**Note to Users**

This Protocol Template is designed to be generic. Some subsections and suggestions will not be appropriate for your specific study. You must tailor the protocol contents to meet the needs of your study. Only include sections pertinent to the study, omit irrelevant sections, reorder and add sections as needed. Once you have finished your template, don’t forget to highlight and right hand click on the contents page and select “update all”, this will automatically update the page and section numbers that have change. Please also ensure you have deleted all of the annotations.

You are reminded that a protocol should be a standalone document. The NEAF does need to be filled out in addition to the protocol, however the NEAF ensures that all ethical requirements in the National Statement are satisfied, whereas a protocol should be a detailed description of every aspect of your project, therefore the two documents meet different requirements.

|  |
| --- |
| protocol  |
| **The Supervised Early Resistance Training (SEcReT) Study: progressive resistance training following median sternotomy.** |
| Protocol Number: 2017.266Version: 1Date: 12/09/2017 |
|  |
| **Author/s:**Miss Jacqueline PengellyProfessor Colin RoyseDr Doa El-AnsaryMr Tim DettmannMr Brett Long |
| **CONFIDENTIAL**This document is confidential and the property of Professor Colin Royse. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the institution.**Statement of Compliance**This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). |

# Table of Contents

Contents

[Table of Contents 3](#_Toc322956411)

[**1.** **Glossary of Abbreviations & Terms** 5](#_Toc322956412)

[**2.** **Study Sites** 5](#_Toc322956413)

[2.1 Study Location/s 5](#_Toc322956414)

[**3.** **Introduction/Background Information** 5](#_Toc322956415)

[3.1 Lay Summary 5](#_Toc322956416)

[3.2 Introduction 5](#_Toc322956417)

[3.3 Background information 6](#_Toc322956418)

[**4.** **Study Objectives** 6](#_Toc322956419)

[4.1 Hypothesis 6](#_Toc322956420)

[4.2 Study Aims 6](#_Toc322956421)

[4.3 Outcome Measures 6](#_Toc322956422)

[**5.** **Study Design** 7](#_Toc322956423)

[5.1 Study Type & Design & Schedule 7](#_Toc322956424)

[5.2 Standard Care and Additional to Standard Care Procedures 8](#_Toc322956425)

[5.3 Randomisation 8](#_Toc322956426)

[5.4 Study methodology 8](#_Toc322956427)

[**6.** **Study Population** 9](#_Toc322956428)

[6.1 Recruitment Procedure 9](#_Toc322956429)

[6.2 Inclusion Criteria 9](#_Toc322956430)

[6.3 Exclusion Criteria 9](#_Toc322956431)

[6.4 Consent 9](#_Toc322956432)

[**7.** **Participant Safety and Withdrawal** 9](#_Toc322956433)

[7.1 Risk Management and Safety 9](#_Toc322956434)

[7.2 Handling of Withdrawals 10](#_Toc322956435)

[7.3 Replacements 10](#_Toc322956436)

[**8.** **Statistical Methods** 10](#_Toc322956437)

[8.1 Sample Size Estimation & Justification 10](#_Toc322956438)

[8.2 Power Calculations 10](#_Toc322956439)

[8.3 Statistical Methods To Be Undertaken 10](#_Toc322956440)

[**9.** **Storage of Blood and Tissue Samples** 10](#_Toc322956441)

[9.1 Details of where samples will be stored, and the type of consent for future use of samples 10](#_Toc322956442)

[**10.** **Data Security & Handling** 11](#_Toc322956443)

[10.1 Details of where records will be kept & How long will they be stored 11](#_Toc322956444)

[10.2 Confidentiality and Security 11](#_Toc322956445)

[10.3 Ancillary data 11](#_Toc322956446)

[**11.** **Appendix** 11](#_Toc322956447)

[**12.** **References** 11](#_Toc322956448)

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| **STUDY SYNOPSIS (please provide brief information)** |  |

|  |  |
| --- | --- |
| Title: | The Supervised Early Resistance Training (SEcReT) Study: progressive resistance training following median sternotomy. |
| Short Title: | SEcReT Study |
| Design: | A multisite, Australian pragmatic randomized pilot study. |
| Study Centres: | Royal Melbourne HospitalMelbourne Private HospitalKieser EssendonKieser South MelbourneKieser Caulfield |
| Hospital: | Royal Melbourne HospitalMelbourne Private Hospital |
| Study Question: | Does moderate intensity progressive resistance training reduce cognitive decline and improve patient-reported recovery beyond that of standard, low intensity physiotherapy following cardiac surgery? |
| Study Objectives: | * To determine whether a moderate intensity resistance training rehabilitation intervention can reduce the development of mild cognitive impairment, or reduce deterioration in those with pre-existing cognitive impairment, six months after cardiac surgery compared to standard low intensity physiotherapy.

As this is a pilot study, the endpoints are aimed at establishing feasibility, safety, compliance and group separation. |
| Primary Objectives: | * Change in cognitive performance after surgery.
 |
| Secondary Objectives | * Major adverse cardiac and cerebral events (MACCE)
* Independent living/Functional Status
* Quality of recovery
* Physical function
* Sternal instability
 |
| Inclusion Criteria: | Adults 65 years and older undergoing elective cardiac surgery involving sternotomy and cardiopulmonary bypass, in Australian hospitals where cardiac surgery is performed and physiotherapy and rehabilitation programs are available, and who speak sufficient English to complete the cognitive and quality of recovery surveys. |
| Exclusion Criteria:  | Participants where there is insufficient time or availability for preoperative (baseline) surveys, who have pre-existing dementia diagnosed, or who do not have sufficient English to complete the survey forms will be excluded. |
| Number of Planned Subjects: | 100 |
| Investigational product: | 12-week moderate intensity resistance training program |
| Safety considerations: | Musculoskeletal injury |
| Statistical Methods: | The analysis will be descriptive, as the size of the pilot study will preclude definitive outcome analysis. The data will be reported in terms of group separation with odds ratio and confidence intervals. |
| Subgroups: | Moderate Intensity Exercise Group (n=50)* 12-week moderate-intensity resistance training program.
* 30 minutes, twice weekly.
* Supervised by an accredited exercise physiologist

(Individual 1:1 for weeks 1-4 and small group 1:4 for weeks 5-12).* Commenced 2-3 weeks after hospital discharge.
* Full body training, targeting large muscle groups.
* Performed at RPE 13-16 on Borg 6-20 Rating of Perceived Exertion scale
* Initial weights will be chosen and then progressed, within the limits of safety, and recovery time reduced to apply progressive overload.

