CANADIAN-AUSTRALASIAN RANDOMISED TRIAL

OF SCREENING KIDNEY TRANSPLANT CANDIDATES

FOR CORONARY ARTERY DISEASE

(CARSK STUDY)

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Statement of Compliance

This document is a protocol for a research project. 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) updated May 2015 and March 2016 and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
CARSK	Canadian-Australasian randomised trial of screening kidney transplant recipients for coronary artery disease
CAD	Coronary artery disease
MACE	Major adverse cardiac event
ESKD	End-stage kidney disease
ANZDATA	Australian and New Zealand
QoL	Quality of life
PTCA	Percutaneous transluminal coronary angiography
CABG	Coronary artery by-pass grafting
CK-MB	Creatinine kinase
SBP	Systolic blood pressure
BARC	Bleeding Academic Research Consortium
eCRF	Electronic case report forms
QALY	Quality adjusted life years
KMSA	Kaplan Meier sample average
IPW	Inverse Probability Weighting
MBS	Medicare benefit schedule
PBS	Pharmaceutical benefits scheme
AR-DRG	Australian-refined Diagnosis related groups
KDQOL-36	Kidney disease quality of life instrument
EQ5D-5L	EuroQol – 5 Dimensions – 5 Levels
REDCap	Research electronic data capture

SLHD	Sydney local health district

2. STUDY SITES

2.1 STUDY LOCATION/S

The study coordinating centre will be at C/O Professor Steven Chadban (2W73), level 2, Kidney node, Charles Perkins Centre, University of Sydney

Site	Site ID	Address	Principal investigator	Phone	Email
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Canada		To be determined

3. FUNDING AND RESOURCES

3.1 SOURCE/S OF FUNDING

Australia	National Health Medical Research Council Funded Clinical Trial Project Grant #1084454
New Zealand	New Zealand Heart Foundation
Canada	To be determined (funding application submitted)

3.2 RESOURCE DISTRIBUTION

Contributing sites will be paid a start-up fee, fee per patient recruited, and fee per patient retained in CARSK.

Australian sites	**Amount A$**	**Payment made**
Site start up	$2500	1 month before anticipated first recruitment, and once local site ethics is submitted
Patient recruitment fee	$250	On randomisation
Patient retention fee	$50	On receipt of annual patient data
Event – coronary artery disease (CAD)	$50	On receipt of event-related data
Event – abnormal CAD screening test	$50	On receipt of results and outcome i.e. documentation of initial screening test, subsequent test, and patient outcomes e.g. relisting versus delisting
Close out	$100	Provision of all required data for patient at withdrawal from study or end of study

4. STUDY SYNOPSIS

4.1 BACKGROUND AND RATIONALE

Cardiovascular disease is the commonest cause of death while on the kidney transplant waiting list and after transplantation. Current standard care involves screening for coronary artery disease prior to waitlist entry, then every 1-2 years, according to perceived risk, until transplanted. The aim of screening is two-fold. Firstly to identify patients with asymptomatic coronary disease to enable either correction, by bypass surgery or angioplasty, or removal of the patient from the list, with the ultimate aim of preventing premature cardiovascular mortality at the time of, or soon after kidney transplantation. Secondly, from a societal perspective, to prevent mis-direction of scarce donor organs into recipients who experience early mortality. This current screening strategy is not evidence based, has substantial known and potential harms, and is very costly. Two major issues of uncertainty require addressing in sequence: (1) whether to periodically screen asymptomatic wait-listed patients for occult coronary artery disease; and (2) whether to revascularise coronary stenoses in asymptomatic patients prior to transplantation. The CARSK study seeks to address the first of these 2 issues.

4.2 STUDY DESIGN

CARSK is a multicentre, non-inferiority, 2- parallel -arm randomised trial.

4.3 STUDY OBJECTIVES

CARSK aims to

1. Test the hypothesis that after screening for wait list entry, no further screening for coronary artery disease (CAD) is non-inferior to the current standard care which is screening all asymptomatic wait-listed patients for CAD at regular intervals.

