities and national advocacy bodies to ensure that this program is sustainable in the real-world in the future.

Significance/Impact: The geriatric population is one of the fastest growing demographics undergoing cardiac surgery in North America (1)(2). With this, the geriatric syndrome, defined as a "constellation of symptoms and signs [that] describe the heterogeneous response of older adults to physiological and metabolic challenges,"(3) has become an important consideration in patients undergoing cardiac surgery. To date, no high-quality study has prospectively examined the impact of preoperative cardiac rehabilitation in the frail-elderly undergoing cardiac surgery and represents a noticeable knowledge gap. The *Prehab* study is specifically aimed to improve the care and establish best practice in frail elderly patients undergoing high-risk cardiac surgery procedures through a rigorous evaluation of the utilization of an inter-disciplinary and multimodal patient optimization protocol. Importantly, we have also planned for a detailed study analysis by key stakeholders at the health region level to determine optimal methodologies to implement this program following the completion of this investigation. Reducing anxiety, improving exercise capacity, promoting a healthy lifestyle that is durable (i.e. long-lasting) and improving *HRQoL* in the elderly are the over-riding goals of this endeavour.

1 General Information

1.1 Title

The *PREHAB* Study - Pre-operative Rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery.

1.2 Study Management Committee

Rakesh C. Arora (project leader), Todd Duhamel (co-site lead Winnipeg), Ansar Hassan (site lead Saint John), Nicholas Giacomantonio (site lead Halifax), Yoan Lamarche (site lead Montreal), Navdeep Tangri, Thang Ngoc Nguyen, Sarvesh Logsetty, Jitender Sareen, Colleen Metge, Hilary Grocott, Jo Anne Sawatzky, Kenneth Rockwood, Sean Bagshaw, Jonathan Afilalo, Jean-Francois Legare.

1.3 Coordinating Centre

The St. Boniface Hospital/I.H. Asper Clinical Research Institute will be the coordinating centre and data custodians for this national study. All data management and analysis will be conducted at the St. Boniface Hospital.

2 Background and Rationale for Project

2.1 Introduction

Growing burdens of heart disease in an aging population has resulted in cardiac surgery being offered to older and increasingly frail patients with multiple co-morbidities. Newer minimally invasive procedures are now being performed in very frail octo- and nonagenarian patients previously deemed inoperable. By 2031, 25% of Canadians will be older than 65 years and by extension, greater numbers of frail elderly will be offered cardiac surgery. As such, it has become critically important for the health care system to develop strategies to improve clinical outcomes and provide patient and caregiver support. In Canada, when a patient requires elective cardiac surgery, they are placed on a "waiting list" for as long as 3-4 months. While this waiting system is safe and very few patients die while waiting for heart surgery, we (see *3.1.1 Preliminary Data Informing Study Methodology*) and others have identified that patients on surgical waitlists engage in very little physical activity as they wait "in fear, and feel powerless". This can be problematic for the already deconditioned frail, elderly patient as at present, there is no formal process for engaging frail elderly patients during this wait period.

2.2 Exercise Rehabilitation

Cardiovascular rehabilitation has been proven to decrease morbidity and mortality in patients with established and unrepaired cardiac disease(4)(5)(6)(7)(8), and to be safe in patients who are elderly,(9)(10)(11)(12)(13) and have heart failure (7)(14)(15)(16) in both hospital and community-based programs. (6)(17)(18) The proposed *Prehab* intervention has been designed with consultation with the 4 cardiac rehabilitation program sites involved in the project and according to the evidence-based best-practice guidelines published by the Canadian Association of Cardiac Rehabilitation(19), the recently published Canadian Cardiovascular Society Quality Indicators for cardiac rehabilitation(20) and the *ACSM* guidelines for exercise prescription in patients with cardiovascular disease (see http://www.acsm.org/docs/current-comments/exercise-for-persons-with-cardiovascular-disease.pdf). (21)All patients, in both aspects of the study, are automatically referred to participate in a postoperative *CR* program, of their own accord, after their cardiac surgery as part of current standard of care.

2.3 Identification of Potential Opportunity

This wait period, therefore, presents a significant opportunity to optimize preoperative risk factors in these vulnerable patients. The *Prehab* study (an interdisciplinary model of care to maximize the physical, nutrition, psychological reserve and cardiac risk profile of "frail" elderly patients undergoing cardiac surgery) will aim to "de-frail" the high-risk elderly patient so as to improve their post- cardiac surgical outcomes, engage patients in active health self-management and provide knowledge translation for the implantation of best practices for this patient population (See *Figure **1***, Table 1, Table 2, Table 3).

2.4 The *PREHAB* Study – Primary Research Questions/Hypotheses

The primary research question(s) for the *Prehab* study include:

i. What is the effect of a preoperative cardiac pre-habilitation ("*Prehab*") program on the proportion of patients with hospital length of stay (*LOS*) > 7 days.
   We hypothesize that the performance of a multifaceted, interdisciplinary cardiac "*Prehab*" program in patients awaiting an elective cardiac surgery will reduce the proportion of frail elderly patients requiring a postoperative hospital *LOS* > 7 days.
ii. What is the effect of a preoperative cardiac pre-habilitation program in high-risk frail elderly patients on (1) pre-operative frailty, (2) exercise capacity, (3) self-managed physical activity behavior, (4) in-hospital outcomes, (5) 3-month clinical outcomes, and (6) 3 month health-related quality of life.
   We hypothesize that the "*Prehab*" program for frail elderly patients awaiting an elective cardiac surgery will reduce frailty, improve exercise capacity, improve self-managed physical activity behavior, improve in-hospital outcomes, improve clinical outcomes 3 months and 1 year postoperatively, and improve health-related quality of life.

3 Study Design

3.1 Methodological Approach

The *Prehab* comprehensive inter-disciplinary program is intended to intervene to decrease frailty in high-risk elderly patients undergoing cardiac surgery.

Knowledge Gap – Will *Prehab* work in the frail, elderly?

Cardiovascular prevention and rehabilitation is a well-established and proven standard of care to decrease morbidity and mortality in patients with established and unrepaired cardiac disease.(4)(5)(6)(7)(8) In a landmark study by Arthur et al, 249 low-risk patients awaiting elective *CABG* were randomized either to an eight-week preoperative cardiac pre-habilitation (*Prehab*) program or to the usual care.(22) *Prehab* patients completed 2 exercise sessions per week and attended education classes on risk factor modification. These patients experienced shorter intensive care unit (*ICU*) and hospital lengths of stay (*LOS*) post-operatively and an improved quality of life compared to the controls, which persisted for 6 months following surgery. However, while this seminal study demonstrated the potential benefits of a "*Prehab*" program, this study was performed in younger, lower-risk patients and therefore did not address the needs of the frail, elderly patients currently being referred for cardiac surgery.

3.1.1 Preliminary Data Informing Study Methodology

The following two groundwork investigations have informed the safety and efficacy of the *Prehab* intervention and the design of the proposed phase II, randomized trial – the *Prehab* Study. We believe that the *Prehab* intervention will be able to "de-frail" high-risk elderly patients preoperatively

and will lead to sustainable motivational changes to engage in long-term healthy living following their cardiac procedure. The implications are that this will be ultimately transferable to percutaneous cardiac intervention and other non-cardiac surgery procedures in the frail elderly.

3.1.1.1 Frailty in the Cardiac Surgery Population at St. Boniface Hospital

We undertook a systematic review of frailty in the elderly undergoing cardiac surgery (see *Table 2* & *Table 3*).(23)(24)(25)(26)(27)(28)(29)(30)(31) This review demonstrated an association with increased frailty and a major negative outcomes ranging from increased institutional care to major adverse cardiac and cerebral event (*MACCE)* and increased in-hospital and long-term mortality after cardiac surgery. However, the lack of a standardized and comprehensive definition of frailty in these studies prevents clarity in understanding the interaction of frailty in the elderly and cardiac surgery. We subsequently completed a prospective examination of frailty in 133 consecutively consenting elderly cardiac surgery patients with high-levels of co-morbid disease (See *Table 4*, *Table 5*, *Table 6* and *Figure 2*). Two definitions of frailty were used (see *Appendix I*): (1) *Modified Fried criteria*: (32)(33)(34) a patient was deemed "frail" if they met ≥3 of the following 7 criteria: slowness (5m gait speed)(35), weakness (handgrip strength measurement)(36) and questionnaires assessing self-reported weight loss, exhaustion (the two-item Center for Epidemiologic Studies Depression (*CES-D Scale*), depression (the 5-point geriatric depression scale (*5-GDS*)(37)(38)), low physical activity (the Paffenbarger Physical Activity Index(39)(40)(41)(42)), and cognitive impairment (the Montreal Cognitive Assessment (*MoCA*)(43)(44)(45)). (2) Short Physical Performance Battery (*SPPB*): a patient was deemed "frail" if his/her composite score was ≤9 based on 5m gait speed, balance tests, and the repeated chair stand test (each scored from 0 to 4)(46). Using the modified Fried or the SPPB criteria, 72 (54.1%) or 69 (51.9%) (respectively), patients studied were deemed frail (See *Table 3*). Frail patients were older, more commonly female, had higher *EuroSCORE II* values (a cardiac surgery specific mortality risk prediction score) and lower self-health ratings. Diabetes, cerebrovascular disease (*CVD*), chronic obstructive pulmonary disease (*COPD*), arthritis, anemia, peripheral vascular disease (*PVD*), and lower serum albumin were also significantly associated with being frail. Notably, frailty correlated with clinically important measures of increased hospital *LOS*: total adjusted hospital *LOS* (median 6 days (IQR: 5 – 9) in non-frail vs. 8 days (IQR 6 – 12) in "frail" patients, $p<0.001$) and a greater proportion of patients in hospital > 7 days (37.7% in non-frail vs. 58.3% in frail patients, $p < 0.02$; See *Table 4* & *Table 5*). This longer hospital stay amongst frail patients has implications for increased healthcare costs and we have observed an association between new and persistent mood disorders and reduced engagement in postoperative physical activity with a hospital LOS > 7 days after cardiac surgery.

3.1.1.2 A Pilot RCT of a Pre-habilitation program

We have completed a pilot, randomized control trial (manuscript proof in appendix), to demonstrate the safety and feasibility of a *Prehab* program for elective coronary artery bypass graft (*CABG*) patients. The primary outcome was walking distance based on a 6-minute walk test (*6MWT*). Secondary outcomes included 5m gait speed (23) and cardiac rehabilitation (*CR*) attendance Postop.

Improving Patient Outcomes

Fourteen patients (*StandC*, n=7; *Prehab*, n=7) completed the study (77% and 88% completion rate, respectively). None of the *Prehab* patients developed cardiac symptoms during study participation. Walking distance and gait speed remained unchanged in the Standard care group. Conversely, patients in the *Prehab* group increased their walking distance by +132 and +145 meters and gait speed improved in all seven *Prehab* group participants by 27% and 33% at Pre-op and Post-op, respectively ($p<0.05$).

Engaging and Empowering Patients:

A notable finding of our pilot study was the sustainability of patient self-management, as supported by a higher post-operative cardiac rehabilitation (*CR*) enrollment amongst *Prehab* (100%) than *StandC* (43%) participants.

3.2 Study Design, Setting, Population

Prehab will be a five centre prospective, randomized, open, blinded endpoint (*PROBE*) (47) controlled trial using assessor blinding and intention-to-treat analysis. The study will be conducted at four academic, tertiary care hospitals (St. Boniface Hospital, Winnipeg, MB, Queen Elizabeth II Health Sciences Centre, Halifax, NS, Montreal Heart Institute, Montreal, QC, Quebec heart and lung institute, Saint-Foy, QC) and one non-academic hospital (Saint John Regional Health Centre, Saint John, NB) that perform cardiac surgery. These sites were chosen based on similar patient populations and surgical waitlist times (48)(49). Additionally, each of these sites are partnered with one or more community-based cardiac rehabilitation (*CR*) centres, which are certified medical fitness facilities dedicated to improving the health of the community through health promotion, disease prevention and rehabilitation services. These facilities offer expert guidance from certified professionals, innovative health enhancement programs, and provide integrated medical, rehabilitative and fitness services.

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria (all need to be fulfilled for eligibility)

1) Patients, aged 60 years or older, undergoing elective isolated coronary artery bypass grafting (*CABG*), aortic valve repair/replacement for moderate aortic stenosis or severe regurgitation, mitral valve repair/replacement for moderate stenosis or severe regurgitation or combined *CABG*/valve procedures.
2) Patients with Clinical Frailty Score (*CFS*) ≥3 (managing well) and < 7 (8 = very severely frail, approaching end-of-life or 9 = terminally ill) at time of acceptance for cardiac surgery.
3) Patients with an estimated ≥ 4 week wait time.

3.3.2 Exclusion Criteria (any of the following factors will result in ineligibility)

1) Patients who have unstable or recent unstable cardiac syndrome as defined by:
    a. Severe heart failure (*NYHA IV*) or angina (*CCS class IV*) symptoms.
    b. Critical left main (*LM*) coronary disease.
    c. Hospitalization for arrhythmias, CHF or acute coronary syndrome prior to randomization.
2) Patients who have severe left ventricular obstructive disease as defined by:
    a. Severe aortic or mitral stenosis (aortic or mitral valve area <1.0cm^2 or mean gradient > 40 mmHg or > 10mmHg respectively)
    b. Dynamic left ventricular (*LV*) outflow obstruction.
3) Patients who have demonstrated exercise induced ventricular arrhythmias or have experienced a recent hospitalization for arrhythmias.
4) Patients who have cognitive deficits that would preclude rehabilitation.
5) Patients who have physical limitations that would preclude rehabilitation. (Unless they have agreed to participate in the follow-up registry)
6) Patients who are unable to attend the *Prehab* program. (Unless they have agreed to participate in the follow-up)

3.4 Operational Definitions

3.4.1 Baseline Clinical Characteristics

Preoperative patient demographics, cardiac risk profile, procedure data, surgical risk scores (*EuroSCORE II* and *STS-PROMM*(50)(51)(52)), medical history and medication profile, cardiac risk factors

and cardiac illness severity are routinely collected for all patients in the pre-existing site surgical databases which will be utilized for this study. Each site will also collect co-variates of co-morbidities (*Charlson Co-morbidity Index*, *Functional Co-morbidity Index* (53), *OARS scale* for activities of daily living (*ADL*) and instrumented activities of daily living (*IADL*)(54) as well as postoperative complications and postoperative hospital *LOS*. In order to avoid issues caused by delayed hospital discharge due to non-medical reasons, patients will be evaluated daily for "readiness for discharge" using a standardized set of criteria. Cognitive function will be measured using the Montreal Cognitive Assessment (*MoCA*) (43)(44)(45).

3.4.2 Frailty Assessments

Our strategy for rapid screening of frailty in a large volume of clinic patients will be to use the 9-point Clinical Frailty Scale (*CFS*) (56)(See *Figure **4*** and appendix). The *CFS* is the simplest tool to implement at multiple centres, has a high inter-observer reliability and shows good performance (by *ROC analysis*) for risk of death or institutionalization. Due to the need to screen a large number of individuals (785 patients; ***Figure 5***) the use of the *Modified* and *SPPB* are less practical to implement as routine practice in the outpatient clinic sites. Therefore our approach is to use a *CFS* score of ≥ 3 as the initial indication of frailty (57) . This approach will allows us to estimate degrees of frailty in a large volume of patients in a rapid, cost-effective and highly feasible manner. All enrolled patients will be further assessed using the modified Fried criteria(33)(32)(34), and a reduction of frailty will be defined as a binary value (i.e. frail/non-frail) using these criteria(33)(32)(34).