Low Intensity Exercise Group (n=50)* Community-based Cardiac Rehabilitation program (formal program or independent program).
* Twice weekly, approximately 120 minutes (education + exercise).
* Low-intensity aerobic training and education for secondary prevention (standard postoperative practice).
* Commenced at least 3 weeks after hospital discharge.
 |

## **Glossary of Abbreviations & Terms**

|  |  |
| --- | --- |
| **Abbreviation** | **Description (using lay language)** |
| MCI | Mild Cognitive Impairment- a stage between the expected cognitive decline of normal aging and that of dementia. This may include problems with memory, language, thinking and judgement. Does not affect activities of daily living. It is associated with risk for progression to Alzheimer’s Disease. |
| POCD | Postoperative Cognitive Decline- a decrease in brain (cognitive) function after surgery. This may include memory and executive functions. |

## **Study Sites**

### Study Location/s

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site** | **Address** | **Contact Person** | **Phone** | **Email** |
| Melbourne Private Hospital | Royal Pde,Parkville 3052 | Lynda TivendaleJacqui Pengelly | 03934289080418555677 | research@heartweb.com |
| Royal Melbourne Hospital | Grattan St, Parkville 3050 | Lynda TivendaleJacqui Pengelly | 03934289080418555677 | research@heartweb.com |
| Kieser Essendon | 26 Leake St,Essendon 3040 | Lynda TivendaleJacqui Pengelly | 03934289080418555677 | research@heartweb.com |
| Kieser South Melbourne | Crn City Rd and Cecil St,South Melbourne 3205 | Lynda TivendaleJacqui Pengelly | 03934289080418555677 | research@heartweb.com |
| Kieser Caulfield | Level 1, 189 Balaclava Rd,North Caulfield 3161 | Lynda TivendaleJacqui Pengelly | 03934289080418555677 | research@heartweb.com |

## **Introduction/Background Information**

### Lay Summary

Heart disease is the number one killer worldwide, with over one million cardiac operations performed each year. Patients undergoing cardiac surgery are typically elderly with multiple health conditions. Whilst cerebral (brain) complications such as stroke are infrequent (3%), a decline in cognitive (brain) function is more prevalent following surgery with reports that concentration, focus, cognitive processing speed and short-term memory is impaired in 15–40% of patients at 3 months or longer after surgery.(1-4) This permanent loss of cognitive function is even higher in elderly patients,(5-7) and results in disability and loss of independence. It may also accelerate the incidence of dementia, as high as 30% in patients 7.5 years after cardiac surgery.(8)

Dementia occurs in approximately 9% of the general population over the age of 65 years, causing substantial personal and family suffering, and a high cost to the health care system. Within the next 20 years, 100 million people are predicted to have dementia, which will pose a serious challenge for the health care system.(9) Furthermore evidence of mild cognitive impairment (MCI), considered a precursor to dementia, is evident in 30-50% of patients prior to undergoing cardiac surgery.(10) Preventing further deterioration of cognitive function after surgery is therefore critical in reducing dementia in this vulnerable cohort.

Previous studies have shown that exercise preserves or even improves cognitive function,(11) as well as reducing long term cognitive decline.(12,13) This study will look at the effect of early weight training exercise, requiring an increased effort and heart rate, following open heart surgery. We aim to determine if there is an optimal dose (type, intensity and duration of exercise) to maximize cognitive and physical health benefits. Participants will be randomly assigned (like tossing a coin) to either a 12-week moderate intensity weight training program or to a 6-week low-intensity exercise program (usual care). Participants in both groups will attend twice weekly exercise rehabilitation, lasting for approximately 60 minutes per session (12-24 sessions). All exercise sessions will be supervised by an accredited exercise physiologist or physiotherapist to ensure patient safety. We predict that the weight training intervention will prevent further cognitive decline, and result in significantly greater improvements in patient-reported recovery, exercise ability and muscular strength up to 6 months after surgery. We anticipate that the participants will return to pre-disease levels of health and function or better.

### Introduction

Patients undergoing cardiac surgery are typically elderly with multiple co-morbidities. We surveyed a patient stakeholder group and determined that the three worst outcomes (of equal importance) after surgery include death, loss of cognitive function and loss of independent living. Dementia occurs in approximately 9% of the general population over the age of 65 years, causing substantial personal, and family suffering, and a high cost to the health care system. However, in patients undergoing major surgery, the incidence of dementia may be accelerated, as high as 30% in patients 7.5 years after cardiac surgery.(8) It is well-known that a proportion of patients (15 to 30%) will suffer permanent cognitive decline after surgery, with this even higher in elderly patients.(5-7) Loss of cognitive function results in disability after cardiac surgery, which has a world-wide importance as more than one million cardiac operations are performed annually. Mild cognitive impairment (MCI) is considered a precursor to dementia, where there is evidence of mild cognitive impairment but preservation of activities of daily living.(14,15) What is less known is that 30-50% of patients undergoing cardiac surgery have preoperative evidence of impaired cognitive function.(10) Importantly, the rate of conversion from normal cognition to mild cognitive impairment over 18 months in an Australian population was 2.5% predominantly effecting memory and naming domains, whereas conversion from mild cognitive impairment to dementia was 30.5%.(16)

***Preventing further deterioration of cognitive function after surgery is therefore critical in reducing dementia in this vulnerable cohort.***

The study will be a pilot study to determine feasibility, protocol compliance, safety and group separation to provide high level information to design **a large scale, pragmatic randomised trial.** We will compare the effect of **a moderate intensity resistance training physiotherapy intervention compared to standard low intensity physiotherapy,** on the development of cognitive decline after cardiac surgery, or further deterioration in those with pre-existing cognitive dysfunction. Animal and human studies have previously shown physiotherapy interventions to preserve or even improve cognitive function,(11) as well as reducing long term cognitive decline.(12,13) We will determine if there is a dose effect for type and intensity of physiotherapy rehabilitation as well as longer duration (12 weeks vs. 6 weeks for standard care) The primary endpoint will be the change in cognition measured using the ADAS-cog subscale, measured prior to and at 6 months after surgery. Interventions to prevent the development of dementia will have enormous impact to patients, families and caregivers in the short and long terms after surgery, and help reduce the health care burden for Australia. This study will help to address the evidence gap of whether specific physiotherapy/rehabilitation intervention can reduce risk of cognitive decline after cardiac surgery.