2. Compare the benefits and costs of not screening versus regular CAD screening from a health system perspective.

4.4 TRIAL INTERVENTIONS

People randomised to the intervention arm will receive no regular cardiac screening.

People randomised to the control arm will receive routine coronary artery disease screening. Additionally all trial participants who develop symptoms or signs of cardiac disease will be investigated and treated as per local protocol.

4.5 STUDY POPULATION

We plan to enrol 900 people on the kidney transplant waiting list in Australia and a total of 3,200 patients for the whole trial, the remainder from Canada and New Zealand.

4.6 STUDY ENDPOINTS

Primary efficacy endpoint: major adverse cardiac event (MACE), defined as any of the following: cardiovascular death, myocardial infarction, emergency revascularisation, hospitalisation with unstable angina.

Primary safety endpoint; the above MACE endpoint plus complications from cardiac diagnosis or treatment including major bleeding requiring transfusions or hospitalizations, vascular intervention subsequent to cardiac interventions stroke and all-cause death.

Secondary endpoints; death, cardiovascular death, procedure-related death, myocardial infarction, emergency revascularisation, stroke, hospitalisation with unstable angina, hospitalisation with heart failure, hospitalisation with arrhythmia, major bleeding, health-related quality of life (QoL), time off list (including number of temporary suspension and duration of each suspension), cost-effectiveness, incidence of permanent removal from list for cardiac causes; incidence of transplantation and cancellation of transplant due to CAD.

4.7 STUDY ANALYSES

Cox models will be used to assess the time to first MACE event and death. Competing risk models will be used to assess the time to all other outcomes, adjusting for death as the competing risk.

5. INTRODUCTION/BACKGROUND INFORMATION

5.1 LAY SUMMARY

The CARSK trial will enrol people who are already on the kidney transplant waiting list, and who don't have any symptoms of new heart problems. The study will last a maximum of 4 years. While they are in the study, people will be followed up as usual – they will not have to have any extra appointments but will receive a 6-monthly phone call to check wait-list status and exclude any CAD events. They will also be asked to complete cost and quality of life questionnaires. The trial will use chance to allocate people to either getting no regular heart testing while they wait for a kidney transplant, or to get regular (every year or every second year) heart testing. We will make sure everyone gets tested if they develop any symptoms of heart problems. The trial will measure what happens to people, and particularly whether they develop any heart problems, whether they get a kidney transplant, and whether they have any heart problems after a transplant. The study is important as we know the commonest cause of death for people on dialysis or after a transplant is heart related. We don't know if finding heart disease and trying to treat it early, before it is bothering people, is a good idea – even though this is what is done at the moment. We think testing and treating people who don't have symptoms might cause more problems than it solves - it might remove them from the waiting list unnecessarily, or put them through tests and procedures or operations that they don't really need, and waste a lot of peoples' time and money without good reason. This CARSK study will help us work out whether regular testing is helpful, by showing us whether there is any difference to what happens to people if they are tested or not. The study investigators think it is likely that there will be no difference, so we have used best scientific principles to design the CARSK study to test whether we are right.

5.2 BACKGROUND INFORMATION

Kidney transplantation prolongs survival, improves quality of life, and is less costly than dialysis for people with end-stage kidney disease (ESKD).(1, 2)There are over 12,000 Australians, 2,600 New Zealanders and 20,000 Canadians who currently depend on dialysis for survival (3, 4). As quality of life and life expectancy are substantially improved by transplantation, the majority of these Australians would like to receive a transplant. However, as only 800-1000 kidney transplants are performed annually, demand for transplantation far exceeds supply. Australians routinely wait on dialysis for an average of 2 to 7 years before they receive a deceased donor kidney transplant.(5, 6) The waiting list is dynamic, with new people joining, some being transplant, and others being removed temporarily or permanently.