The *SPPB* criteria will be used as a third measure.(46) As a fourth measure, our data collection protocol will also enable a Frailty Index (*FI*) calculation.(29)(56)(58)(30) The inclusion of the more definitive frailty evaluations are intended to gain more information about the different domains of frailty in the elderly to further improve the clinical frailty assessments that will be used in the future. To ensure reliability of this approach, we have compared the three measures of frailty (*CFS*, *Modified* and *SPPB*) on 169 elective cardiac surgery patients at the St. Boniface Hospital. The spearman correlation was ~0.65 for all three comparisons and the Cohen's Kappa, which is a concordance measure between the different frailty definitions is ~0.50. These values indicate a moderately strong link between all three measures; however it is possible that they capture somewhat different domains of frailty.

3.4.3 In-Hospital Outcomes

Postoperative *ICU* and hospital *LOS*, 30-day mortality, major adverse events (death, *MI*, stroke or renal failure requiring dialysis) will be collected using existing site surgical databases. Post-operative *CR* enrollment will be assessed using administrative data from the participating *CR* centers.
In our preliminary analysis, we have identified a strong association between frailty and the occurrence of delirium (Table 5). The participating Cardiac *ICU*s currently perform an agitation and delirium assessment once every 8 hours as standard practice. Delirium assessment will be performed in the ICU using the Richmond Agitation-Sedation Scale (*RASS*)(59) and the Confusion Assessment Method for the Intensive Care Unit (*CAM-ICU*). (60)(61)(62). As part of standard of care a blood sample will be collected upon placement of the arterial line in the operating room to ascertain the patient's sodium, potassium, glucose, white blood cell count, hematocrit, creatinine and albumin and this data will also be collected.(49)(65)

3.4.5 Three-Month Clinical Outcomes and Health-Related Quality of Life (HRQoL)

The EuroQual-5D (*EQ-5D*)(66) will be administered preoperatively and at 12 weeks (time of routine surgical follow-up). The EQ-5D is a validated measures of *HRQoL* and was selected due to its simplicity and proven clinical relevance. (67)(68)(69)

3.4.6 One-Year Clinical Outcomes and Health-Related Quality of Life (HRQoL)

The EuroQual-5D (*EQ-5D*) will be administered preoperatively and at 1 year following surgery. The EQ-5D is a validated measures of *HRQoL* and was selected due to its simplicity and proven clinical relevance.

3.4.7 Physical Activity

We will assess exercise capacity using a 6-minute walking test (*6MWT*). The *6MWT* is a practical and simple test that has is a negative correlation between total distance walked and length of hospital stay (r= -0.62) (70) and is suitable for use amongst patients with moderate-severe heart and lung disease. (71)Physical activity behavior will be measured using multi-directional accelerometers over a seven-day period, based on the methods described by Colley et al. (72) We have previously used these approaches to assess physical fitness and activity amongst cardiac patients.

3.4.8 Patient Interview Questionnaires/Instruments – The Interview Package

The following questionnaires will be completed at baseline, preoperatively, 3-months following surgery and one year following surgery for both arms of the study. The questionnaires will be administered using the REDCap software with the participant completing the survey on a computer.

1. Seattle Angina Questionnaire (SAQ)
2. Kansas City Cardiomyopathy Questionnaire (KCCQ)
3. Montreal Cognitive Assessment Form (MoCA)
4. 5-Item Geriatric Depression Scale (GDS-5)
5. Generalized Anxiety Disorder 7 Item Scale (GAD-7)
6. OARS Scale for Activities of Daily Living (ADL)/Instrumental Activities of Daily Living (IADL)
7. EuroQol 5-Dimension 5-Level (EQ-5D5L)
8. EuroQol Visual Analog Scale (EQ-VAS)
9. Paffenbarger Physical Activity Scale
10. Nutrition/Exhaustion Questionnaire
11. Self-efficacy for Exercise Questionnaire
12. Baseline Demographics (only done once at baseline)

Patients who prefer to enrol in the registry will not complete any preoperative questionnaires. They will be contacted over the telephone at 3-months and one year following surgery and complete the following questionnaires:

1. Demographic information
2. Generalized Anxiety Disorder 7 Item Scale (GAD-7)
3. Geriatric Depression Scale (GDS)
4. OARS Scale for Activities of Daily Living (ADL)/Instrumental Activities of Daily Living (IADL)

3.4.9 Data Collection Instruments – The Data Collection Package

The following variables will be collected for participants in both arms of the trial, as well as the registry. This information will be obtained from existing electronic databases as well as hospital charts.

1. Patient Demographics/Hospital Length of Stay
2. Preoperative Cardiac Information
3. Preoperative Comorbidities
4. Lab Results (pre and post-op)
5. Echocardiogram Information
6. Angiogram Information
7. Procedure Information

8. Medications (pre and post-op)
9. Post-Operative Delirium
10. Post-Operative Complications
11. 30 Day Readmission
12. 12 Month Readmission

3.5 Study Protocol

3.5.1 Screening implementation Plan

Following training, clinicians will complete a *CFS* score for every new cardiac surgery consult at each of the participating sites. Patients with a *CFS* ≥ 3 will be eligible for enrolment and notification will be sent to the site coordinator. Patients who are eligible for the study (CFS ≥ 3) will either be consented in person or via telephone consent process. Patients with a *CFS* ≥ 3 that either refuse to be randomized or are deemed "unsafe" will be given the opportunity to enroll in a follow up registry.

3.5.2 Safety and Baseline Assessments

A medical director, at each site, will oversee all cases and ensure patient eligibility and safety for program initiation and throughout program attendance for the study duration. All eligible and consented patients will be evaluated at baseline to ensure angina stability. Exercise prescription will be determined utilizing the standard practice of the Karvonen Equation adjusted according to pre-program exercise stress test. (21)Patients will also undergo a standard *6MWT* (73)(74)(75)(76)(77)(78) and will repeat the *6MWT* at the preoperative time point in both the control and *Prehab* groups to determine impact of the intervention. The *6MWT* was chosen because it requires minimal infrastructure and personnel to complete and has been demonstrated to be a valid prognostic tool for patient outcomes and is comparable to an exercise-stress test. (73)(75)(76)(77)This approach enables us to avoid potential scheduling issues that occur if a patient's surgical date is moved up.

Patients who are deemed appropriate for enrolment into study will be randomized, following the completion of the baseline data collection, to one of two trial arms – control (standard of care (*StandC*) or treatment (*Prehab*). Baseline risk factor evaluation, anthropometrics, clinical markers, patient questionnaires (including frailty scores, cognitive assessment, and quality of life data) and physical activity data measured using accelerometers will be collected for all patients and repeated pre-operatively and at three-month follow up. Safety data including new hospitalization, worsening angina or heart failure and arrhythmias will be captured and all adverse events will be reportable to the study Data Safety Monitoring Board (*DSMB*). All patients in both groups will be referred to postoperative *CR* programming, as per local practice.

3.5.3 Randomization

Trial Randomization using *REDCap*: The Randomization Module within *REDCap* allows researchers to randomly assign participants to specific groups. Dr. Logsetty has experience and will be responsible for study randomization. Assessors of pre- and post-operative data will be blinded to treatment group allocation.(47)

3.5.4 Standard care

Patients in the *StandC* group will receive care as is currently delivered to patients awaiting cardiac surgery at each site. At present, patients are advised to rest and participate in very light intensity physical activity while awaiting surgery. At 1-2 weeks prior to their scheduled surgical date, the patient attends a single three hour cardiac pre-assessment with a nurse practitioner and cardiac anesthesiologist. In addition, a cardiac nurse counsels each patient on healthy behaviors (e.g. smoking cessation, diet, exercise).

3.5.5 *Prehab* Intervention

Patients in the *Prehab* group will receive, in addition to the above standard of care, an eight-week comprehensive exercise therapy and education program at a community-based *CR* facility. This program will target both the physical and psycho-social-cognitive aspects of cardiac disease and frailty. In brief, participants will be required to complete an intake health status assessment by the *CR* team including a physiotherapist, cardiovascular nurse, and dietitian and complete a symptom-limited graded exercise stress test according to the American College of Sports Medicine Guidelines for Exercise Testing and Prescription 7th Edition.(79) Patients will be asked to complete at least two sessions of supervised, structured exercise class plus have the option to attend one additional exercise class per week for eight-weeks, with progression to a moderate to high-intensity interval program based on the supervised assessment of the patient's capabilities. This has been shown to be safe and effective in unrepaired heart failure and elderly patients.(7)(8)(9)(14)(16)(80)(81) *Prehab* participants will also attend four education sessions on topics such as risk factor reduction, medication use, cardiovascular physiology, smoking cessation, healthy eating, exercise, and stress management and promotion of self-managed care.(82)(83)(84) Principles of shared decision-making will be utilized with the *Prehab* intervention, where training for providers and patients involved in the intervention will have shared control of treatment decisions.(82)(83)(84)

Participants in the intervention group will receive a baseline health assessment at their local cardiac rehabilitation facility. This assessment will include the facility's standard health and fitness assessment: health screening, blood pressure, lung function, lab work, and body composition. This assessment will provide the basis for an individualized exercise prescription, to include an 8 week, individualized, symptom limited, exercise program.

Briefly, patients will be required to attend a minimum of 2 structured exercise sessions per week. The program will last a total of 8 weeks, or until the patient undergoes their cardiac procedure (minimum of 4 weeks for data collection purposes). Patients will be encouraged to walk daily in addition to attending the scheduled exercise sessions. Exercise will be prescribed according to standardized procedures at the medical fitness facility for their cardiac rehabilitation program. Briefly, participants will complete a warm-up/stretching session of approximately 15 minutes at the beginning of each session. Aerobic exercise will be prescribed at 40-60% of heart rate reserve (Karvonen Formula) based on baseline exercise stress test data. Aerobic exercise will last approximately 10-30 minutes depending on individual tolerance and level of conditioning. Aerobic prescription will progress to high intensity exercise in the context of symptom-limited, interval training up to 85% of maximal aerobic capacity based upon recommendations by the cardiologist. Individual interest will determine the modality of exercise chosen. Options will include walking, cycling, stretching and resistance training with body weight or resistance bands following clearance by a cardiologist. Intensity will be progressed based on close communication between healthcare providers and participants. Sessions will be concluded with a 10-minute cool down period.

In addition to the exercise program, patients will be required to participate in 4 educational sessions tailored to self-management for cardiac rehabilitation. Examples of educational sessions offered by professional staff at the medical fitness facility include:

Exercise and Action Planning (Kinesiologist)
Risk Factor Modification (Nurse/Physiotherapist)
Cardiac Electrical System (Nurse/Physiotherapist)
Cardiac Circulation (Nurse/Physiotherapist)
Cardiac Muscle Function (Nurse/Physiotherapist)
Resistance Training (Kinesiologist)
Body-Mind Connection (Social Worker)

Heart Healthy Eating (Dietician)
Looking Forward; transitions, barriers, self-management (Kinesiologist)
Diabetes Education (Dietician)
Emotional Impact of Heart Disease (Social Worker)
Label Reading (Dietician)
Preventing Relapse (Social Work)
Stress Busters (Psychologist)
Tracking Food Choices (Dietician)
Smoking Cessation (Social Worker)
Relaxation Techniques (Psychologist)

Participants in the intervention group will be asked to keep a log of their attendance at both the exercise and educational session. Additionally, an exercise log completed by individual patients will track the mode of exercise completed in addition to monitoring compliance with the intervention.

3.5.5.1 Patient orientation

All patients enrolled in the *PREHAB CR* intervention program (*PREHAB* patients) will meet with a nurse or fitness professional delivers this session or fitness professional, who gives patients a tour of the *CR* centre facility, outlines the programs offered, describes who the *CR* staff are and their roles, and explains the overall goal of cardiac rehabilitation. Patients are also given the opportunity to ask questions regarding the *CR* program.

3.5.5.2 Program delivery

The *PREHAB CR* program will be delivered by a multi-disciplinary group consisting of physicians, nurses, fitness professionals, physiotherapists, dieticians, and psychologists. This approach allows the *CR* team to share knowledge, skills, and patient care responsibilities. A medical advisor, at each site, is responsible for the safety of enrolled *PREHAB* patients. Additionally to support patient safety, an emergency plan is in place with appropriate equipment (e.g. Defibrillator, nitroglycerine) and medical staff is available during patient care hours.

3.5.5.3 Core Components of Cardiac Rehabilitation

The *PREHAB CR* program adheres to the core components of *CR* outlined by the Canadian Association for Cardiac Rehabilitation Guidelines (85). These core components include: systematic patient referral processes, patient assessments, health behavior interventions and risk factor modification, exercise training, leisure time activities, outcomes assessment programs, continuous quality improvement programs, and continuous professional development programs.

3.5.5.4 Patient assessment

All patients complete a series of assessments that are kept in a client case file. All patient health information collected and will be is kept in a secure room and a lockable filing cabinet. Patient health information is used to assist the *CR* health care team to optimize patient treatment during the *CR* program.

3.5.5.4.1 Risk factor assessment

Patients who are enrolled in *PREHAB* will complete a one hour patient assessment from nurse or fitness professional. This assessment includes a medical history and physical examination to collect information on cardiac risk factors or other underlying conditions that could affect their treatment. Furthermore, each center collects blood samples for information on patient cholesterol, fasting blood glucose, and hemoglobin. In most cases, patients have received screening and diagnostic procedures from the

hospital in which their cardiac event was acutely managed. This information serves as a decision-making tool for *CR* staff to make informed decisions on patient treatment during *CR*. The information collected from this patient assessment is used to stratify a patient's risk for experiencing a future cardiac event.

3.5.5.4.2 Exercise stress test and 6-minute walk test (6MWT)

All *PREHAB* patients complete a graded maximal exercise stress test (*GXT*), which is supervised by an MD, exercise specialist, nurse, and electrocardiogram technician. Patients complete the Modified Bruce treadmill protocol. This protocol was designed specifically for testing patient cardiac function during exercise. Briefly, each stage of the test lasts three minutes, where speed and grade is increased at each stage. The first stage starts at 1.7 miles per hour and a 10% grade for the first three minutes and is progressively increased thereafter by increasing both speed and grade. There are a total of seven stages. The test is terminated if the patient voluntarily withdraws, or if the *CR* staff notices any cardiac abnormalities during the test (e.g., ST-abnormalities, no increase in heart rate with an increase in workload). Information collected from the stress test is then used to assist *CR* staff to prescribe exercise for the patient. A *6MWT* will performed in all patients along with the *GXT* as described in the methodology.

3.5.5.4.3 Psychosocial assessment

The research literature supports the contention that depression and anxiety negatively affect the cardiovascular health status of patients. Therefore, patients are encouraged, particularly if they had a previous psychosocial disorder, to see a clinical psychologist for an initial assessment. This assessment is used to counsel the patient on ways in which they can appropriately manage their cardiac disease in combination with their psychosocial disorder. Patients also complete the 5 item Geriatric Depression Scale (*GDS-5*).