### Background information

**Defining the problem**

One of the most pressing challenges for the health care system is that within the next 2 decades 100 million persons are predicted to have dementia.(9) Each year over one million cardiac surgery operations are performed worldwide. Whilst cerebral complications such as cerebral infarction and transient ischaemic attacks are infrequent (3%), a decline in cognitive function is more prevalent following surgery with reports that concentration, focus, cognitive processing speed and short-term memory is impaired in 15–40% at 3 months or longer after surgery.(1-4) Risk factors associated with postoperative cognitive impairments include advanced age, perioperative dysrhythmias of the heart, those with early cognitive impairment and comorbid disease (cardiovascular disease, hypertension and diabetes).(2,7) In Australia, patients are presenting for cardiac surgery at an older age (mean age: 70 years of age) with increasing comorbidities (ANZCTS annual report, 2015) putting them at more risk of adverse cerebral outcomes. The proposed mechanisms responsible for cognitive impairment are multifactorial and include cerebral embolization, anaesthesia and other physiological demands of surgery.(1) However, the literature shows associations with cognitive decline that are not consistent. For example, there is a disconnect between cerebral embolization seen on MRI after surgery and Postoperative Cognitive Decline (POCD).(17,18) Despite the substantial number of studies reporting cognitive impairment after cardiac surgery a paucity of studies have investigated interventions aimed at preventing the progression of cognitive impairment to dementia after cardiac surgery.

Dementia occurs in approximately 9% of the general population over the age of 65 years, causing enormous personal, and family suffering, and a huge cost to the health care system.(16) In patients undergoing major surgery, the incidence of dementia may be as high as 30% in patients 7.5 years after cardiac surgery.(19) It is well-known that a proportion of patients will suffer permanent cognitive decline after surgery, with a higher proportion in elderly patients.(5) It is unknown yet whether postoperative cognitive decline will lead to increased risk of dementia. Mild cognitive impairment (MCI) is considered a precursor to dementia, with evidence of mild cognitive impairment, but preservation of activities of daily living, whereas dementia will involve cognitive decline sufficient to also cause functional impairment.(14,15) MCI is frequent in elderly patients presenting for surgery, and in patients requiring hospital admission for nonsurgical disease, present in 32% of patients presenting for hip replacement surgery.(20) In cardiac surgery, the incidence of low preoperative cognition with preservation of activities of daily living (ADL), is as high as 50% in high-risk cardiac surgery patients.(10) Patients undergoing cardiac surgery may be a particularly vulnerable cohort to the development of, or worsening of cognition and risk of dementia in the longer term.

What is also unknown, is whether cognitive impairment *before* surgery or hospital admission or cognitive decline after surgery, will lead to increased risk of dementia in the longer term. Preliminary evidence would suggest that postoperative cognitive decline is more common after surgery in patients with preoperative cognitive impairment.(8,20) By the time dementia is diagnosed, it is be too late for effective interventions, and so represents a lost opportunity to reduce the risk of dementia.

**Physiotherapy interventions can improve clinical and cognitive outcomes**

The current standard of care for physiotherapy after cardiac surgery, including rehabilitation programs, is to provide low intensity exercise. In Australia, patients are not routinely seen by physiotherapists preoperatively, and typically the first visit is following extubation the day after surgery.(21,22) Patients are routinely assessed and screened for postoperative pulmonary complications; commence a progressive mobilization program (i.e. walking); and, participate in active upper limb, foot and ankle exercises. Prior to discharge the physiotherapist may educate the patient in continuing sternal precautions and a progressive program of mobilization. Patients are usually referred to a Cardiac Rehabilitation program in the community setting and are able to commence this program 3 weeks following surgery, pending availability (Australian Cardiovascular Health and Rehabilitation Association website, 2016). Cardiac Rehabilitation programs predominantly consist of cardiovascular aerobic exercise training and education for secondary prevention twice weekly for a typical duration of 6 weeks.

There is experimental evidence that exercise interventions of as little as one session per week can result in improved cognitive function (memory, focus and reaction time) and thus may present as effective primary prevention strategies for cognitive decline and progression to dementia.(11,12) A meta-analysis of prospective studies reported that higher physical activity levels correlated with a 28% reduction in dementia.(13) It has been estimated that reducing physical inactivity by 25% may prevent one million cases of dementia worldwide.(23) Resistance or strength exercise training has been reported to result in more significant improvement in cognitive function with a larger effect size (0.53) than typical isolated aerobic training (0.41), and is comparable to a combination of aerobic and strength training protocols.(24) Resistance training accelerates improvements in cardiovascular fitness; cognitive function; muscle function quality (mass, quality and strength), induction and regulation of growth factors and modulation of systemic inflammation.(12) Progressive resistance training augments the effects on insulin-like growth factor-1, insulin sensitivity; mediates inflammation and neurotrophic factor pathways that are associated with cognitive decline and sarcopenia.(25,26) More importantly, it may present less burden to patients as each exercise session takes less time to complete than usual rehabilitation, and is more feasible in elderly who are frail and have mobility impairments. *However, there have been no studies that have investigated the effects of pre-operative exercise education and the minimum frequency of training to influence adherence and prevent progression to dementia after cardiac surgery****.***

Although published data are few, there is strong preliminary evidence that a physiotherapy intervention may also reduce physical complications, particularly related to respiratory function. The LIPPSMACK POP study has been presented in abstract form only (Australian and New Zealand College of Anaesthetists Annual Scientific Meeting, 2015), but was a randomised trial of 441 participants receiving minimal education using a booklet versus the booklet plus practice physiotherapy prior to major abdominal surgery. The primary endpoint of post-operative pulmonary complications was reduced from 27% in the control group to 10.5% in the intervention group (P < 0.001, NNT = 6, Risk ratio 16.5), as well as reductions in intensive care and hospital length of stay.

***Taken together, these data are strongly supportive that a physiotherapy intervention may be effective in reducing the development of cognitive decline, as well as improving overall physical recovery.***

**Moderate intensity resistance training is safe after cardiac surgery**

In prior research, bilateral unloaded and loaded (1RM) upper limb exercises were well tolerated and resulted in minimal sternal micromotion of the bone edges in patients following a sternotomy with and without sternal instability, respectively.(21,22) The shorter duration of a progressive focused resistance training session (20-30 minutes) is safe for those with compromised cardiovascular function such as heart failure; will minimise fatigue and promote adherence. It can also be easily integrated by the participant with standard care independent aerobic activity in line with current recommendations.(27) This type of physiotherapy intervention can be conducted by any physiotherapist, and therefore can be widely implemented with a small additional cost.