Wait-listed patients are at high risk for coronary artery disease (CAD) compared to the general population but are commonly asymptomatic. Exposure to dialysis is a major factor increasing the risk of cardiac events before and after transplantation.(7) Due to prolonged waiting times for a deceased donor kidney, the cardiac fitness of wait-listed patients must be maintained for long time periods. The risk of cardiac events and death in wait-listed patients is bi-modally distributed, being high whilst on dialysis, a transient increase immediately following transplantation in association with

surgical stresses and high dose immunosuppression, then substantially reduced to a lower baseline after successful transplantation. (8, 9) The cumulative incidence of myocardial infarction ranges from 8.7% to 16.7% by 3 years after wait-listing, and from 4.7% to 11.1% after 3 years of kidney transplantation.(10, 11) Cardiovascular disease is the most common cause of death in both wait-listed patients and patients with a functioning transplant, accounting for 30% of mortality overall.(12) CAD is difficult to diagnose in ESKD patients who may not develop the classic symptoms of angina because of uraemia, physical limitations, diabetes, neuropathies and other factors. For example, among patients hospitalized with myocardial infarction, chest pain at presentation was less common in dialysis (44%) compared to non-dialysis patients (68%).(13)

The average age and medical complexity of wait-listed patients is increasing. The proportion of transplant candidates 50 years and above increased by 62% between 1991 and 2011,(12) while the percentage with diabetes increased from 23% to 28% between 1998 and 2008.(14) Approximately 15% of waitlisted Australians, and 19% of those living with a functioning transplant are over 65 years.(6) Increasing age and co-morbidity substantially increases the risk of CAD. Changing donor characteristics are also likely to increase CAD risk after transplantation. In a bid to expand the donor pool and address the organ shortage, kidneys from 'extended criteria' donors (particularly older people with medical illnesses), are increasing in number (22% total donors in 2012). Recipients of these kidneys have more peri-operative complications, and a higher risk of peri-operative cardiac events, likely due to the higher incidence of delayed graft function (requirement for dialysis after transplantation) and related complications. The average donor age has increased by approximately 0.5 years per annum for the past 10 years and was 49.7 years in 2012 – the highest on record. (15)

Current CAD screening practice is not evidence based. Current transplant clinical practice guidelines recommend two phases of screening for CAD i) *prior* to acceptance onto the waiting list, *and* ii) screening at regular intervals (every 1-2 years) *after* wait-listing.(16) The aim of screening is to identify CAD by non-invasive tests (i.e. Exercise Stress test, Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo or similar). Patients with abnormal non-invasive tests are typically removed from the waiting list and undergo coronary angiography followed by revascularization of any hemodynamically critical stenosis by coronary angioplasty with or without coronary stenting, or coronary artery bypass grafting. (16) Once the procedure is deemed successful and the patient recovered, they may be returned to the active transplant waiting list. Those with advanced, unmodifiable CAD are unlikely to have a survival benefit from transplantation and so are not listed, or if already on the list, are delisted. This strategy aims to promote survival peri-operatively and in the short-medium term after transplantation. From a societal perspective, it is also imperative to prevent mortality in the early post-transplant period as this also results in the loss of a donated kidney, which incurs an opportunity cost for those who remain on the waiting list.

Although regular, non-invasive cardiac screening is the current standard of care, only 1 randomized single centre trial performed in 1992 has ever been performed to evaluate this strategy. (17) This study recruited 26 insulin dependent diabetic transplant candidates with coronary artery stenoses greater than 75%, atypical or no chest pain, and a left ventricular ejection fraction greater than 35%, and randomised them to medical therapy (calcium channel blocker plus aspirin) or revascularization with angioplasty or coronary artery bypass grafting (CABG). Among the 13 patients assigned to

medical therapy, 10 incurred a cardiac end point (including 4 deaths) compared to 2/13 revascularised patients (p <0.01).(17) The study was prematurely terminated because of the imbalance of events between groups and slow recruitment. The applicability of this study is limited for several reasons: i) medical therapy has improved substantially ii) the study focused on a specific high-risk population (type 1 diabetics) who now represent < 10% of the wait-listed population (18); iii) the study evaluated one time screening in an era when transplant waiting times were dramatically shorter; iv) the trial had few events overall hence the results have substantial fragility, and the trial was stopped early for a "too good to be true" treatment effect.