3.5.5.4.4 Nutritional assessment

PREHAB patients will see the Registered Dietician at the *CR* Centre to optimize their diet to help manage their disease. Prior to the assessment, patients complete a 3-day food recall to help the Dietician in developing a personalized message and treatment strategy. Furthermore, this assessment assists patients in gaining a better understanding of the ways in which different types of fats, salt intake, as well as other components of the diet affect cardiovascular health. Patients also have the option to receive a follow-up visit to receive further counseling.

3.5.5.5 Health behavior interventions and risk factor modification

PREHAB patients all receive a comprehensive, multi-faceted health behavior intervention with the goal of positively modifying their risk factor profile. This includes nutritional counseling, lipid management, hypertension management, smoking cessation, weight management, diabetes management, adherence to prescribed pharmacotherapy, psychosocial management, and physical activity counseling.

3.5.5.6 Exercise training and leisure time activities

After the baseline assessments described above are completed, the *PREHAB* patient will engage in the 8-week *PREHAB CR* exercise therapy program. The first four weeks of the program constitutes a more structured program, the CR Centre staff closely monitor the patient during their exercise program and follows their progress. The patient attends the CR Centre for two 1 hour sessions of exercise training for the first four weeks. Exercise intensity is typically prescribed at 85% of their maximum heart rate-reserve, unless advised otherwise by the Internist. The remaining 4 weeks is less-structured and the patient is given more autonomy on the manner in which they complete their exercise therapy program. The patient engages in an individually prescribed exercise program consisting of aerobic, strength, and flexibility training. Frequency, time, and type of exercise varies depending on what the patient chooses. The majority of aerobic exercises consist of walking, cycling, rowing, and many machine-based aerobic

exercises. A Strength and Stretch class is also offered to increase muscle strength and endurance, and flexibility.

In addition to participating in physical activity at the *CR* Centre, patients are encouraged to participate in physical activities during their leisure time. This includes, but is not limited to, walking outdoors, gardening, household chores, grocery shopping, and cycling. This component of the *CR* program is designed to help patients manage their cardiac disease after they complete *CR*. Patients will be assigned an accelerometer to wear to be able to compare self-assessed exercise reporting with objective measurements.

3.5.5.7 Outcomes assessment

Patients are evaluated after they complete the *CR* program based on their outcomes. Patients are assessed based on several different outcomes, including clinical, health, educational, and behavioral outcomes. To assess these outcomes, patients complete the baseline assessments (described under the Patient assessment section) after they complete the 8-week *PREHAB CR* program. A key evaluation will be the *6MWT* to assess exercise capacity pre and post-program.

3.5.5.8 Continuous quality improvement programs

Each *CR* program will engage in continuous evaluation of their program to provide high quality care for their patients. The key components of this evaluation include:

- Eliminating defects in the *CR* delivery process and adding features to better meet the needs of the patient needs and preferences.
- Focusing on the core processes to improve the *CR* program. This includes statistical methods and tools to identify desired performance levels, measurement of current performance, and to interpret and take action as necessary.
- Involvement of all *CR* staff in quality improvement. Utilization of structured teams and councils to advise and plan quality improvement strategies are utilized.
- Setting high standards for performance.

3.5.5.9 Continuous professional development programs

This process involves keeping up to date with the most relevant knowledge on delivering the appropriate care to patients. Continuous professional development includes:

- Continuous learning processes that update relevant knowledge, skills, and attitudes.
- Maintenance of professional continuing education credits.
- Keeping up to date on the appropriate certifications (e.g., CPR training)
- Staff engagement in employee mentorship of students and other professionals, professional certification programs, and attendance in annual meetings relevant to *CR*.

3.5.6 Variable Waitlist Time

We acknowledge that the time on the waiting list may be variable. For example, in Manitoba the median waitlist time is 12 weeks (range: 3-31 weeks). The median waitlist time for our preliminary study was 62 days and such we believe that enrolled patients will not be subjected to any undue harm. The recommended standard wait for elective cardiovascular surgery should not exceed six weeks,(86) however the best physiological outcomes for patients attending cardiac rehabilitation is at least eight weeks(21)(19)(20)(79), or occur by participants who attend more than 25 sessions of *CR*.(11) After consulting with the associated *CR* program sites and our expert co-investigators, it was determined that the preferred *Prehab* intervention would be 8 weeks because it was deemed that clinically stable, frail, elderly patients could feasibly achieve measurable health benefits and risk factor modification over this

time frame.(87) However due to the variability in the waitlist times participants would still be eligible with a waitlist time of 4 weeks minimum.

What if patients are unable to complete the** Prehab **program due to a change in surgical date?
It is possible that a patient may not complete the full 8 week program due to scheduling changes for their procedure. We and others (78)(11)have seen functional and health behavior improvements in as little as 2-4 weeks. Notably, 2 patients in our pilot *Prehab* project participated in the program for only 3.5 weeks but still improved their total distance walked by an average of 174 meters (43% improvement). Our data is supported by Fiorina and associates and indicates that as few as 15 days of *CR* can improve total distance walked by as much as 40%. With this in mind, the *Prehab* program has been structured to provide the more intensive nutritional counselling, educational, psychosocial and exercise therapy during the first four weeks of the program and engage *Prehab* participants to take control of their self-managed care for the remaining program. This will enable participants to gain meaningful benefits in the event scheduling changes prevent the completion of the 8 week program.

3.5.6 Qualitative review of PREHAB Study

We engaged patients prior to conducting the PREHAB study to uncover whether patients would participate in a prehabilitation intervention. After study completion we want to continue the conversation with all patients both in the intervention arm, standard care arm as well as registry participants.

During the post study intervention we will conduct a series of individual interviews and survey components to enlist patient-centered response and opinion to the study intervention. We wish to know if there were barriers for participation, any factors that reduced adherence to the study as well as an overall satisfaction with the intervention. We also would like to discuss how improvements can be made after a participant has finished the intervention part of the study. For non-intervention patients we want to see if they went to cardiac rehab post-surgery and what its impact was on their recovery.

Additionally, A small group of participants and their caregivers from the primary site will be contacted and asked to participate in a more extensive patient panel session to better understand the patient valued experience of the intervention that was provided to participants and ways to improve delivery and adherence. We will conduct 3 group sessions of patients and their caregivers lasting approximately 2-3 hours. We will be following a general format with topic questions; however, we expect a very open conversation. All information will be transcribed and stored. Information identified within these sessions may be used to develop tool to be used to improve communication and adherence to care based interventions during the perioperative process. (See PREHAB Patient panel protocol)

We will conduct interviews with patients based on availability. As we are a multi-site intervention we will interview patients from the study who are not local to the primary site. We will contact current participants and enroll patients who are interested in the study. We will also identify patient perspective with cardiac rehabilitation post-surgery .

3.6 Data collection

All participants will meet with the research staff at nine time points: 1) twice at time of enrolment after their acceptance for a surgical procedure (i.e. baseline pre-intervention); 2) 4 weeks following randomization into either standard care or intervention group; 3) twice, 1-week

preoperatively (i.e. Pre-op); 4) twice, 3 months postoperatively; and, 5) twice, 1 year postoperatively (Figs. 4 and 5). Data collection will occur from both written and electronic medical records sources (i.e. patient information systems, where applicable). Existing perioperative surgical, *ICU* and hospital data will be used to capture patient demographics, procedure urgency, intraoperative procedure and anesthetic variables, cardiopulmonary bypass information, blood product utilization, mechanical ventilation, delirium/coma, *ICU* and hospital *LOS*, major adverse events, infection and *ICU* and hospital recidivism are collected in institutional databases.

Patients deemed "unsafe" to be enrolled in the exercise portion of the study or that have refused to be randomized but have consented to participate in the follow up registry will be contacted via telephone by research staff after their surgeries at two time points: 1) 3-months after surgery; and, 2) 12-months after surgery. A data sharing agreement, in compliance with provincial patient confidentiality legislation will be created to permit planned analysis. We have previously utilized these data collection methods.(49)(65)(88)(89)(90)

4 Safety Monitoring

Safety data including new hospitalization, worsening angina or heart failure and arrhythmias will be captured and all adverse events will be reportable to the study Data Safety Monitoring Board (*DSMB*). The DSMB is an independent group of experts that advises study investigators. They are responsible to periodically evaluate the study data for participant safety and study conduct, in addition to making recommendations concerning the modification and/or termination of the trial.

Safety Monitoring: Clinical stability during the pre-habilitation period is to be evaluated twice per week by the *CR* team using clinical questioning in comparison to their baseline stress test. All cases will be reviewed in conjunction with the attending physician.

5 Statistical Analysis Plan

5.1 Measures/Outcomes:

For the *PREHAB* study, we propose to capture data to enable evaluation of effect of a preoperative cardiac pre-habilitation program on:

5.1.1 Primary Outcome

Proportion of patients with hospital length of stay >7 days.

5.1.2 Secondary Outcomes

(1) pre-operative frailty, (2) exercise capacity, (3) physical activity behavior, (4) in-hospital outcomes, (5) 1-year clinical outcomes, (6) 1-year health-related quality of life, (7) cost-analysis.

5.2 Statistical/Analytical Plan

Objective 1: To determine if *Prehab* reduces the proportion of frail elderly patients requiring a prolonged hospital length of stay of >7 days. A univariable analysis will be undertaken to determine if hospital *LOS* > 7 days is associated with frailty and other patient-level factors. A stepwise multivariable logistic regression model will then be developed to determine if *Prehab* attendance is independently associated with a decreased risk of prolonged hospital length of stay > 7 days. As a secondary analysis, hospital *LOS* will also be compared as a continuous variable between the *Prehab* and standard care groups using a Mann-Whitney test.

Objective 2: Does attending *Prehab* influence frailty, exercise capacity, physical activity behavior, in-hospital complications, and *HRQoL*? Although we will employ four different measures of frailty, based on our preliminary data and based on a Task Force's position statement(90), the Modified Fried Criteria will be the primary frailty outcome over time from baseline to the end of *Prehab* program (pre-operatively), or from baseline to the 3-month post-operative follow-up. The primary measure of exercise capacity will be the *6MWT* and will be analysed with univariable linear regression models to evaluate the association between the *6MWT* and *Prehab* attendance. Accelerometers will be used to objectively measure the number of minutes spent performing moderate to vigorous physical activity (*MVPA*) and total physical activity (*TPA*) per day for a period of 7 days and compared between groups. A composite outcome for a major adverse cardiac event (i.e. *MACCE* = in-hospital stroke, myocardial infarction, renal failure requiring dialysis and death) and delirium will be compared between groups using a Chi-Square or Fisher's Exact test. A multivariable logistic regression will be used to identify if *Prehab* is independently associated with in-hospital delirium. The *SF-12v2* and *EQ-5D* scores, after normative standardization, will be analyzed through use of a repeated *ANOVA* to allow for a standardized group and group/time interaction effect estimation.

5.3 Sample Size Calculation

The sample size calculation was based on the primary objective – determining the effect of *Prehab* on rates of prolonged hospital length of stay > 7 days. Our preliminary data, demonstrated the proportion of frail patients in the Control group with a hospital length of stay > 7 days to be 58.3%. For the *Prehab* group, based on improvements in functional capacity in our pilot *RCT* and the work by Arthur et al14, we believe an absolute 20% reduction in proportion of patients that require prolonged hospital length of stay of greater than 7 days, is feasible. A sample size of 194 individuals (97 in each group) will be required for a two-tailed test at an alpha of 0.05 and power of 80%. All patients assigned to the pilot *Prehab* group completed the intervention, however, we are mindful that we will be recruiting frail, elderly patients who may have a higher dropout rate. Hence, we are estimating a 20% dropout rate and plan to recruit 244 individuals (122 in each study arm) to achieve an eventual sample size of 194 after dropout.

5.4 Cost Analysis

All patients in the study population will have a total cost calculated for their cardiac surgery hospital stay. This cost will be determined by tabulating cost of the *Prehab* intervention and different aspects of inpatient resource utilization for each study participant, and assign the best estimate of cost for each component. Pre- and post-operative hospital *LOS* on the hospital ward along with *LOS* in the cardiac surgery intensive care unit (CS-*ICU*) are expected to be the major drivers of a patient's overall cost. A sensitivity analysis will also be performed to account for uncertainty in any of the costs by simulating several different scenarios, and developing a range of cost estimates for each patient.

6 Data Management

The data management and analysis will be undertaken by the St. Boniface Hospital/I.H. Asper Clinical Research Institute. The principal means of data collection and data processing will be via electronic data entry at each site. Data will be exported to the St. Boniface Hospital/I.H. Asper Clinical Research Institute stripped of any patient identifiers. Each patient will be given a site and an anonymous unique study number.

6.1 Site Monitoring

Site monitoring will be performed by the site leads at their respective sites.

6.2 Data Recording and Document Retention

De-identified data will be entered by each participating site into an electronic REDCap e*CRF*. The data will be housed in a secure server located at the University of Manitoba Faculty Of Medicine. Each site will only be able to access their own data and only the project manager and principal investigator will be able to view identifying data. Each person having access to the REDCap software will be issued their own unique number generator key fob which will allow for audits of data entry. All data collected will be by the study will be kept for a minimum of 7 years or as otherwise required by regulatory agencies.

6.3 Data quality assurance

Data entered by each site will be password-protected and the ability to access or change data prior to locking of the database will be restricted to the project manager. Once initial data collection has been completed, missing data and implausible values will be identified using predetermined objective criteria, and queries resolved through direct communication with sites if required. This data cleaning process will be overseen by the *PREHAB* management committee. Treatment of outliers and missing data will be in accordance with the statistical analysis plan.

6.4 Funding

Canadian Institutes for Health Research (CIHR)

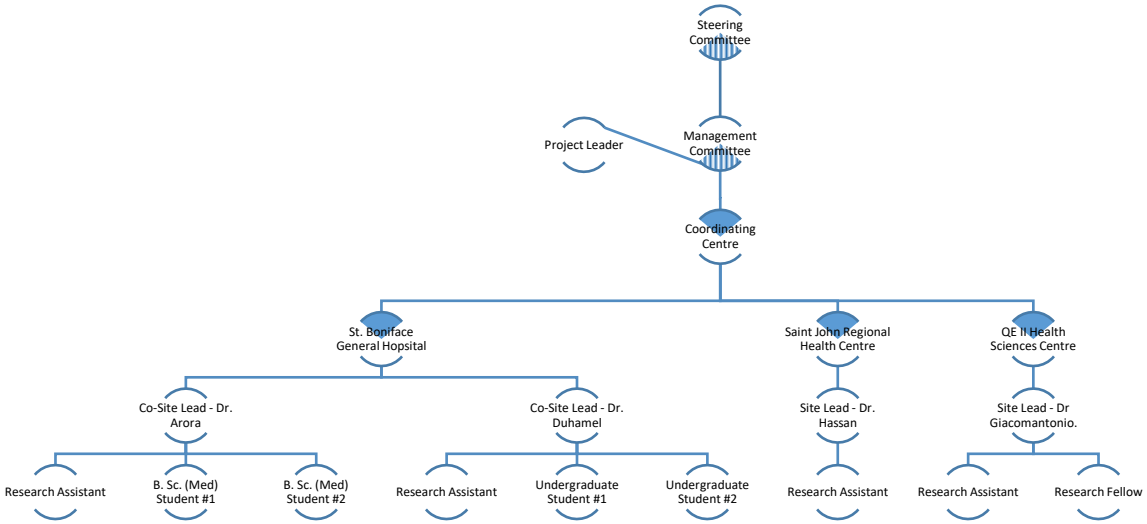
Term and Budget Requested: $619,784 (4-year term)

7 Participating Sites

The study will be conducted at four academic, tertiary care hospitals (St. Boniface Hospital, Winnipeg, MB, Queen Elizabeth II Health Sciences Centre, Halifax, NS, Montreal Heart Institute, Montreal, QC, Quebec heart and lung institute, Saint-Foy, QC) and one non-academic hospital (Saint John Regional Health Centre, Saint John, NB) that perform cardiac surgery

8 Operations Structure

8.1 Organization Chart



8.2 Steering Committee

The steering committee is responsible for all aspects of study design, management, analysis and publication of results. The steering committee will be comprised of the following individuals: Rakesh C. Arora (project leader), Todd Duhamel (co-site lead Winnipeg), Ansar Hassan (site lead Saint John), Nicholas Giacomantonio (site lead Halifax), Yoan Lamarche (site lead Montreal), Navdeep Tangri, Thang Ngoc Nguyen, Sarvesh Logsetty, Jitender Sareen, Colleen Metge, Hilary Grocott, Jo Anne Sawatzky, Kenneth Rockwood, Sean Bagshaw, Jonathan Afilalo, Jean-Francois Legare.