**Postoperative Quality of Recovery**

The post-operative quality of recovery scale (PostopQRS), is a multidimensional survey tool primarily designed for assessing quality of recovery after surgery.(28) Scoring recovery involves comparing post-surgery performance to pre-surgery baseline values. The domains include physiological, nociceptive, emotive, activities of daily living, and cognition. The pre-surgery baseline values serve as an excellent phenotype for patients with respect to the five domains. The scale is conducted either face-to-face whilst in hospital, or via telephone interview after discharge.(29) The ability to conduct the scale via telephone makes this a highly feasible tool for extended patient follow-up. Importantly, the scale only takes 5 – 6 minutes to conduct on each occasion and does not require highly specialised staff to perform it.

Specifically, the cognitive domain examines both memory and executive function (word generation task), allowing more than just memory to be tested.(14) Because the scale has both cognitive and functional dimensions (assessment of ADL), it is suitable to use as an early indicator screening tool for cognitive impairment and dementia, as cognitive impairment can be identified with or without impairment of function. Further, the scale has defined cut off scores for low baseline cognition which can identify preoperative cognitive impairment.(29) The application of the scale is appropriate for patients having hospital admission, as it will be used to track change over time from their baseline values on admission. It is already validated and used widely, and is set up for multi-user web-based access (www.postopQRS.com). Scoring of the scale is automatically conducted by the system, and individual recovery outcomes are available in real time.

Preoperatively, the PostopQRS can be used to capture the multidimensional aspects of quality of recovery from the patient perspective. This can be used to identify the association of cognitive decline other quality of recovery parameters. Because it is a simple to perform tool that is validated for telephone use, the PostopQRS can be used to track deterioration in cognitive and functional domains over time, and will complement the assessment using the ADAS-cog and Mini Mental State Examination (MMSE) scales.

**Project justification and value for money**

Prevention of cognitive decline is a much better and more cost-effective strategy than trying to modulate cognitive dysfunction once it has developed. Cardiac surgery patients are a particularly vulnerable cohort for the development of cognitive decline, or for further deterioration of cognition for those who have pre-existing cognitive impairment. Patients with cognitive impairment have a much faster rate of progression to dementia than patients with normal cognition. Major surgery such as cardiac surgery can have a large effect on accelerating cognitive decline and progression to dementia. Value for money can be measured in human as well as resource terms. We have engaged a patient and stakeholder group of 31 participants, which includes family members and caregivers, healthcare professionals, hospital administrators and hospital insurers to help us determine what the most important endpoints to measure in the study are. They advised us that the most important outcomes after surgery included “staying alive” (90%), “maintaining brain function” (83.9%), and (“avoidance of physical complications” (77.4%). However, survival was not the most important issue for participants, rather maintenance of independence, good pain management and being safe and well cared for were deemed very important outcomes. They also advised that the worst outcomes were loss of brain function (80%), suffering a permanent disability (80%), and death (77%). Other adverse outcomes that were frequent included loss of independence and requirement for long term aged care. Prevention of cognitive impairment, and by implication delaying or preventing the onset of dementia, is one of the most important outcomes to study and the most meaningful to the patients and their families, as well as the healthcare industry.

The physiotherapy intervention is relatively cheap and simple to implement. Standard cardiac physiotherapy and rehabilitation costs around $500 for a 6-week program, whereas the moderate intensity resistance training for a 12-week program costs approximately $1100. The additional cost covers more physiotherapy time and duration, and is very small compared to the costs associated with the development of dementia. Once damage is done, therapy is focused on preventing further decline, but largely on managing patients who cannot look after themselves in an aged care setting. This can be devastating to the patient their families, and very expensive for the community. Once dementia has occurred, the care and expense is lifelong. If even a small fraction of patients can be prevented from developing cognitive impairment and later dementia, then the physiotherapy intervention will provide exceptional value for money.

## **Study Objectives**

### Hypothesis

Moderate intensity resistance training will result in a superior difference of at least 2 on the ADAS-cog scale at six months after cardiac surgery compared to standard low intensity physiotherapy.

### Study Aims

1. **Primary:** To determine whether a moderate intensity resistance training physiotherapy intervention can reduce the development of mild cognitive impairment, or deterioration in those with pre-existing cognitive impairment, six months after cardiac surgery compared to standard low intensity physiotherapy.
2. **Secondary**: To determine whether quality of recovery, muscle strength and lung capacity is improved after a 12 week supervised moderate intensity resistance training intervention compared to a low intensity program in patients after cardiac surgery.
3. To determine group separation for the primary outcome, intervention feasibility and compliance, and any safety issues with the exercise program.

### Outcome Measures

The **primary outcome** will be the change from pre-surgery cognitive score using the ADAS-cog scale at six months after cardiac surgery. This outcome (deterioration of cognitive function) was determined as extremely important by our patient and stakeholder group, and the six-month time period was selected as recovery after cardiac surgery tends to plateau around six months with minimal increases beyond that, thereby predominantly removing the potentially confounding effect of continual recovery, or need for medications such as analgesia.

**Secondary outcomes**

Our patient and stakeholder group identified survival, independent living, and quality of recovery as very important outcomes. In addition, we wish to identify whether the intervention has long-term outcome differences with regard to cognitive outcomes, and the incidence of progression to dementia.

1. **Major adverse cardiac and cerebral events (MACCE).** Data collected at six months. MACCE endpoints includes all-cause mortality, cerebral vascular event (stroke), documented myocardial infarction, or repeat coronary intervention (percutaneous coronary intervention or redo cardiac surgery).
2. **Functional Status/Independent Living.** Functional Disability Questionnaire and Lawton & Brody Instrumental Activities of Daily Living Scale. Data collected at baseline (pre-operatively) and 6 months post-hospital discharge. The Lawton & Brody IADL Scale assesses the living skills deemed necessary to live independently in the community. These skills are considered more complex than the basic activities of daily living. It is useful to determine how an individual is currently functioning and monitoring improvement or deterioration over time.(30)

The short-form Functional Disability Questionnaire (FDQ) is a 13-item questionnaire which asks the participant to rate the difficulty they experience when completing a series of 13 upper limb and trunk activities by placing a mark along a 10cm line, with anchors indicating “no difficulty” and “maximum difficulty”.(31) For those activities that participants could not attempt whilst completing the questionnaire due to the institution sternal precautions, they are asked to think back to the last time they performed the task.(31) Individual scores, measured to the nearest centimeter (cm), are aggregated to form a total out of 130 with higher scores representing greater difficulty experienced during functional activities.