The rationale for screening is challenged by observations that not all the excess cardiovascular disease burden of ESKD is related to CAD. ESKD patients most frequently die of sudden cardiac death, that may be arrhythmogenic in origin or may be related to uremic cardiomyopathy, and not atheromatous disease.(19) The rationale for screening for critical coronary stenoses also ignores evidence that the usual mechanism of myocardial infarction is atherosclerotic plaque rupture followed by thrombosis and occlusion of the affected coronary artery.(20) The risk of plaque rupture in the peri-operative period is related to tachycardia, increased sheer stress, and a hypercoagulable state.(21, 22) The most occlusive plaques are not necessarily prone to rupture and thrombosis.(23) One third of patients with peri-operative myocardial infarction sustain damage in areas distal to noncritical stenoses.(23) Finally, the available screening tests do not necessarily identify plaques at risk of rupture and thrombosis.

Does routine screening have other downsides? Screening may paradoxically increase morbidity and mortality by: i) exposing patients to risk of angiography and revascularization procedures; or ii) by delaying or excluding patients from life saving kidney transplantation because of their perceived CAD status. In other settings, for example in most surgical candidates, screening is not beneficial. (24) However, the goals of screening transplant candidates differ somewhat from other settings, and include not only prevention of peri-operative cardiac events, but also maintenance of transplant eligibility during wait-listing, and long-term post transplant survival. The current standard of care may be harmful. The potential harmful outcomes related to the current strategy of screening and revascularization of asymptomatic transplant candidates are summarized in Table 1 below.

A recent joint Scientific Statement form the American Heart Association and the American College of Cardiology Foundation concluded "that there is no strong evidence for or against routine cardiac screening of asymptomatic transplant candidates" and that more evidence from randomized clinical trials was needed. (11) The lack of evidence in the transplant setting has led to confusion about the optimal management of transplant candidates: The two major issues of uncertainty are whether to screen asymptomatic patients for occult CAD, and whether to revascularise coronary stenoses in asymptomatic, screen-detected patients.

Table 1: Evidence of increased harm from CAD screening in ESKD

1	Complications of revascularization are higher in people with ESKD			
	Population	*Event Type*	*Event Rate*	***citation***
	U.S. Dialysis patients 1978-95	2year mortality post PTCA	52%	**(23)**
		2year mortality post CABG	44%	**(23)**
	U.S. Transplant recipient 1995-99	2year mortality post PTCA	18%	**(24)**
		2year mortality post CABG	17-26%	**(24)**
	Non-ESKD patients reported by Bari Investigators	5 year mortality post PTCA	14%	**(25)**
		5 year mortality post CABG	12%	**(25)**
2	Asymptomatic ESKD patients may be considered too high risk for surgery and excluded from transplantation rather than revascularized			**(26)**
3	Screening prolongs waiting time prior to transplantation: Audit of 130 wait-list candidates in Canada found 45 were put on hold for transplantation because of abnormal screening tests for a mean of 446 days (only 5/45 were ever revascularized).			Audit for grant
4	Relative increased bleeding risk with use of anti-coagulation after revascularization in ESKD patients and most surgeons will not transplant anti-coagulated patients. In particular, clopidogrel is commonly prescribed for 6 months after coronary stent placement, but is a relative contraindication to transplant surgery.			**(27)** **(9)**
5	Angiography causes loss of residual kidney function. Preservation of residual kidney function is associated with increased dialysis survival			**(28)**