8.3 Study management committee

The study management committee is responsible for ensuring that the study meets the proposed milestones and deadlines. The management committee will be comprised of the following individuals: Rakesh C. Arora (project leader), Todd Duhamel (co-site lead Winnipeg), Ansar Hassan (site lead Saint John), Nicholas Giacomantonio (site lead Halifax), Yoan Lamarche (site lead Montreal), Navdeep Tangri, Thang Ngoc Nguyen, Sarvesh Logsetty, Jitender Sareen, Colleen Metge, Hilary Grocott, Jo Anne Sawatzky, Kenneth Rockwood, Sean Bagshaw, Jonathan Afilalo, Jean-Francois Legare.

8.4 Coordinating Centre

The coordinating centre for this project will be the St. Boniface Hospital/I.H. Asper Clinical Research Institute located in Winnipeg, Manitoba.

8.5 Principal Investigator/Project Lead

The principal investigator for this project is Dr. Rakesh Arora.

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8.6 Regional PI's/Site Leads

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University of Laval (Quebec heart and lung institute)	**Dr. Francois Dagenaise**	*francois.dagenais@chg.ulaval.ca*

8.7 Research Coordinator

The research/project coordinator will be responsible for the day-to-day coordination of activities between the three sites and will be based out of the coordinating center (St. Boniface General Hospital, Winnipeg).

- Ensuring ethics submissions are up-to-date and properly stored.
- Responsible for data handling and will liaise with the other two study sites.
- Will travel from Winnipeg to Halifax and St. John project sites to train the fee-for-service research staff located at those sites.
- Coordinate weekly teleconferences to support study implementation.
- Dissemination of the overall study

PROJECT COORDINATOR AND SITE COORDINATOR RESPONSIBILITIES	
Phase 1: Planning	• Coordinate study planning activities • Arrange stakeholder/researcher meetings • Complete research ethics for the overall project and work with sites to complete local ethics applications/access committee submissions • Orientate site personnel
Phase 2: Implementation	• Coordinate study implementation for all sites. • Make initial contact with potential. participants/screen/recruit in Winnipeg. • Complete baseline, pre-operative and follow-up. measures/assessments on participants in Winnipeg. • Data entry, to include baseline, pre-operative and follow-up measures; chart reviews; site data.
Phase 3: Evaluation/ Dissemination	• Coordinate study evaluation/dissemination. • Update review of literature.

	• Participate in knowledge dissemination.

8.7 Research Assistants

Site Coordinator #1 (Halifax, Nova Scotia): In order to implement the proposed study in Halifax, we plan to hire a 0.5 part time Site Coordinator for 2 years.

Site Coordinator #2 (Saint John, New Brunswick): In order to implement the proposed study in Saint John, we plan to hire a 0.5 part time Site Coordinator for 2 years.

Site Coordinator #3 (Montreal, Quebec): In order to implement the proposed study in Montreal, one year into study launch, we plan to hire a 0.5 part time Site Coordinator for 1 year.

Site Coordinator #4 (Quebec City, Quebec): In order to implement the proposed study in Quebec City, two years into study launch, we will utilize their existing infrastructure for a minimum of 1 year.

8.8 Students

Master's *Graduate Student*: Under the supervision of the Dr. Duhamel, the Graduate Student will work directly on the proposed project to: i) conduct a review of the literature to guide the development and refinement of the recruitment and screening approaches and to conduct the project evaluation; ii) work with the Program Coordinator to collect data by administering surveys/questionnaires and collect objective measures of physical activity; iii) liaise with the cardiac rehab sites to facilitate project outcomes.

Postdoctoral fellow: Dr. Rockwood has recruited Dr. Roxanne Streniczuk to complete a postdoctoral training program under his mentorship and she will devote 25% of her time to this project. Both Drs. Rockwood and Duhamel will support her application for the Integrated and Mentored Pulmonary and Cardiovascular Training (IMPACT) program, a CIHR Strategic Training Program in Health Research training program at the St. Boniface Hospital. The overall objective of the IMPACT program is to create the next generation of investigators with the capacity to generate scientific knowledge and, equally importantly, with the skills and linkages to rapidly advance those discoveries to clinic and health care systems. Notably, Dr. Todd Duhamel is the Program Director for the IMPACT program at the University of Manitoba; whereas, Dr. Rakesh Arora has specifically mentored several trainees within the program. As a result, Dr. Arora and Dr. Duhamel (Dalhousie) will co-mentor Roxanne Streniczuk (postdoctoral fellow).

Dr. Arora will recruit two B.Sc. Med students from the Faculty of Medicine, University of Manitoba to work on the Prehab project. Additionally, Dr. Duhamel will recruit two undergraduate students from the Faculty of Kinesiology and Recreation Management, University of Manitoba for a Directed Studies Research Internship for course credit so they can work directly on the project. Dr. Giacomantonio will

also supervise a research fellow, Dr. Colin Yeung, at Dalhousie University. He will contribute 100% of his time to this project.

9 Project Timeline

April 2, 2014 to July 1, 2014 (Ethics Submission/Project Coordination)

Obtain all relevant approvals from internal and external ethics boards. Assign duties and responsibilities to all individuals involved in the project.

July 1, 2014 to October 1, 2014

Begin holding focus groups to identify perceptions about physical activity in frail patients and their families. After an initial concentrated focus group session, we plan to continue ongoing sessions with key stakeholders as part of an integrated knowledge translation process.

October 1, 2014 to December 1, 2015 (Patient Recruitment)

Final goal is to recruit 244 total participants (122 individuals in each cohort).

March 1, 2016 (Recruitment and Procedures Completed)

Anticipated date by which all recruited patients will have undergone cardiac procedure and have been discharged from hospital. Primary outcome (hospital length of stay) is available.

June 1, 2016 (All Patients Completed 3-Month Follow-Up)

Anticipated date by which all recruited patients will be eligible for 3-month follow-up and quality of life questionnaire.

March 1, 2017 (All Patients Completed 1-Year Follow-Up)

Anticipated date by which all recruited patients will be eligible for 1-year follow-up and quality of life questionnaire.

March 1, 2017 (Data Analysis and Manuscript Development)

Preliminary data analysis will be conducted, drafts of manuscripts will be developed, iKT activities planned and performed.

May 1, 2017 (Project Completion Date)

All results have been finalized, manuscripts and abstracts have been submitted to various sources. Half-day symposium, joint with CACPR finalized.

9.1 Research Deliverables and Milestones

We anticipate the *PREHAB* study will require 3.5-years to complete (see Table below).

9.2 Preliminary Project Schedule

Timeframe	Milestone	Detail
April – Oct., 2014	• Continue with weekly teleconferences • Finalization of *DSMB* terms of reference • *HREB* protocol submissions to each of the sites	Following a meeting at the Canadian Cardiovascular Congress in October, 2013, We have held a series of teleconferences to: (1) Create a *HREB* template based on the successful previous submissions (2) Begin the process of nominating a three member data safety and monitoring board (*DSMB*) panel to review all adverse/severe adverse

	• *iKT* elements	events. We will draft a formal terms of reference with a plan to have meetings every six months via teleconference with the principal investigator. (3) Will begin holding focus groups to identify perceptions about physical activity in frail elderly patients and their families. After initial concentrated focus group sessions, we will continue ongoing sessions with key stakeholders as part of our *iKT* process.
Oct., 2014	Recruitment Begins	We plan to allow for a 14-month recruitment period for initial randomization of patients (see ***Figure 5***)
Jan., 2015	• 3-month follow-up begins	This is will allow for the 8 week *Prehab* program, surgery and 12 week follow-up (to coincide with the follow-up visit with the patient's surgeon).
Oct., 2015	• 1-year follow-up begins	1-year follow up for exercise test and quality of life questionnaire.
March, 2016	• Recruitment and Procedures Completed	Anticipated date by which all recruited patients will have undergone cardiac procedure and have been discharged from hospital. Primary outcome (hospital length of stay) is completely available.
June, 2016	• All Patients Completed 3-month follow-up	Anticipated date by which all recruited patients will be eligible for 3-month follow-up and quality of life questionnaire.
March, 2017	• All Patients Completed 1-Year Follow-Up	Anticipated date by which all recruited patients will be eligible for 1-year follow-up and quality of life questionnaire.
March, 2017 – May, 2017	• Data analysis/proposed publications • *iKT* elements • Peer review grant preparation (CIHR)	Data analysis will be conducted, drafts of manuscripts will be developed, *iKT* activities planned. Abstract preparation for presentation by trainees at scientific meetings. Initiation of planning with the CANCARE Society and CACR for educational sessions.

10 Project Impact

10.1 Project relevance and impact

The geriatric population is one of the fastest growing demographics undergoing cardiac surgery in North America.(1)(2) With this, the geriatric syndrome, defined as a "constellation of symptoms and signs [that] describe the heterogeneous response of older adults to physiological and metabolic challenges,"(3) has become an important consideration in patients undergoing cardiac surgery. To date, no high-quality study has prospectively examined the impact of preoperative cardiac rehabilitation in the frail-elderly undergoing cardiac surgery and represents a noticeable knowledge gap.

The *PREHAB* study is specifically aimed to improve the care and establish best practice in frail elderly patients undergoing high-risk cardiac surgery procedures through a rigorous evaluation of the utilization of an inter-disciplinary and multimodal patient optimization protocol. Importantly, we have

also planned for a detailed study analysis by key stakeholders at the health region level to determine optimal methodologies to implement this program following the completion of this investigation. Reducing anxiety, improving exercise capacity, promoting a healthy lifestyle that is durable (i.e. long-lasting) and improving *HRQoL* in the elderly are the over-riding goals of this endeavour. This investigation directly fits with the Network's Strategic Research Priorities of improving clinical outcomes in frail elderly patients.

10.2 Contributions to HQP

Training initiatives in *HQP* in the project will have a strong emphasis on clinical cardiovascular research. This focus will attract trainees interested in kinesiology and medicine. Two B.Sc. Medicine students, two Kinesiology undergraduate students, one Kinesiology M.Sc. trainee and two postdoctoral fellows will be will be mentored by Dr. Rakesh Arora, Dr. Todd Duhamel, Dr. Ken Rockwood and Dr. Nicholas Giacomantonio during this project.

- Dr. Arora will recruit two B.Sc. Med students from the Faculty of Medicine, University of Manitoba (http://umanitoba.ca/faculties/medicine/research/bsc_med.html).
- Dr. Duhamel will recruit two undergraduate students from the Faculty of Kinesiology and Recreation Management, University of Manitoba for a Directed Studies Research Internship (http://umanitoba.ca/faculties/kinrec/undergrad/directed_study.html) for course credit so they can work directly on the project. Dr. Duhamel will mentor Mr. Andrew Stammers to work on the proposed project if it is funded. Mr. Stammers has previously received an NSERC and a University of Manitoba Undergraduate Student Research Award ($12000).
- Dr. Rockwood has recruited Dr. Roxanne Streniczuk to complete a postdoctoral training program under his mentorship and she will devote 25% of her time to this project. Both Drs. Rockwood and Duhamel will support her application for the Integrated and Mentored Pulmonary and Cardiovascular Training (IMPACT) program, a CIHR Strategic Training Program in Health Research training program at the St. Boniface Hospital. The overall objective of the IMPACT program is to create the next generation of investigators with the capacity to generate scientific knowledge and, equally importantly, with the skills and linkages to rapidly advance those discoveries to clinic and health care systems.
- Dr. Giacomantonio will supervise a research fellow, Dr. Colin Yeung, at Dalhousie University. He has been awarded a Dalhousie research fellowship for $50,000/year for 2 years. He will contribute 100% of his time to this project.

10.3 KT framework/platform

A major component of the proposed project is to collect information that is appropriate to enable knowledge users to glean the information they need to inform new initiatives within their own organizations (i.e. knowledge-to-action).(91) The integrated (*iKT*) approach enhances the likelihood that the *Prehab* intervention will be implemented in the Canadian health care system and be sustainable over the long term. We have already taken the initial steps to implement an *iKT* approach to this application. Our intention of doing so was to include key stakeholders and potential knowledge users early in the process "to shape the research process by collaborating to determine the research questions, deciding on the methodology, being involved in data collection and tools development, interpreting the findings, and helping disseminate the research results".(2) We have open relationships with the partners and key stakeholders needed to design and operate our study. Our 'push' efforts to link research to action will include patients/families (through shared decision-making efforts),(82)(83)(84) primary care providers, cardiac surgeons and cardiac rehab centres; while 'pull' efforts by our stakeholders will be enhanced by their involvement in the design and reporting of the study. Finally, we have included a solid evaluation of our efforts to link research to action (ref: Ellen M. WHO Knowledge Translation Framework for Ageing and Health. April 2012). By using an *iKT* approach

and best practice evidence to inform a model of care for frail elderly persons needing cardiac surgery, the project will be able to influence the health system in a variety of ways.

10.4 Project engagement

Although we have already taken the initial steps to implement the *iKT* approach during the development of the grant application, once the project has begun we will convene a group of community stakeholders that include representatives from all the project sites, patients with higher levels of frailty who have previously undergone cardiac surgery and their family caregivers. Our intention of bringing these stakeholders together with the research team is to optimize the project intervention within the context of the patient experience prior to cardiac surgery, thereby facilitating 'pull' efforts (WHO 2012). Moreover, this group will identify ways to address the barriers that may arise as the *Prehab* intervention is implemented at each site; this effort is aided by the climate for research that exists in our context. This *iKT* approach will inform our work plan, ensuring that the voices and experiences of stakeholders, patients and families have been considered. These stakeholders will also serve as the steering committee to provide input to refine the *Prehab* approach.