1. **Cognitive decline after surgery stratified by pre-existing cognitive and functional status.** Mild cognitive impairment is a clinical diagnosis, and is a recognised precursor to the development of dementia. Formal diagnosis involves assessment of cognition, especially of memory, and using an instrumental activities of daily living scale (such as the Lawton and Brody IADL scale(30)), with exclusion if there is a physical explanation for failure of IADL. There are multiple approaches used by clinicians to assess memory, but the MMSE is a commonly used tool. The MMSE is a valid tool commonly used to assess cognitive function. The MMSE separates patients with cognitive disturbances from those without, indicating level of cognitive impairment.(32)  For the purposes of this trial, pre-existing cognitive impairment will be defined as
	1. normal – MMSE score 27-30 and normal IADL (score 8 females and 5 males)
	2. mild – MMSE score 24-26 and normal IADL (score 8 females and 5 males)
	3. moderate - MMSE score 18-23 and normal IADL (score 8 females and 5 males)
	4. severe - MMSE score <18 and impaired IADL (score <8 females and <5 males)

Analysis of cognitive function using the ADAS-cog scale will be stratified by the groups above to identify if the intervention has different efficacy based on preoperative cognitive classification.

1. **Quality of Recovery** will be assessed using the Post-Operative Quality of Recovery Scale performed prior to surgery and then at 1, 3-5 and 7 days, 6 weeks, 3 and 6 months after surgery via face-to-face or telephone interview. The Post-opQRS is a quality of recovery scale that aims to detect change in multiple domains of recovery over time. Recovery is broadly defined as return to baseline or better.(33) The scale will measure outcomes in physiological, nociceptive (including pain), emotive, functional (ADL), cognitive domains as well as overall patient perspective including satisfaction with care.
2. **Physical function** assessment to identify whether the moderate intensity resistance training has been effective will be measured at the first and last physiotherapy session (pre-intervention, 6 and 12 weeks), and at 6 months after hospital discharge, and will include:
	1. **Isometric muscular strength:** isometrictesting will be performed on resistance machines that stabilise the joint and isolate the muscle during testing. Each test is of 15-20 second duration to ensure safety. Peak torque is measured using a dynamometer placed in the shaft of the equipment. Measures are taken twice and the highest measure is recorded, a 3rd repeat is conducted if there is greater than 10% differential between the first 2 readings. (Kieser Training AG, Zurich)
	2. **Grip strength:** Hand-grip strength will be measured in kilograms with a hand-held JAMAR dynamometer (Sammons Preston Rolyan, Brooklyn, USA). The participant will be tested in the position recommended by the American Society for Hand Therapists (participant seated with shoulder adducted, neutrally rotated, elbow flexed to 90 degrees). The peak value of the maximal squeeze over 5 seconds will be recorded. Three serial tests of maximum grip strength with the dominant hand will be performed, and best of the 3 values will be recorded. Hand-held dynamometry is a reliable, objective tool for muscle strength measurement, and a predictor of postoperative complications, mortality, functional decline and cardiovascular risk.(34) The test is a reliable and responsive measure for patients in cardiac rehabilitation (ICC = 0.97).(34)
	3. **Lung capacity:** VO2peak will be estimated via breath gas analysis on a Spirobank II Advanced spirometer.(35) The test takes no longer than 60 seconds to complete. The participant will be asked to breathe normally for 3 breaths before being asked to take a big breath in, breathe out as hard and as fast as they can and then take another big breath in.
	4. **Four Square Step Test:** this is a measure of dynamic standing balance, assessing a person’s ability to step over objects, forward sideways and backwards. The time taken to complete the sequence is recorded in seconds.
	5. **Body Composition:** Waist Circumference and Body Mass Index (BMI) will be collected to determine any compositional changes.
* Waist circumference is a measure of central adiposity (excess body fat around your middle) and is an indicator of risk of developing ongoing health problems. It will be measured with a measuring tape in centimeters (cm).
* BMI give you an idea of whether your weight is healthy for your height. It will be calculated from height in meters (m) and weight in kilograms (kg), using the formula BMI= weight (kg) ÷ height2(m). It is also an indicator of health disease risk.
1. **Sternal Stability** will be assessed using sternal ultrasound and the Sternal Instability Scale (SIS). This will allow the researchers to measure any sternal movement occurring and monitor patient safety during the exercise.
	1. **Ultrasound:** Previous research has shown that ultrasound measures are a valid and reliable indicator of the motion at the sternal edges in patients post-median sternotomy.(36) It has demonstrated excellent test-retest reliability with intra-class correlation coefficients ranging from 0.90 to 0.93.(36)
	2. **Sternal Instability Scale (SIS):** The SIS is a manual test that measures the stability of the sternum based on a 4-point scale.(37) A score of 0 corresponds to a clinically stable sternum with no detectable motion or separation of the sternal edges, whilst a score of 3 corresponds to a completely separated sternum with marked increased motion or separation of the sternal edges. Previous research has shown that the SIS is both a valid and reliable clinical tool for measuring the stability of the sternum in patients following a median sternotomy. It has demonstrated excellent inter- and intra-rater reliability, with intra-class correlation coefficients of 0.97 and 0.98, respectively.(38)

# **Study Design**

### Study Type & Design & Schedule

1. Specify the type of study e.g., Cohort-study (retrospective or prospective), case-control study, cross-sectional study. Prospective randomised pilot trial.
2. Specify the basic design elements including the population to be studied (e.g., Adults aged 18-35), any risk factors present. Adults aged 65 years and over, presenting for median sternotomy for coronary artery disease.
3. Specify if this study will be a single-centre or multi-centre (national or international) study. Multi-centre national trial (Royal Melbourne Hospital and Melbourne Private Hospital)
4. Specify how the design will achieve the aims and objective

This is a RCT which aims to evaluate the effects of a moderate intensity strength training program on cognitive recovery and patient-reported outcomes and compare this to standard cardiac rehabilitation in a cohort of cardiac surgery patients. The outcome measures selected to address the primary aims of the study are reliable and robust. Details of each of these outcomes have been outlined previously.

1. Please state what data will be collected e.g., blood tests, MRI’s, genetic testing, videos, photos, questionnaires etc... For each item, specify if the data collected will be identifiable, re-identifiable or non-identifiable.
* Questionnaires- re-identifiable
* Physical/Functional Tests- re-identifiable
* Major adverse cardiac and cerebral events- re-identifiable
* Sternal Stability (manual palpation and ultrasound)- re-identifiable
1. Describe how you will collect, handle and store all types of data collected.

Information is entered into the CRF and into the investigator electronic databases. Only group data will be analysed and presented. The PostopQRS survey is entered into an online database www.postopqrs.com, which only allows de-identified data to be entered. Access to the PostopQRS database is limited to researchers and password protected. All data will be stored for a minimum of 15 years.

Information collected from participants will be stored securely in both hard copy (paper) and soft copy (electronic). The information will be stored on paper records at the University of Melbourne in a locked cabinet, and the data entered into an electronic web-based database (www.postopQRS.com, located at City, University of London) and other research documents stored on a secure file server based at the University of Melbourne.

1. Specify the time frame for each component of the study, this should include study visits, how long recruitment is open for and how long analysis will take etc..
* *Recruitment:* 01/11/2017 to 31/12/2018
* *Exercise Intervention & Follow-up Period:* 01/11/2017 to 30/06/2019
* *Data Analysis:* 3 months from the last data entry.
1. Specify if the study requires any home visits, and what the home visit policy and procedures are. Home visits will not be required as part of this study.
2. Ensure you have included all information on all required contingency plans within your study outline.

The chief investigator, Prof Colin Royse, will be ensuring that the study will be conducted in accordance with the CONSORT guidelines. Any aspects of the trial that require contingency plans will be discussed with the chief investigator.

1. State if this protocol will be used towards a student project, and if so, state what course and degree the student will undertake. This project will be used as part of Miss Jacqueline Pengelly’s Doctorate of Philosophy (PhD), undertaken at the University of Melbourne.
2. Provide a flowchart or table specifying visits, interventions and other relevant details

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### Standard Care and Additional to Standard Care Procedures

|  |  |  |
| --- | --- | --- |
| **Standard Care Procedures** |  | **Additional To Standard Care** |
| **Procedure** | **Time/Visit** | **Dosage/Volume** |  | **Procedure** | **Time/Visit** | **Dosage/Volume** |
| Community outpatient Cardiac Rehabilitation | 2x/week | As per patient signs & symptomBorg RPE 8-11/20 |  | Patients will be asked to keep a diary of their daily physical activity time. |  |  |

**Interventions**

Following surgery, participants will receive standard care physiotherapy whilst in hospital. They will then transition to either a 6-week low intensity exercise program (standard care) or a 12 week program of moderate intensity resistance training program.

**Low Intensity Exercise (Standard Care):**

In Australia patients are not routinely seen by physiotherapists pre-operatively. Physiotherapy care commences following extubation the day after surgery. Patients are routinely assessed and screened for postoperative pulmonary complications; commence a progressive mobilization program (i.e. walking); and, participate in active upper limb, foot and ankle exercises. Prior to discharge the Physiotherapist may educate the patient in continuing sternal precautions and a progressive program of mobilization. Patients are usually referred to a Cardiac Rehabilitation program in the community setting and are able to commence this program 3 weeks following surgery pending availability. Cardiac Rehabilitation programs predominantly consist of cardiovascular aerobic exercise training and education for secondary prevention twice weekly for a typical duration of 6 weeks.

**Moderate Intensity Exercise Intervention:**

Participants in the moderate intensity intervention group will be asked to attend one assessment session pre-operatively to obtain baseline data and educate the participant on the training protocol and the exercise equipment to be used. This will be done at the hospital, when patients are admitted on the night prior to surgery. Education and training of patients prior to their surgical procedure may facilitate memory and recall of their program; promote connectivity and proactive behaviour at a time when relatively well are a captive audience. Participants will attend a 12-week resistance training program twice weekly. They will be small group sessions conducted under the supervision of an accredited exercise physiologist or a physiotherapist with a staff to participant ratio of 1:4. The increased duration over standard care has been shown to have an important dose effect for strength gains.(39,40) The program will commence with 6-8 exercises for weeks 1-3 and progress to 8-10 exercises by week 4. Transition time between exercises will be reduced from 2-3 minutes to 1-2 minutes in the 4th week. Exercises may include: hip abduction, hip adduction, leg press, knee extension, lumbar extension, seated row and chest press. The strength training sessions will consist of a full body program, completed at a moderate intensity of 13-16 on the Borg 6-20 scale. One set of each exercise will be performed to the point of local muscular fatigue (90-120 seconds), at a 4-2-4 cadence (4 second concentric contraction, 2 second isometric hold, 4 second eccentric contraction). To apply progressive overload, initial weights will be chosen and then progressed, using the formula that if the exercise can be completed for 120 seconds, within the intensity guidelines, the weight will be increased by 1–2 kg. To facilitate active engagement and potential cognitive enhancing effects of the strength training, a new exercise will be introduced every 4 sessions. Participants will also be encouraged to actively count out loud, breathe correctly, be self-directed in monitoring their progress and proactive in increasing their weights by 1– 2 kg if the exercise is perceived to be too easy.

The sessions will begin and terminate with a warm-up and cool-down to avoid any adverse cardiac events.

|  |  |  |
| --- | --- | --- |
| **#** | **Initial Exercise** | **Progression** |
| **1** | B1 Leg Extension\* | B6 Leg Press |
| **2** | B7 Seated Leg Curl\* | A3 Hip Abductors\* |
| **3** | D7 Seated Dip | A4 Hip Adductors |
| **4** | C1 Pullover | C2 Torso Arm Front/ OR C3 Torso Arm |
| **5** | E5 Neck Extension | E3 Overhead Press |
| **6** | F3 Lower Back- Starting in neutral | F3- Progressing to trunk flexion (position 1/2) |
| **7** | J9 Side Bend | C5 Rowing Torso OR C7 Row |
| **8** | E2 Lateral Raise\* |   |

*\*Machine suitable for strength testing*

*Start with more isolated muscle groups, moving to multiple muscle groups.*

### Randomisation

**Randomisation**–Randomisation codes will be computer generated in uneven blocks.

**Allocation concealment and implementation*–*** The allocation sequence will be concealed using double sealed opaque envelopes, as this is a small pilot study. Following recruitment, the exercise physiologist and physiotherapist will be informed and they will be given the allocation and then arrange for the preoperative education session if allocation is to the intervention group.

**Blinding–** The surgical team will be blinded to allocation. The patient and physiotherapy team will not be blinded. The accredited exercise physiologist or physiotherapist will conduct the secondary outcome assessment for muscle strength outcomes, which will be unblinded.

## Study methodology

Information needs to be re-identifiable in the event that a participant experiences adverse effects or serious adverse effects. Information that affects the long-term health of the participant will be forwarded to the local health practitioner for ongoing medical care and support services.