Tables

Table 1 - How the PREHAB Study fits in the Technology Evaluation Framework

	Exploratory	Efficacy	Effectiveness (current state)	Cost-effectiveness
Patients and Families	We have examined the effects of prolonged hospitalization and its impact on new mood disorders and reduced cardiac rehab (CR) activity (Horne et al., 2013).	**Low to High Tech:** 1. Implementation of a frailty screening protocol in elective cardiac surgery patients and determination of a clinically meaningful endpoint of patient care/healthy living 2. Performed a pilot RCT on pre-operative cardiac rehabilitation ("prehab") on elective cardiac surgery patient to determine feasibility and safety.	**Engage, Empower and Support:** We plan to hold focus group discussions to learn more about attitudes of the value of Prehab for the treatment of frail elderly patients. This will involve interaction with the patient and their families and determine methods to ensure shared decision making and post-operative healthy living & sustainable well-being	
Health Care Professionals	Utilization of the Canadian Cardiovascular Critical Care (CANCARE) Society Network to identify the lack of peri-operative protocols for frail elderly persons and care of the cardiac surgery patient (Lamarche et al., 2012)	**Improving Outcomes:** We have identified Canadian centers capable of engaging in multicenter Prehab RCT, including Winnipeg, Halifax and Saint John. This includes both academic and non-academic cardiac surgery centers.	We plan to complete a Phase II, multicentre RCT examining the outcomes of patients undergoing Prehab during the patient journey from time of surgical referral to time of surgical procedure.	We plan to determine the cost effectiveness of the PREHAB model of care to determine if the intervention reduces different aspects of inpatient resource utilization .
Health Care System	We have completed a systematic review of current outcome(s) of frail elderly persons undergoing cardiac surgery and have determined that frailty is associated with increased mortality and other negative outcomes (see tables 1 & 2)	**Develop, Evaluate and Disseminate** 1. We have engaged local community cardiac rehabilitation programs in 3 provinces. 2. We have engaged a local regional health authority for study evaluation and developed an integrated knowledge translation plan (iKT) for patients/patient families, primary and specialist health care providers to ensure program sustainability	**Improving care across the continuum:** We have already engaged and will continue to engage a national cardiac rehabilitation organization (CACR) to support our project through network development, patient advocacy, knowledge translation and knowledge transfer to the patients, their families and the inter-disciplinary healthcare teams involved in the care of the frail elderly person with cardiac disease.	Our long term plan is to access administrative data to determine if the Prehab intervention helps to reduce health care utilization for patients over a 1 and 5 year period. However, this aspect is a next stage beyond the scope of the current proposal.

Table 2 - Characteristics of Included Studies In Frailty and Cardiac Surgery Systematic Review

First Author, Year	Population	n°	Frailty Measurement	Outcomes Measured	Association
Lee, 2010	Patients undergoing cardiac surgery	3826	Katz index of Activities of Daily Living (ADL), Independence in ambulation, and previous diagnosis of dementia	In-hospital mortality, midterm all-cause mortality, discharge to an institution, and secondary in-hospital outcomes	Frailty was linked to increased unadjusted In-Hospital Outcomes, increased In-hospital Mortality, increased institutional discharge, and reduced midterm survival
Singh, 2011	Patients ≥ 65 years undergoing Percutaneous Intervention	629	Fried Frailty Criteria	All cause mortality and MI during follow up	Frailty was an independent predictor of long-term mortality and MI
Sundermann, 2011	Patients ≥ 74 years undergoing cardiac surgery	400	Simplified Comprehensive Assessment of Frailty (CAF)	One year all cause mortality, and MACCE	Frailty showed a good predictive ability concerning one year mortality
Afilalo, 2012	Patients ≥ 70 years undergoing CABG and/or valve surgery	152	4 scales used: 5 item Cardiovascular Health Study (CHS) 7 item expanded CHS 4 item MacArthur Study of Successful Aging (MSSA) Gait Speed	Postoperative mortality or major morbidity	Only frailty measured through gait speed showed a statistically significant association with an increased mortality or major morbidity
Green, 2012	Patients ≥ 60 years with advanced aortic disease undergoing Transcathetar Aortic Valve Repair (TAVR)	159	Modified Fried Frailty Criteria	All cause mortality, and procedural outcomes	Frailty was independently associated with reduced long term survival after TAVR
Stortecky, 2012	Patients ≥ 70 years undergoing Transcathetar Aortic Valve Implantation (TAVI)	100	Modified Multidimensional Geriatric Assessment	All cause mortality, and major adverse cardiac and cerebrovascular events (MACCE)	Strong evidence for an association between the frailty index with all cause mortality and MACCE at one year post-TAVI
Schoenenberger, 2013	Patients ≥ 70 years undergoing Transcathetar Aortic Valve Implantation (TAVI)	119	Modified Geriatric Baseline Examination	Functional decline, and functional decline or death	Frailty index was strongly associated with functional decline as well as mortality

Table 3 - Outcomes of Included Frailty and Cardiac Surgery Studies

First Author, Year	Association	
Lee, 2010	After Cardiac Surgery, Frailty is associated with In-Hospital Mortality After Cardiac Surgery, Frailty is associated with Prolonged Institutional Care After Cardiac Surgery, Frailty is associated with Mid-Term Mortality	OR 1.8, 95% CI 1.1-3.0 OR 6.3, 95% CI 4.2-9.4 HR 1.5, 95% CI 1.1-2.2
Singh, 2011	Frailty is associated with Death following Percutaneous Revascularization Frailty is associated with MI/Death following Percutaneous Revascularization	HR 5.36, 95% CI 2.41-11.9 HR 3.04, 95% CI 1.80-5.15
Sundermann, 2011	Frailty is associated with one-year mortality after cardiac surgery	OR 1.097, 95% CI 1.038-1.160
Afilalo, 2012	Frailty as measured through gait speed is associated with Mortality or Major Morbidity after CABG and/or valve surgery	OR 2.63, 95% CI 1.17-5.90
Green, 2012	Frailty is associated with increased one year mortality post TAVR	HR 3.16, 95% CI 1.33-7.51
Stortecky, 2012	Frailty is associated with increased all cause mortality one year post TAVI Frailty is associated with increased MACCE one year post TAVI	OR 3.68, 95% CI 1.21-11.19 OR 4.89, 95% CI 1.64-14.60
Schoenenberger, 2013	Post TAVI, Frailty is associated with functional decline Post TAVI, Frailty is associated functional decline or death	OR 3.31, 95% CI 1.21-9.03 OR 4.46, 95%CI 1.85-10.75

ADL, Activities of Daily Living; MI, Myocardial Infarction; CAF, Comprehensive Assessment of Frailty; MACCE, Major Adverse Cardiac and Cerebrovascular Events; CABG, Coronary Artery Bypass Graft; CHS, Cardiovascular Health Study; MSSA, MacArthur Study of Successful Aging; TAVR, Trans-catheter Aortic Valve Repair; TAVI, Trans-catheter Aortic Valve Implantation; BMI, Body Mass Index; MMSE, Mini Mental State Exam; MNA, Mini Nutritional Assessment; TUG, Timed Get Up and Go test; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living

[a] study sample size

Table 4 - Characteristics of "not frail" versus "frail" patients, according to the Modified Fried definition of frailty

Pre-Operative Characteristics	Not Frail (N=61)	Frail (N=72)	P-Value
Age (years)	68.7 (7.4)	73.0 (8.2)	0.0023
Female sex	11 (18.0%)	24 (33.3%)	0.0459
BMI (kg/m^2)	29.0 (6.0)	29.3 (5.8)	0.8079
Diabetes	13 (21.3%)	29 (40.3%)	0.0190
HbA1c (%)	5.9 (5.7 – 6.6)	6.1 (5.9 – 7.1)	0.2312
CVD	4 (6.6%)	15 (20.8%)	0.0191
COPD	1 (1.6%)	15 (20.8%)	0.0008
Clinical depression	5 (8.2%)	10 (13.9%)	0.3011
Arthritis	5 (8.2%)	17 (23.6%)	0.0171
Angina	37 (61.7%)	50 (69.4%)	0.3479
Smoking history	39 (63.9%)	44 (62.0%)	0.8160
Current smoker	1 (1.6%)	5 (7.0%)	0.2162
Anemia	9 (14.8%)	22 (30.6%)	0.0317
Albumin (g/L)	39.0 (3.1)	36.4 (4.5)	0.0011
Chronic renal failure	0 (0.0%)	4 (5.6%)	0.1245
Creatinine (µmol/L)	90 (76 – 100)	85 (71 – 116)	0.8231
GI disease	14 (23.0%)	27 (37.5%)	0.0702
PVD	4 (6.6%)	13 (18.1%)	0.0478
Dyslipidemia	40 (65.6%)	51 (70.8%)	0.5155
Pulmonary hypertension	2 (3.3%)	4 (5.6%)	0.6870
Hypertension	48 (78.7%)	65 (90.3%)	0.0624
CHF	30 (49.2%)	40 (55.6%)	0.4631
MI	20 (32.8%)	31 (43.1%)	0.2249
Atrial fibrillation	7 (11.5%)	15 (20.8%)	0.1478
Prior angioplasty or stent	5 (8.2%)	18 (25.0%)	0.0107
Prior cardiac surgery	4 (6.6%)	2 (2.8%)	0.4124
Visual impairment	17 (27.9%)	19 (26.4%)	0.8482
Hearing impairment	3 (4.9%)	5 (6.9%)	0.7260
EuroSCORE II (%)	1.42 (0.87 – 1.94)	2.02 (1.25 – 4.28)	0.0001
Self-health rating (0-4)	3 (2 – 3)	2 (1 – 2)	<0.0001
MoCA score (0-30)	26 (24 – 27)	22 (20 – 25)	<0.0001

Table 5 - Intraoperative Variables

Intra-Operative Characteristics	Not Frail (n=61)	Frail (n=72)	P-Value	OR (95% CI)
Procedure type			0.5729	
- **Isolated CABG**	26 (42.6%)	39 (54.2%)		
- **Isolated Valve**	19 (31.2%)	17 (23.6%)		
- **CABG + Valve**	12 (16.7%)	13 (18.1%)		
- **Other**	4 (6.6%)	3 (4.2%)		
CPB time (minutes)	102 (80 – 132)	89 (68 – 121)	0.1712	

Table 6 - Unadjusted Association of Frailty and Risk of Negative Postoperative Outcome

Post-Operative Outcomes	Not Frail (n=61)	Frail (n=72)	P-Value	OR (95% CI)
ICU LOS (days)	2 (1 – 3)	2 (1 – 3)	0.2819	
Hospital LOS (days)	6 (5 – 9)	8 (6 – 12)	0.0098	
ICU LOS > 72 hours	10 (16.4%)	17 (23.6%)	0.3025	1.58 (0.66 – 3.76)
Hospital LOS > 7 days	23 (37.7%)	42 (58.3%)	0.0177	2.31 (1.15 – 4.65)
Major adverse event	1 (1.6%)	4 (5.6%)	0.3742	3.52 (0.38 – 32.45)
Post-operative Delirium	4 (6.6%)	20 (27.8%)	0.0015	5.48 (1.76 – 17.09)
In-hospital mortality	0 (0.0%)	2 (2.8%)	0.4997	undefined
Discharge to Institution	1 (1.6%)	4 (5.6%)	0.3713	3.64 (0.40 – 33.45)

Categorical variables are listed as frequency values (%), continuous variables are listed as mean (standard deviation) or median (interquartile range). Statistical comparisons were calculated using Chi-Square or Fisher Exact Test for categorical variables, T-Test or Mann-Whitney Test for continuous variables.

Table 7 - Comparison of baseline data between Standard care and Prehab groups

	Standard care (n= 7)	Prehab (n= 7)	P-value
Demographics			
Age (years)	63 ± 3	64 ± 4	0.63
Gender (% female per group)	1 (14%)	2 (25%)	0.99
Height (cm)	172.6 ± 2.3	173.0 ± 4.1	0.79
Weight (kg)	89.4 ± 2.4	94.1 ± 5.5	0.46
BMI	30.0 ± 1.0	29.9 ± 1.2	0.43
Pre-operative Characteristics			
Ejection fraction	62% ± 4%	58% ± 4%	0.51
CCS class	2.4 ± 0.2	2.4 ± 0.4	1.00
Previous MI	4 (57%)	4 (50%)	1.00
Arrhythmia	3 (43%)	2 (25%)	1.00
Hypertension	6 (86%)	6 (75%)	1.00
CVA/TIA	1 (14%)	1 (13%)	1.00
Psychiatric Diagnosis	2 (29%)	1 (13%)	1.00
Diabetes	1 (14%)	3 (38%)	1.00
Hyperlipidemia	7 (100%)	6 (75%)	1.00
Medications			
Beta-blocker	7 (100%)	2 (25%)	0.02
ACE/ARB	4 (57%)	3 (75%)	1.00
Statin	7 (100%)	7 (88%)	1.00
Anti-platelet	3 (43%)	2 (25%)	1.00
Nitrate	5 (71%)	4 (50%)	1.00
Anti-depressant	2 (29%)	0 (0%)	0.46

Continuous variables expressed as mean ± standard error. Categorical variables expressed in frequencies (percentage of group).

CCS= Canadian cardiovascular society angina score; MI= myocardial infarction; CVA= cerebrovascular accident; TIA= transient ischemic attack; ARB= angiotensin receptor blocker; ACE= angiotensin converting enzyme.

Table 8 - Comparison of operative characteristics between Standard care and *Prehab* groups

	Standard care (n= 7)	Pre-Hab (n= 7)	P-value
Time on wait list (days)	66 ± 6	92 ± 19	0.46
2-3x CABG	5 (71%)	5 (63%)	0.99
4-5x CABG	2 (29%)	3 (38%)	0.99
Cardiopulmonary by pass time (minutes)	69 ± 18	67 ± 6	0.92
ICU length of stay (hours)	25 ± 3	24 ± 4	0.80
Length of hospital stay (days)	5.3 ± 0.4	5.1 ± 0.5	0.81

Continuous variables expressed as mean ± standard error. Categorical variables expressed in frequencies (percentage of group). CABG = coronary artery bypass graft; ICU = intensive care unit.

Table 9 – Comparison of physical activity as measured by accelerometry between the Standard care and Prehab groups at baseline and Postop

	Baseline	Postop	ANOVA p-values		
			Group	**Time**	**Interaction**
10 minute bouts					
$MVPA_{10min}$			0.62	0.10	0.44
- **Standard care**	82 ± 58	130 ± 51			
- **Prehab**	21 ± 15	147 ± 53			
$TotalPA_{10min}$			0.49	0.07	0.56
- **Standard care**	103 ± 66	198 ± 89			
- **Prehab**	23 ± 150	193 ± 65			
Sporadic bouts					
$MVPA_{spor}$			0.87	0.03	0.73
- **Standard care**	132 ± 64	281 ± 72			
- **Prehab**	139 ± 64	250 ± 53			
$TotalPA_{spor}$			0.66	0.10	0.75
- **Standard care**	576 ± 89	872 ± 197			
- **Prehab**	574 ± 100	780 ± 84			

Values are means ± standard error; Standard care n= 6; Prehab n= 7. MVPA= moderate to vigorous physical activity.