Information collected:

* **Demographics.** Sex, age, marital status, occupational status, educational status, comorbidities.
* **Feasibility data.** Recruitment, attendance, drop-out rates, adverse events, intervention safety and completion, inclusion criteria and consent.
* **Major adverse cardiac and cerebral events (MACCE).** Endpoints include all-cause mortality, cerebral vascular event (stroke), documented myocardial infarction, or repeat coronary intervention (percutaneous coronary intervention or redo cardiac surgery).
* **Short-Form Functional Disability Questionnaire *(see appendix).*** The short-form Functional Disability Questionnaire (FDQ) is a 13-item questionnaire which asks the participant to rate the difficulty they experience when completing a series of 13 upper limb and trunk activities by placing a mark along a 10cm line, with anchors indicating “no difficulty” and “maximum difficulty”.(31) For those activities that participants could not attempt whilst completing the questionnaire due to the institution sternal precautions, they are asked to think back to the last time they performed the task.(31) Individual scores, measured to the nearest centimeter (cm), are aggregated to form a total out of 130 with higher scores representing greater difficulty experienced during functional activities.
* **Mini Mental State Examination (MMSE) *(see appendix).***The MMSE is a valid tool commonly used to assess cognitive function. It separates patients with cognitive disturbances from those without, indicating level of cognitive impairment.(32) For the purposes of this trial, pre-existing cognitive impairment will be defined as
	1. normal – MMSE score 27-30 and normal IADL (score 8 females and 5 males)
	2. mild – MMSE score 24-26 and normal IADL (score 8 females and 5 males)
	3. moderate - MMSE score 18-23 and normal IADL (score 8 females and 5 males)
	4. severe - MMSE score <18 and impaired IADL (score <8 females and <5 males)
* **Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-cog) *(see appendix).*** Evaluates cognition and helps to differentiate between normal and impaired cognitive functioning. It is a useful tool in measuring the extent of cognitive decline and evaluate the stage of Alzheimer’s Disease a person is in.
* **Lawton & Brody IADL scale *(see appendix).*** The Lawton & Brody IADL Scale assesses the living skills deemed necessary to live independently in the community. These skills are considered more complex than the basic activities of daily living. It is useful to determine how an individual is currently functioning and monitoring improvement or deterioration over time.(30)
* **Post-operative Quality of Recovery Scale (Post-opQRS) *(see appendix).*** The Post-opQRS is a quality of recovery scale that aims to detect change in multiple domains of recovery over time. Recovery is broadly defined as return to baseline or better.(33) The scale will measure outcomes in physiological, nociceptive (including pain), emotive, functional (ADL), cognitive domains as well as overall patient perspective including satisfaction with care.
* **Lung capacity (spirometry).** Is a method of determining lung capacity (VO2) through breath analysis.(35) The average test duration is no longer than 60 seconds. The participant will be asked to breathe normally for 3 breaths before being asked to take a big breath in, breathe out as hard and as fast as they can and then take another big breath in.
* **Body composition.** Will be measured to assess body compositional changes and used as an indicator of risk of ongoing health problems.
1. ***Waist circumference*** is a measure of central adiposity (excess body fat around your middle). It will be measured with a measuring tape in centimeters (cm).
2. ***Body Mass Index (BMI)*** will give you an idea of whether your weight is healthy for your height. It will be calculated from height in meters (m) and weight in kilograms (kg), using the formula BMI= weight (kg) ÷ height2(m).
* **Isometric muscular strength.** Isometrictesting will be performed on resistance machines that stabilise the joint and isolate the muscles during testing. Each test is of 15-20 second duration to ensure safety. Peak torque is measured using a dynamometer placed in the shaft of the equipment. Measures are taken twice and the highest measure is recorded, a 3rd repeat is conducted if there is greater than 10% differential between the first 2 readings. (Kieser Training AG, Zurich) Measured in Newtons (N).
* **Handgrip strength.** Hand-grip strength will be measured in kilograms with a hand-held JAMAR dynamometer (Sammons Preston Rolyan, Brooklyn, USA). The participant will be tested in the position recommended by the American Society for Hand Therapists (participant seated with shoulder adducted, neutrally rotated, elbow flexed to 90 degrees). The peak value of the maximal squeeze over 5 seconds will be recorded. Three serial tests of maximum grip strength with the dominant hand will be performed, and best of the 3 values will be recorded. Hand-held dynamometry is a reliable, objective tool for muscle strength measurement, and a predictor of postoperative complications, mortality, functional decline and cardiovascular risk.(34) The test is a reliable and responsive measure for patients in cardiac rehabilitation (ICC = 0.97).(34)
* **Four square step test (FSST).** A measure of dynamic standing balance, assessing a person’s ability to step over objects, forward sideways and backwards. The time taken to complete the sequence is recorded in seconds.
* **Sternal Stability.** Will be assessed using sternal ultrasound and the Sternal Instability Scale (SIS). This will allow the researchers to measure any sternal movement occurring and monitor patient safety during the exercise.
1. ***Ultrasound:*** Previous research has shown that ultrasound measures are a valid and reliable indicator of the motion at the sternal edges in patients post-median sternotomy.(36) It has demonstrated excellent test-retest reliability with intra-class correlation coefficients ranging from 0.90 to 0.93.(36)
2. ***Sternal Instability Scale (SIS):*** The SIS is a manual test that measures the stability of the sternum based on a 4-point scale.(37) A score of 0 corresponds to a clinically stable sternum with no detectable motion or separation of the sternal edges, whilst a score of 3 corresponds to a completely separated sternum with marked increased motion or separation of the sternal edges. Previous research has shown that the SIS is both a valid and reliable clinical tool for measuring the stability of the sternum in patients following a median sternotomy. It has demonstrated excellent inter- and intra-rater reliability, with intra-class correlation coefficients of 0.97 and 0.98, respectively.(38)

## **Study Population**

### Recruitment Procedure

Participants who are scheduled for cardiac surgery will be screened and recruited from the Cardiac Surgery operation lists, surgeons clinics, preadmission clinic and pre-operative ward.

The initial contact will be made in person during the first contact session prior to surgery. Inpatients scheduled for cardiac surgery will be screened on the ward.

Medical histories will be reviewed and screened for participant suitability and eligibility.

###  Inclusion Criteria

The study population will include adults aged 65 years and over, undergoing elective cardiac surgery involving sternotomy and cardiopulmonary bypass, in Australian hospitals where cardiac surgery is performed and physiotherapy and rehabilitation programs are available, and who speak sufficient English to complete the cognitive and quality of recovery surveys.