Table 9 - Seven step Formative Evaluation Plan

Aspects of the Implementation Process	Evaluation Component	Description of the evaluation component at different levels	Data collection method(s)
Adoption	Recruitment	Site level [primary care practice & specialist(s)]: Procedures used to approach and attract sites Patient level: Procedures used to approach patients for participation in pre-operative rehabilitation	Observation Questionnaire, interview
Implementation	Reach	Site level: proportion of different sites approached and then accepting contribution to the study Patient level: proportion of patients approached and then participating in the intervention	Monitoring
	Effectiveness	Site & Project levels: Proportion of primary care sites and specialists who delivered (project level) and received (site level) the 7-step strategy	Monitoring, questionnaires, interviews
	Fidelity	Project group: extent to which the 7-step strategy was adhered to and adherence to the project's implementation plan	Monitoring, questionnaires, interviews
	Satisfaction	Site level: opinion/satisfaction about the study and intervention Project level: opinion/satisfaction about the 7-step strategy Patient level: opinion/satisfaction about the pre-operative rehabilitation strategy	Questionnaires, interviews
Continuation	Maintenance	Site level: the extent to which pre-operative rehabilitation becomes routine and a part of everyday culture and norms practices.	Monitoring, questionnaires, interviews
Implementation Determinants	Context	Determinants of implementation which have either hindered or facilitated the use of the 7-step strategy and pre-operative rehabilitation intervention. Specifically, we will examine the characteristics of the (a) socio-political context (e.g., willingness to be involved), (b) organization (e.g., decision making processes, capacity, financial resources), (c) adopting practices/patients (e.g., self-efficacy, support from colleagues/family, benefits), and (d) intervention (e.g., clarity of process)	Monitoring, questionnaires, interviews

Figures

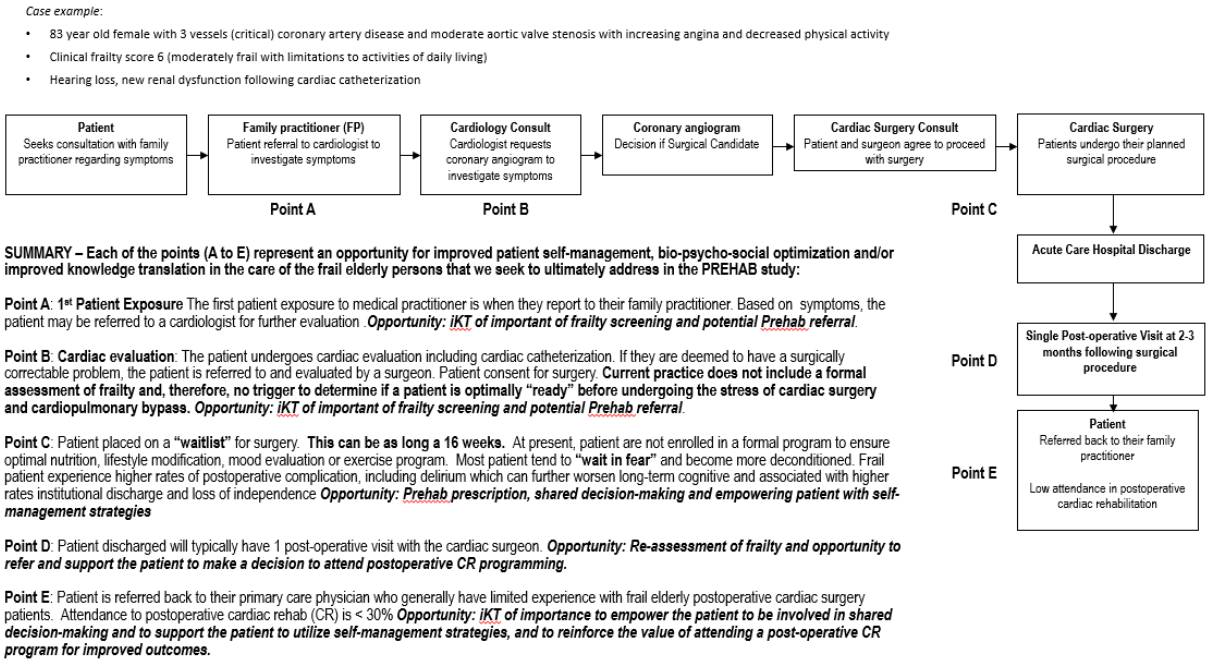

Figure 1 - An example of the journey faced by a "typical" frail elderly person undergoing cardiac surgery

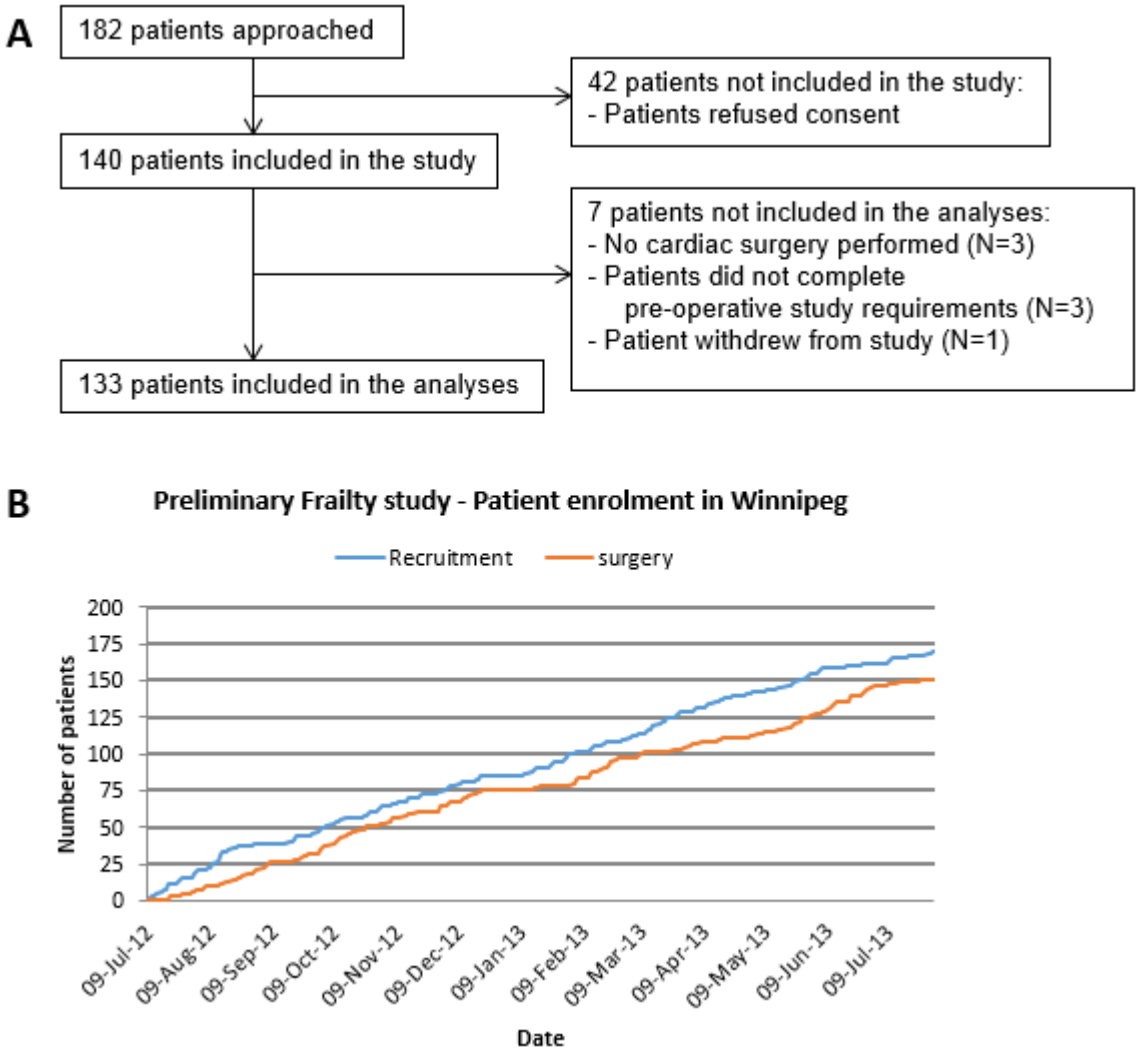

Figure 2 - (Panel A) Flowchart of preliminary frailty study cohort recruitment over a 12-month period (July 9, 2012-July 31, 2013). Overall consent rate 77% with a study completion rate of 73%.
(Panel B): Recruitment of patients over time (July 9, 2012 – July 9, 2013). Blue curve indicates patient recruited in the cardiac pre-admission clinic; Red curve the number of patients that have undergone their schedule cardiac surgery procedure.

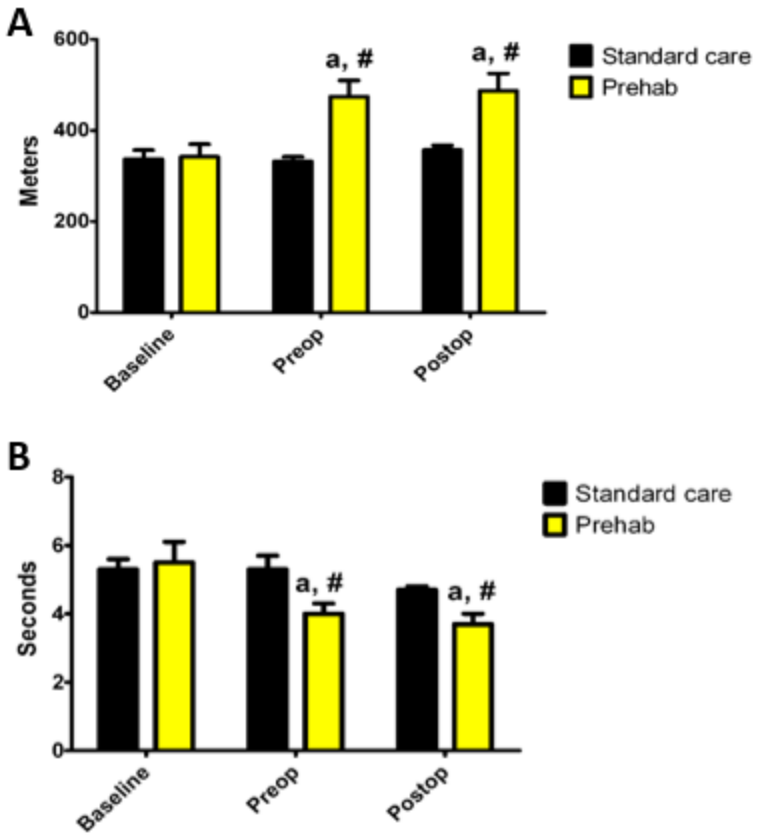

Figure 3 - (Panel A): Total walking distance achieved by Standard care and Prehab patients during a 6-minute walking test. Values are mean ± standard error; Standard care n= 7; Prehab n=7. a different from baseline (p<0.05); # different from Standard care (p<0.05). Preop= one week pre-oeratively; Postop= three months post-operatively.
(Panel B): Total time required by Standard care and Prehab participants to complete the 5-meter gait speed test. Values are mean ± standard error; Standard care n=7; Prehab n=7. adifferent from Baseline (p<0.05); #different from Standard care (p<0.05). Preop= one week pre-operatively; Postop= three months post-operatively.

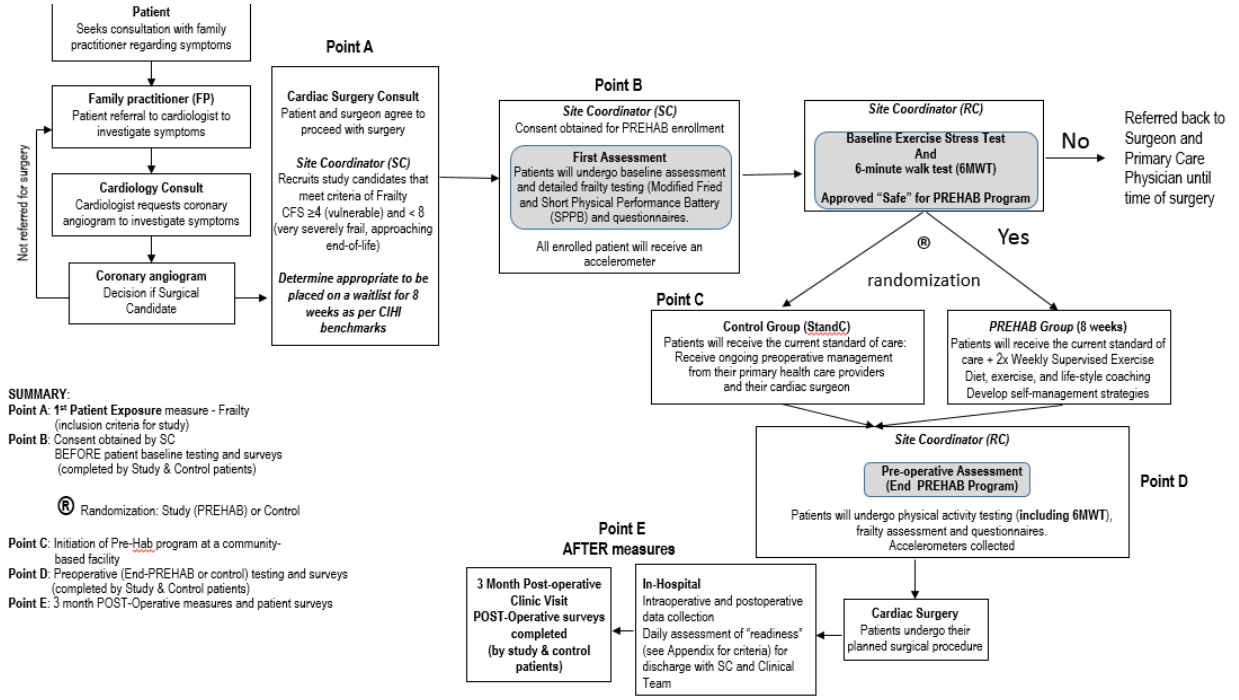

Figure 4 - Proposed PREHAB Study Process Overview – Recruitment and Study Protocol

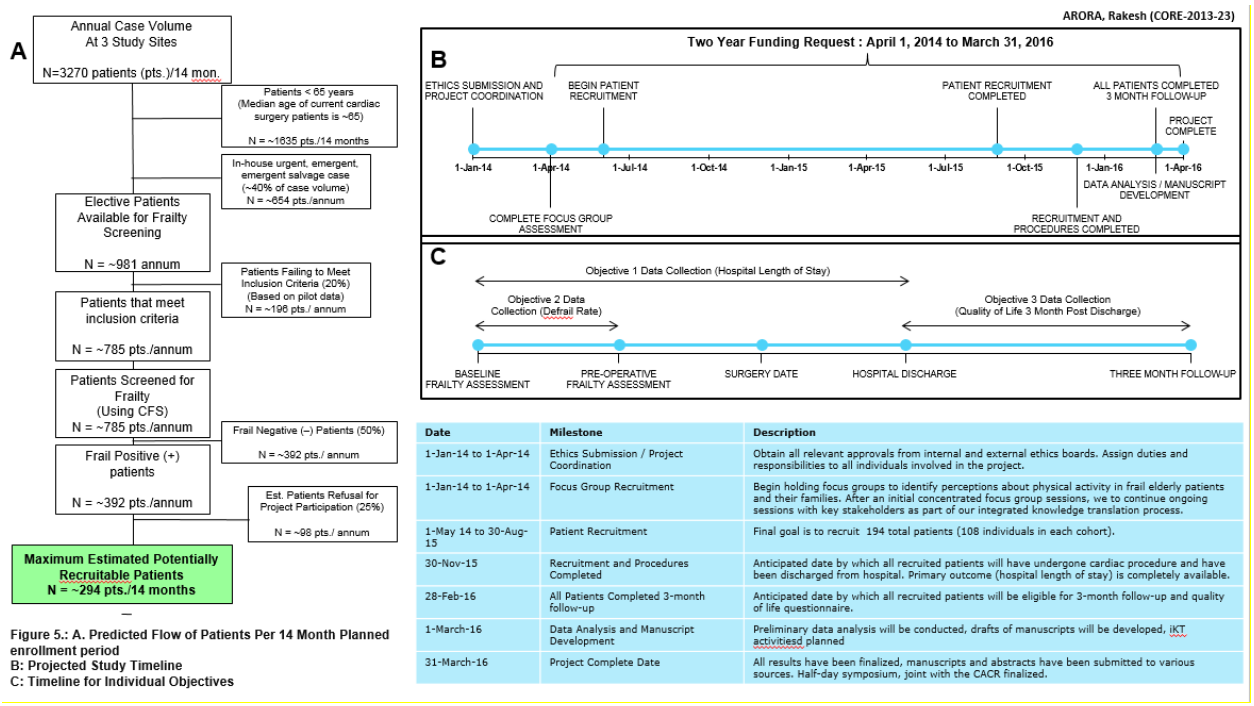

Figure 5.: A. Predicted Flow of Patients Per 14 Month Planned enrollment period
B: Projected Study Timeline
C: Timeline for Individual Objectives

Date	Milestone	Description
1-Jan-14 to 1-Apr-14	Ethics Submission / Project Coordination	Obtain all relevant approvals from internal and external ethics boards. Assign duties and responsibilities to all individuals involved in the project.
1-Jan-14 to 1-Apr-14	Focus Group Recruitment	Begin holding focus groups to identify perceptions about physical activity in frail elderly patients and their families. After an initial concentrated focus group sessions, we to continue ongoing sessions with key stakeholders as part of our integrated knowledge translation process.
1-May 14 to 30-Aug-15	Patient Recruitment	Final goal is to recruit 194 total patients (108 individuals in each cohort).
30-Nov-15	Recruitment and Procedures Completed	Anticipated date by which all recruited patients will have undergone cardiac procedure and have been discharged from hospital. Primary outcome (hospital length of stay) is completely available.
28-Feb-16	All Patients Completed 3-month follow-up	Anticipated date by which all recruited patients will be eligible for 3-month follow-up and quality of life questionnaire.
1-March-16	Data Analysis and Manuscript Development	Preliminary data analysis will be conducted, drafts of manuscripts will be developed, iKT activitiesd planned
31-March-16	Project Complete Date	All results have been finalized, manuscripts and abstracts have been submitted to various sources. Half-day symposium, joint with the CACR finalized.

Figure 5 - A. Predicted Flow of Patients Per 14 Month Planned enrollment period. B: Projected Study Timeline. C: Timeline for Individual Objectives

Appendices

Appendix I - Modified Fried Criteria (1-7)

	Frailty Domain	Method of Measurement	Cutoffs for Measurement
1	Slowness	4-meter gait speed *Measures the time required to walk 4 meters at a normal pace (use the best of two times)*	<4.82 sec: **4 pt** 4.82-6.20 sec: **3 pt** 6.21-8.70 sec: **2 pt** >8.7 sec: **1 pt** Unable: **0 pt**
2	Weakness	Handgrip strength *The patient is asked to squeeze the handgrip dynamometer as hard as possible, this is repeated 3 times (with each hand and then with the strongest hand) and the maximum value is recorded*	Sex- and BSA-based cutoff ♂ ≤24 kg/m²: **≤29 kg** 24.1-28 kg/m²: **≤30 kg** >28 kg/m²: **≤32 kg** ♀ ≤26 kg/m²: **≤17 kg** 26.1-29 kg/m²: **≤18 kg** >29 kg/m²: **≤21 kg** Simplified cutoff ♂: **≤30 kg** ♀: **≤20 kg**
3	Low physical activity	PASE & Paffenbarger Physical Activity Questionnaire	♂: <383 kcal/week ♀: <270 kcal/week
4	Weight loss	Self-reported	**>10 pounds or >5% in past year**
5	Exhaustion	a) 2 questions from CES-D: How often in the last week did you feel this way: i. I felt that everything was an effort ii. I could not get going	Positive if answered either question **Most of the time** or **Moderate amount of the time**
6	Cognitive impairment	Montreal Cognitive Assessment (MoCA) Trails A and B	**Score <26/30**
7	Depressed mood	Geriatric depression scale (5-item)	**Score** ≥2/5
		≥3 Criteria Required for Diagnosis of Frailty	

Appendix II - Five item Geriatric Depression Scale (5-GDS)

Five item Geriatric Depression Scale

VII.	MOOD		
7.1	Are you basically satisfied with your life?	[ ] Yes	[ ] No
7.2	Do you often get bored?	[ ] Yes	[ ] No
7.3	Do you often feel helpless?	[ ] Yes	[ ] No
7.4	Do you prefer to stay at home rather than going out and doing new things?	[ ] Yes	[ ] No
7.5	Do you feel pretty worthless the way you are now?	[ ] Yes	[ ] No

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Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study

Jo-Ann V Sawatzky[1], D Scott Kehler[2,3], A Elizabeth Ready[2], Neal Lerner[4], Sue Boreskie[4], Darlene Lamont[4], Dean Luchik[4], Rakesh C Arora[5] and Todd A Duhamel[2,3,6]

Abstract

Objective: To determine the feasibility of a cardiac prehabilitation (Prehab) program for patients waiting for elective coronary artery bypass graft (CABG).

Design: A two-group parallel randomized controlled trial.

Setting: Medical fitness facility.

Subjects: Seventeen preoperative elective CABG surgery patients were randomized to standard care (n = 9) or Prehab (n = 8).

Intervention: Standard care: three-hour preassessment appointment. Prehab: exercise and education classes for 60 minutes/day, twice weekly for at least four weeks.

Main measures: Data were collected at baseline, one week preoperatively, and three months postoperatively. The primary outcome measure was walking distance using a 6-minute walk test. Secondary outcome variables included 5-meter gait speed, and cardiac rehabilitation attendance three months postoperatively.

Results: Fifteen patients (standard care, n = 7; Prehab, n = 8) completed the study. No Prehab patients developed cardiac symptoms during study participation. Walking distance remained unchanged in the standard care group; whereas, the Prehab group increased their walking distance to mean ± SD 474 ±101 and 487 ±106 m at the preoperative and three month postoperative assessments ($p < 0.05$). Gait speed was unchanged in the standard care group, but improved in the Prehab group by 27% and 33% preoperatively and three months postoperatively, respectively ($p < 0.05$). Enrollment in cardiac rehabilitation three months postoperatively was higher for Prehab participants (100%) than standard care participants (43%; $p < 0.05$).

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Conclusion: These data provide evidence for the feasibility of a Prehab intervention to improve the health status of patients waiting for elective CABG surgery. A larger trial of 92 patients will be utilized to demonstrate the safety and efficacy of Prehab.

Keywords
Coronary artery bypass, exercise therapy, pre-habilitation

Received: 26 August 2013; accepted: 16 November 2013

Introduction

Patients who are waiting for coronary artery bypass graft (CABG) surgery are often fearful of being physically active.[1] However, this wait period offers an opportunity for preoperative rehabilitation, which might improve the safety and outcome of their prospective surgical intervention and encourage ongoing engagement in rehabilitation postoperatively. Our pilot, randomized controlled trial sought to demonstrate the feasibility of cardiac "prehabilitation" (Prehab) for patients waiting for first time elective CABG surgery.

Long wait times (> one month) for elective CABG surgery are associated with increased mortality rates compared with short wait times (< one month).[2] During this wait time, patients report being fearful of participating in physical activity and thus experience further cardiovascular de-conditioning.[1] Furthermore, poor physical fitness preoperatively is associated with a longer hospital stay.[3] Therefore, the safety, as well as the feasibility of enhancing preoperative physical fitness in the cardiac surgery population must be explored.

Cardiac Rehabilitation Programs (CRPs) enhance physical fitness among cardiac patients and significantly their reduce mortality rates;[4] however, elective CABG patients are generally not referred to CRPs until after their surgical intervention. Preoperative physical therapy has been utilized prior to cardiac surgery[5] and in other disease conditions, including lung cancer,[6] joint replacement, and abdominal surgery,[5] and is shown to reduce postoperative complications, such as postoperative atelectasis and pneumonia, and length of hospital stay – at least in cardiac and abdominal surgery.[5,7] However, these studies have primarily focused on inspiratory muscle training as a form of preoperative physical therapy; thus, less is known about the application of exercise therapy before CABG surgery to enhance physical fitness preoperatively.

Currently, there is little evidence demonstrating the feasibility of a Prehab program for elective CABG patients, with the strongest data showing that exercise therapy and education classes reduce the length of hospital stay by one day and intensive care unit length of stay by 2 hours.[8] It is also unknown if Prehab programs improve physical fitness prior to elective CABG surgery. Therefore, the purpose of this pilot, randomized controlled trial, was to determine the feasibility of a cardiac Prehab program for patients waiting for elective CABG surgery. We hypothesized that a Prehab intervention would improve physical fitness to a greater extent than current standard care before surgery (preoperatively).

Methods

This pilot study used a randomized controlled trial, parallel two-group (n = 17), repeated measures design. We recruited and enrolled patients scheduled to undergo first-time elective CABG surgery from February 2011 to May 2012 (Figure 1) at baseline, preoperatively and three months postoperatively. We included patients with a minimum estimated four week wait-time, with no history of unstable angina, myocardial infarction in the last week, or dementia, ejection fraction >30%, and who were sedentary prior to enrollment. We excluded patients with physical limitations or exercise-induced arrhythmias. Study procedures were initiated following ethical approval from the

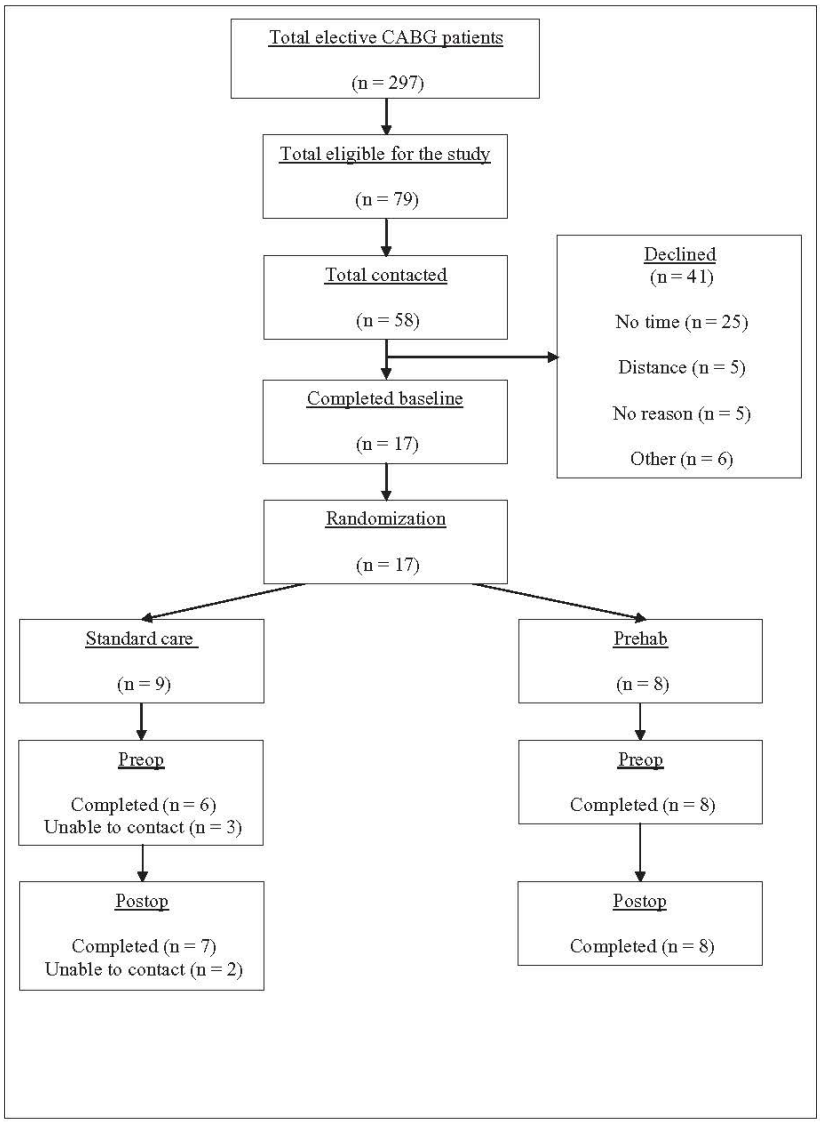

Figure 1. Flow diagram: participant recruitment.
CABG, coronary artery bypass graft; Preop, one week pre-operatively; Postop, three months post-operatively.

university, regional, and hospital research review committees.

This study was conducted at a 500-bed tertiary center in Western Canada. A research assistant at the tertiary center collected data from all study participants at baseline, preoperatively, and three months postoperatively. After baseline data collection, the research assistant randomly assigned patients to receive standard care ($n = 9$) or the Prehab intervention ($n = 8$) by opening a sealed envelope

containing a third party, computer-generated random group assignment. The research assistant was aware of which patients were randomly assigned to standard care and Prehab, thus increasing the risk of detection bias.

As a part of standard care, all participants attended a three-hour cardiac preassessment meeting, where a nurse practitioner and anesthetist assessed each patient's cardiac status and other underlying conditions that may have affected their surgical outcomes. Participants were counselled on healthy lifestyle behaviors during their preassessment visit.

Patients randomized to the Prehab group received standard care plus a Prehab intervention at a medical fitness facility. Key healthcare providers at the medical fitness facility (i.e. CEO, Director of Health and Fitness, cardiologists, nurses, and exercise specialists) were involved in facilitating the participation of Prehab participants in the study in order to address the practical aspects of the study. Accordingly, the Prehab participants joined a larger group of patients attending the facility's 16-week CRP. Prehab participants completed a minimum of two 60-minute structured exercise sessions/week until their surgery date or for the duration of the 16-week Prehab intervention. Prehab participants also attended additional voluntary exercise sessions at the facility. Care providers prescribed the Prehab program by following standardized procedures at the medical fitness facility for their CRP. Aerobic exercise intensity was prescribed at 85% of their maximal oxygen consumption based on their stress test results. The intensity and duration of aerobic exercise was progressively increased based on close communications between the healthcare providers and participants enrolled in Prehab. Types of exercises were prescribed by healthcare providers based on individual interests and abilities, which included walking (8/8 participants), stationary cycling (2/8 participants), light resistance exercise with body weight and resistance bands (2/8 participants), and stretching (2/8 participants). Prehab participants also attended 12 class-based education sessions concerning medication use, exercise, stress, diet, and cardiovascular risk factor management.