### Exclusion Criteria

Participants where there is insufficient time or availability for preoperative assessment and education, who have pre-existing dementia diagnosed, or who do not have sufficient English to complete the survey forms will be excluded.

### Consent

Individual written informed consent will be obtained.

# **Participant Safety and Withdrawal**

### Risk Management and Safety

Risk of injury- risk of injury is very unlikely, as the exercise testing and exercise training will be supervised by an Accredited Exercise Physiologist and/or Physiotherapist, and participant’s signs and symptoms will be closely monitored. The significant improvement participants are likely to experience greatly outweighs the small risk of injury.

It is hypothesised that participants will return to their premorbid levels of function or better, as a direct result of the exercise intervention. Moderate intensity exercise, inclusive of upper limb and trunk exercise, has been shown to be safe in the cardiac population and should not increase the risk of harm any more than conventional cardiac rehabilitation.

### Handling of Withdrawals

Participants will be informed that they are free to withdraw from the study at any time. They will also be informed that their withdrawal will not affect the relationship between them and the treating doctors or the hospitals. They will be informed that any data collected to point of withdrawal will be used to prevent bias in the results, unless they specifically refuse that request. From the time of withdrawal, no further data will be acquired for that participant.

### Replacements

Participants will not be replaced if they withdraw from the study. Data collected to point of withdrawal will be used to prevent bias in the results. As this is a pilot study, this data is required to determine study feasibility and group separation, and will represent a low risk of bias to the study.

# **Statistical Methods**

### Sample Size Estimation & Justification

As the effect size is currently unknown, we aim to perform pilot studies to determine group separation and feasibility. The results will allow sample size estimates for future definitive trials. A sample size of 100 participants is feasible for the institutions and resources, and able to be completed in the PhD timeframe.

### Power Calculations

We include a sample size estimate for the definitive study. However, the current proposal is for a pilot study, which will inform us more accurately than the summation of the literature. As such, the sample size determination for this pilot study is large enough to be reasonably confident of demonstrating group separation, as well as identifying any major aspects of heterogeneity, which will provide greater accuracy for the definitive trial.

**For the definitive study** we have estimated a sample size for the study to have 90% power to detect a difference of 2 or more in the primary outcome of 6 month ADAS-COG score. From previous literature we expect in our control group that mild cognitive impairment patients will have a mean ± SD of ADAS-COG at 6 months of approximately 18 ±10 and normal 7 ± 4. From previous literature we also expect about 1/3 of patients to have mild cognitive impairment and 2/3 to be normal. Combining these 2 groups (pooling the means and SDs) we thus assume that the control group will have mean ± SD of about 11± 7. A total of 320 patients per group (640 total) would be needed to have 90% power to detect a difference of 2 in the mean of ADAS-COG between intervention and control groups with analysis of covariance adjusting for baseline ADAS-COG as a covariate. This sample size would also give about 90% power to detect a location shift of 2 points on the ADAS-COG using a Wilcoxon rank-sum test (either on the 6-month score or on change from baseline to 6-months). Adjusting for interim analyses at each 25% of maximum enrollment, a maximum of 672 participants would be needed. This will be increased to a total of 700 participants to account for loss to follow up through death or permanent disability.

### Statistical Methods To Be Undertaken

*Data Analysis*

The analysis will be descriptive, as the size of the pilot study will preclude definitive outcome analysis. The data will be reported in terms of group separation with odds ratio and confidence intervals. The following parameters would indicate clinically important relative differences between groups:

* ADAS-cog: difference of at least 2 on the ADAS-cog scale;
* VO2peak: relative difference in VO2peak between groups of 3mL/kg/min; and,
* Muscular strength: ≥15% improvement in strength.

*Evaluation*

As these are pilot studies, the endpoints are aimed at establishing feasibility, safety, compliance and group separation.

1. Group separation: Completion of preoperative and postoperative management plans and analysis for difference in diagnosis and management between groups: aim ≥20% difference between groups.
2. Feasibility: screening:recruitment ratio <2 and recruitment of ≥1 participant/site/week.
3. Safety: adverse events and serious adverse events.
4. Protocol compliance: ≥80% protocol compliance and exercise intervention commenced at one postoperative week.

# **Storage of Blood and Tissue Samples**

## Details of where samples will be stored, and the type of consent for future use of samples

No blood or tissue samples will be collected as part of this study.

# **Data Security & Handling**

### Details of where records will be kept & How long will they be stored

Information collected from participants will be stored securely in both hard copy (paper) and soft copy (electronic).

The information will be stored on paper records at the University of Melbourne in a locked cabinet, and the data entered into an electronic web-based database (www.postopQRS.com, located at City, University of London) and other research documents stored on a secure file server based at the University of Melbourne.

All database storage is protected with login and password for individual researchers. The PostopQRS database only permits non-identified data to be entered into the system. Paper records will be stored in a locked cabinet and in a locked research office in a secure department. All computers will be password protected.

All paper records used during the study are kept after the project has been completed for a minimum of 15 years, as per Good Clinical Practice. After the 15 years, information will be disposed of via shredding of all paper records, and deletion from databanks.

Re-identifiable data is used during the conduct of the study in order to contact patients for follow-up visits. The code will be kept separately to the case report forms.

### Confidentiality and Security

Only HREC authorised researchers who are involved in data collection and entry into the database will have access to the information.

There are no separate student supervisors who are not associate investigators, research monitors or other company monitors involved in the study. Access to the information is provided by the Chief Investigator using login and password process.

Information will remain at the University of Melbourne. If the chief/principal investigator ceases to be engaged at the current organisation the principal investigator will inform the HREC that they will no longer be part of the study.

Responsibility of the project will be handed over to an associate researcher working on the study already. HREC will be informed of relevant changes made.

No identifiable information will be sent to the Data Management Centre where the data will be kept and analysed for publication. Only group data will be published.

### Ancillary data

No videos, photographs or images that can identify the participant, will be collected during this study. Ultrasound images of the sternum are collected as an endpoint to the study.

# **Appendix**

**List of Attachments included:**

|  |  |  |
| --- | --- | --- |
| **Document Name** | **Version Number** | **Date (e.g., 18 January 2012)** |
| 2017.266 SEcReT CRF | 1 | 14 September 2017 |
| 2017.266 SEcReT Appointment Card | 1 | 13 September 2017 |
| 2017.266 SEcReT Telephone Script | 1 | 13 September 2017 |
| 2017.266 SEcReT Follow-up Telephone Script | 1 | 13 September 2017 |
| 2017.266 SEcReT Participant Letter | 1 | 13 September 2017 |

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