To address patient safety, all Prehab participants underwent a standardized exercise stress test prior to the initiation of the Prehab program.[9] Additionally, during the Prehab program, trained medical staff, including a cardiologist, nurses, and an exercise specialist monitored the participants. Data related to Prehab safety outcomes were collected from patient charts at the medical fitness facility after patients had completed the Prehab program and included fatal or non-fatal myocardial infarctions, exercise-induced arrhythmias, unstable angina, and hospitalization owing to Prehab participation. In addition, data on operative and postoperative complications were collected from hospital chart reviews and included 30-day mortality, atelectasis, atrial fibrillation, stroke, renal failure requiring dialysis, prolonged ventilation, sternal wound infection, reoperation, and re-hospitalization.

The primary study outcome was a change in walking distance assessed using the 6-minute walk test (6MWT), based on standardized guidelines.[10] The 6MWT correlates with physical fitness as assessed by a maximal graded exercise test.[11] In accordance with standardized guidelines, gait speed was measured using a 5-m gait speed test, a predictor of mortality and morbidity in patients undergoing cardiac surgery.[12]

Physical activity was objectively measured using an actical accelerometer (Phillips–Respironics[13]). Accelerometer data were analyzed utilizing the protocol described by Colley et al.[13] Specifically, physical activity intensity was measured in counts/min (light activity = 100–750 counts/min; moderate to vigorous physical activity (MVPA) ≥750 counts/min), which was subsequently analyzed in minutes/week. Participants wore an accelerometer during their waking hours for seven-day periods. A valid day of accelerometer data was defined as >10 hours of wear time. Accelerometer data were analyzed in ≥10-minute intervals (i.e. $MVPA_{10min}$, $TotalPA_{10min}$), as well as sporadically in bouts of ≥30 seconds (i.e. $MVPA_{spor}$, $TotalPA_{spor}$,). Physical activity accumulated in 10-minute bouts or more is currently recommended by the *Canadian Physical Activity Guidelines* for health benefits.[14] We chose to analyze physical

activity in sporadic bouts owing to emerging evidence suggesting that even very short activity bouts are associated with health physical fitness.[15]

Quality of life was assessed using the validated short-form health survey (SF-36) questionnaire.[16] Symptoms of depression were assessed using the Patient Health Questionnaire-9 (PHQ-9).[17] The 18-item Cardiac Anxiety Questionnaire (CAQ) was utilized to assess participants' perceptions of their anxiety related to their heart health.[18] Participant exercise self-efficacy was measured using the 16-item Cardiac Exercise Self-Efficacy Index (CESEI).[19]

Based on previous research showing a 40% increase in 6-minute walking distance in CABG patients after participation in a CRP,[20] we determined a sample size of 20 (10 participants per arm) would have sufficient power (0.8) with an alpha = 0.05 to detect a change in walking distance from baseline to preoperatively. Based on our preliminary analysis preoperatively (standard care, $n = 6$; Prehab, $n = 6$), we found the mean difference in 6-minute walking distance was statistically different between the standard care and Prehab groups ($p < 0.05$). Therefore, to account for 10%–15% attrition, a drop-out rate used in previous literature utilizing a Prehab program,[8] we completed participant recruitment with nine patients in the standard care group and eight patients in the Prehab group.

Data were expressed as mean ± SD and frequency (%). Continuous variables were analyzed using a two-way analysis of variance (ANOVA), using one repeated measure (time) and one between-group comparison. An independent *t*-test was used to compare group differences in baseline characteristics. An intent-to-treat analysis was utilized for drop-outs/missing data points. A *p*-value <0.05 was considered statistically significant. A Neuman–Kuels post-hoc analysis was used to identify differences between specific means.

Results

During the study period, 79/297 patients referred for CABG surgery during the conduction of the study met our recruitment criteria (see flow diagram, Figure 1). Of the 17 participants who enrolled in the study at baseline, 7/9 in the standard care group and 8/8 participants in the Prehab group completed the study. Baseline characteristics between standard care and Prehab participants did not differ except for beta-blocker use, which was significantly higher in the standard care group (Table 1).

Patients in the Prehab group attended a mean ± SD 19 ± 7 exercise sessions over a mean exposure time of 8.2 ± 2.2 weeks. Based on chart reviews at the medical fitness facility after Prehab completion, no adverse events occurred during participation in the Prehab program. Neither surgery parameters nor prevalent postoperative complications differed between the two groups (Table 1).

No differences were observed at baseline for total distance walked on the 6MWT between the standard care and Prehab groups (Table 2). In contrast, compared with baseline, participants in Prehab walked significantly further preoperatively and three months postoperatively ($p < 0.05$) than standard care. Similarly, baseline gait speeds (Table 2) between the standard care and Prehab groups were non-significant. Over time, standard care participants did not improve gait speed preoperatively or three months postoperatively. However, in the Prehab group, an interaction effect was observed ($p < 0.05$), where gait speed was improved preoperatively and three months postoperatively, respectively, as compared with the standard care group.

We attempted to capture accelerometer data at all time points (i.e. baseline, preoperatively, and three months postoperatively); however, 11 of 15 participants in the study had their surgeries within 1–3 days of receiving notification, which was less than the minimum required accelerometer wear time of 4 days. Based on this limitation, we analyzed accelerometer data for the baseline and three month postoperative time points only (Table 3). When physical activity was assessed in 10-minute bouts, no differences were found for any intensity of physical activity at any time. Additionally, no differences between groups were observed when physical activity was analyzed in sporadic bouts for $TotalPA_{spor}$ at any time. However, a main effect of time was observed for both groups, where

Table 1. Comparison of baseline characteristics and surgery parameters between groups.

	Standard care (n = 7)	Prehab (n = 8)	p-value
Demographics			
Age (years)	63 ± 9	64 ± 7	0.63
Gender (% female per group)	1 (14%)	2 (25%)	0.99
Height (cm)	172.6 ± 6.1	173.0 ± 11.7	0.79
Weight (kg)	89.4 ± 6.2	94.1 ± 15.5	0.46
BMI	30.0 ± 2.7	31.5 ± 4.4	0.43
Preoperative summary			
Ejection fraction	62% ± 10%	58% ± 11%	0.51
CCS class angina score*	2 (1–3)	2 (1–3)	1.00
Previous MI	4 (57%)	4 (50%)	1.00
Arrhythmia	3 (43%)	2 (25%)	1.00
Hypertension	6 (86%)	6 (75%)	1.00
CVA/TIA	1 (14%)	1 (13%)	1.00
Psychiatric diagnosis	2 (29%)	1 (13%)	1.00
Diabetes	1 (14%)	3 (38%)	1.00
Hyperlipidemia	7 (100%)	6 (75%)	1.00
Medications			
Beta-blocker	7 (100%)	2 (25%)	0.02
ACEI/ARB	4 (57%)	3 (75%)	1.00
ASA	7 (100%)	8 (100%)	1.00
Statin	7 (100%)	7 (88%)	1.00
Antiplatelet	3 (43%)	2 (25%)	1.00
Nitrate	5 (71%)	4 (50%)	1.00
Antidepressant	2 (29%)	0 (0%)	0.46
Surgery parameters			
Time on wait list (days)	66 ± 15	92 ± 25	0.46
2–3× CABG	5 (71%)	5 (63%)	0.99
4–5× CABG	2 (29%)	3 (38%)	0.99
Cardiopulmonary bypass time (minutes)	64 ± 17	69 ± 15	0.92
ICU length of stay (hours)	25 ± 7	24 ± 12	0.80
Length of hospital stay (days)	5.3 ± 1.0	5.1 ± 1.4	0.81
Operative complications†			
Atelectasis	0 (0%)	2 (25%)	0.47
Atrial fibrillation	4 (57%)	2 (25%)	0.31

Continuous variables expressed as mean ± SD. Categorical variables expressed in frequencies (percentage of group).
*CCS class expressed as median (interquartile range).
†Only data on complications that were prevalent are presented.
ACI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; ICU, intensive care unit; MI, myocardial infarction; TIA, transient ischemic attack.

$MVPA_{spor}$ increased three months postoperatively, as compared with baseline ($p < 0.05$).

The SF-36 scores did not improve from baseline to preoperatively in either group. However, six of eight quality of life subscales (i.e. general health, physical functioning, role limitations owing to physical health, role limitations owing to emotional problems, energy/fatigue and social functioning) improved postoperatively in both groups, as compared with baseline and preoperatively ($p < 0.05$). Similarly, baseline PHQ-9, exercise self-efficacy (i.e. CESEI), and the total CAQ score,

Table 2. Comparison of functional walking tests between groups.

	Baseline	Preop	Postop	Differences between group means (95% CI)	
				Preop minus baseline	Postop minus baseline
6-min walking distance (meters)				136 (61 to 209)	123 (62 to 209)
Standard care	337 ± 52	332 ± 27	357 ± 27		
Prehab	342 ± 79	474 ± 101*†	487 ± 106*†		
5-meter gait speed (seconds)				–1.6 (–0.5 to –2.7)	–1.2 (0.26 to –2.6)
Standard care	5.3 ± 0.9	5.3 ± 1.0	4.7 ± 0.2		
Prehab	5.5 ± 1.7	4.0 ± 0.7*†	3.7 ± 0.9*†		

Values are means ± SD; standard care, $n = 7$; Prehab, $n = 8$.
Two-way repeated measures ANOVA revealed significant differences: *different than baseline: $p < 0.05$; †different than standard care: $p < 0.05$.
CI, confidence interval; Postop, postoperatively Preop, preoperatively.

Table 3. Comparison of physical activity as measured by accelerometry between groups at baseline and postoperatively in minutes per week.

	Baseline	Postop	Differences between group means (95% CI)
			Postop minus baseline
10 minute bouts			
$MVPA_{10min}$			78 (–135 to 291)
Standard care	82 ± 58	130 ± 51	
Prehab	21 ± 15	147 ± 53	
$TotalPA_{10min}$			75 (–221 to 370)
Standard care	103 ± 66	198 ± 89	
Prehab	23 ± 150	193 ± 65	
Sporadic bouts			
$MVPA_{spor}$			–37 (–274 to 198)
Standard care	132 ± 64	281 ± 72	
Prehab	139 ± 64	250 ± 53	
$TotalPA_{spor}$			–91 (–700 to 518)
Standard care	576 ± 89	872 ± 197	
Prehab	574 ± 100	780 ± 84	

Values are means ± SD; standard care, $n = 6$; Prehab, $n = 7$.
CI, confidence interval; MVPA, moderate-to-vigorous physical activity; Postop, three months post-operativley.

fear, and avoidance CAQ subscales were not different between groups, but all showed a main effect of time, where the three month postoperative time point was significantly lower than baseline and preoperatively ($p < 0.05$). Three (43%) of the standard care and eight (100%) of the Prehab group participants chose to enrol in cardiac rehabilitation postoperatively ($p < 0.05$).

Discussion

We have demonstrated the feasibility of utilizing preoperative exercise therapy for patients waiting for first time elective CABG. Notably, no patients enrolled in Prehab experienced an adverse event, suggesting that a Prehab program may be a safe therapy for patients waiting for a first time elective CABG. Our novel data also shows for the first time that patients who are on a waiting list for elective CABG surgery improve their physical fitness as assessed by the 6MWT before surgery, and that this outcome is maintained postoperatively, as compared with a group that received standard care. Similarly, Prehab improved 5-meter gait speed preoperatively and was maintained postoperatively; whereas, participants in the standard care group had no change in 5-meter gait speed over time. Interestingly, while only three (43%) of the standard care participants chose to enroll in cardiac rehabilitation postoperatively, all eight (100%) participants in the Prehab group had chosen to attend. Collectively, our data suggests that there is an opportunity to utilize a Prehab program to significantly improve the health status of patients waiting for elective CABG. However, the results of our study should be interpreted with caution, and a larger study is needed to establish the safety and efficacy of Prehab.

Physical fitness is an important prognostic factor for predicting adverse cardiac events and mortality. Patients with stable coronary artery disease who walk <419 meters on a 6MWT have a two-fold increased risk of experiencing an adverse cardiac event, as compared with patients who walk >481 meters.[21] In our patient cohort, all patients walked <419 meters at baseline, which did not change in the standard care group. However, after the Prehab intervention, patients were able to walk >481 meters. Therefore, our innovative study data makes an important contribution to this body of literature, because it is the first to demonstrate that a Prehab program enhances physical fitness among a cohort of patients waiting for elective CABG surgery.

Our data did not show a difference in length of hospital stay between standard care and Prehab participants. Over the past decade, length of stay following elective cardiac surgery has declined from an average seven days to five days,[22] which coincides with the average length of hospital stay in our study. Therefore, recent advances in surgical procedures, as well as a small sample size in the current study, could account for the differences observed in our study, as compared with the cardinal study by Arthur et al. published in 2000, where they found a reduction in the length of hospital stay of one day.

Our data shows that all eight (100%) of the Prehab patients chose to enroll in cardiac rehabilitation postoperatively, which was significantly different from the three (43%) standard care patients who chose to enroll. These data add to the previous literature, where Arthur et al.[8] found that CRP attendance rates postoperatively were 70% among Prehab participants, and only 57% among standard care participants. Collectively, a Prehab intervention for elective CABG surgery patients could enhance CRP attendance postoperatively because current estimates indicate that only 15%–20% of North Americans of the referred cardiac population chooses to enroll.[23] However, we acknowledge that only 29% of the eligible elective CABG surgery patients who were contacted chose to participate in the study (Figure 1).

This pilot study has several limitations. The research assistant was not blinded to which participants were in each group, thus increasing detection bias. However, data collection by the research assistant was conducted in accordance with standardized procedures for each outcome variable. In the context of generalizability, beta-blocker use was significantly higher in the standard care group compared with the Prehab group. Furthermore, our recruitment criteria limited us to 79/297 (27%) of the elective CABG surgery cohort. We also did not recruit patients scheduled for other surgeries (i.e. valve repair/replacement, combination surgeries); however, this was a safety feature of our study based on the consensus of cardiac surgeons and cardiologists at the hospital site, that the lack of supportive evidence concerning the safety of a Prehab intervention warranted the exclusion of more complex procedures.

Antiplatelet use was quite low in our patient cohort. However, medications were prescribed by the referring doctor (a cardiologist) to the patients' respective cardiac surgeon and were not altered at the time of their surgery. Finally, several characteristics, including stage of behavior change for a healthier lifestyle,[24] socioeconomic status,[25] and type A personality,[26] which could have influenced our results, were not collected.

In conclusion, our study demonstrates the feasibility of exercise Prehab to improve the health status for patients waiting for elective CABG surgery. Importantly, no Prehab participants developed cardiac symptoms as a result of participation. However, a larger sample size is required to demonstrate the safety and efficacy of this approach. Based on our data, 25% of Prehab patients went from walking <419 meters at baseline to >544 meters, which is suggested to be associated with a three-fold decreased risk (in comparison to a two-fold decreased risk among participants who walked between 419–543 meters) in cardiac morbidity and mortality.[21] Thus, in order to establish the efficacy, as well as the safety of Prehab, a power analysis with an alpha of 0.01, a beta of 0.8, and an anticipated 15% drop-out rate, indicates that 92 elective CABG patients should be recruited (standard care, $n = 46$; Prehab, $n = 46$) for our future Prehab study.

Clinical messages

- Exercise prehabilitation for patients waiting for elective CABG surgery is feasible within this patient cohort and can improve physical fitness preoperatively.
- We will recruit 92 patients in a future randomized controlled trial to demonstrate the efficacy and safety of exercise prehabilitation in patients waiting for elective CABG surgery.

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Conflict of interest

Authors report no conflicts of interest.

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