PTCA= percutaneous coronary angiography, CABG= coronary artery bypass grafting

Data to justify the focus on CAD screening tests only after people are wait listed The CARSK trial will focus on the use of screening tests *after* activation to the waiting list because *Physicians are unwilling to forgo initial cardiac evaluation* because these tests are considered essential to determine initial transplant eligibility. This assumption was proven by surveying current Canadian transplant centres: of 15 adult Transplant Centres, all centres screen for CAD during the initial transplant evaluation. Most (13/15) did not support randomization of patients to use or non-use of cardiac investigations during the initial evaluation of patients for activation onto the waiting list. *In contrast, there is clinical equipoise around the use of screening tests for CAD after wait-listing:* All centres reported screening for CAD after wait-listing. The majority of transplant centres (11/15) had a screening protocol, while in 4/15 centres transplant physicians individually selected patients for screening. The frequency of screening reported in hypothetical patient scenarios equalled or exceeded that recommended in current transplant guidelines.(18) All 15 centres were willing to randomize patients to regular or selective screening after wait-listing. The largest health services burden is related to screening practices after wait-listing (typically 2-7 years), rather than the one time testing prior to placement on the waiting-list.

Data to demonstrate screening for CAD is expensive. Our Canadian investigators studied costs in a pilot study and found, of 604 wait-listed patients in British Columbia followed for 3.7± 1.8 years, 530 non-invasive cardiac screening tests with an estimated cost of over C$530,000 were required by current guidelines.(18) When the additional costs of program administration, coronary angiography, consultations and revascularization procedures in patients with abnormal screening tests were considered, the current non-evidence based strategy costs a minimum of $15 million per year in Canada.(25) The estimated cost of a single screening test for those wait listed in Australia is in excess of $1.1 million each year, and for the over 90,000 wait-listed patients in the United States is $210

million.(26, 27) To date no studies have examined the cost-effectiveness of screening strategies for coronary artery disease. In order to ensure health care system sustainability and maximize patient outcomes given finite health care resources, it is critical that the effectiveness and cost-effectiveness of screening strategies be determined.

Data to suggest selective screening may be safe in wait listed patients: The 604 wait listed Canadians in the above pilot study only underwent screening based on on-going clinical evaluation.(18) This strategy resulted in fewer screening tests than recommended by guidelines (n =171 versus 530 tests), and no difference in cardiovascular events (cardiovascular event rate in patients without the recommended frequency of cardiac tests was 6.7 [95% CI, 5.2 to 8.7] per 100 patient-years, and in those screened regularly was 9.9 [95% CI, 7.1 to 13.7].(18) Two other observational studies also suggest that selective screening may be safe: in a single centre study of 514 wait-listed candidates who were screened based on clinical judgment of the treating physician, the incidence of cardiac events at 5 years in the 224 patient who were not screened was 5.3% compared to 19.7% among the 290 patients who were screened. (28) Similarly, in another study of 600 wait-listed patients, 174 patients were considered high risk based on clinical criteria and underwent screening for CAD and only 5 (2.9%) were revascularised. Cardiac events were higher in screened patients 12/174 (6.9%) versus unscreened patients 19/426 (4.5%).(29) Selection bias is likely in all these studies: only an RCT can answer the question definitively. The first phase will confirm protocol adherence, patient enrolment and consent rates of the 144 wait-listed participants who will be randomised to no screening versus routine screening for CAD, aiming to produce a 95% confidence interval equal to the sample adherence prevalence plus or minus 5% when the true prevalence of adherent patients is hypothesized to be 90%.

6. STUDY OBJECTIVES

6.1 RESEARCH QUESTION

Using randomised controlled trial design, with participants wait listed for kidney transplantation we will

- test the hypothesis that after screening for wait list entry, no cardiac screening tests is non-inferior versus the current standard care which is screening all asymptomatic wait-listed patients for coronary artery disease (CAD) at regular intervals
- compare the benefits and costs of screening and subsequent treatment at wait list entry versus regular CAD screening from a health system perspective**.**

6.2 OUTCOME MEASURES

Primary efficacy endpoint: major adverse cardiac event (MACE), defined as any of the following: cardiovascular death, myocardial infarction, emergency revascularisation, hospitalisation with unstable angina.

Primary safety endpoint; the above MACE endpoint plus complications from cardiac diagnosis or treatment including major bleeding requiring transfusions or hospitalizations, vascular intervention subsequent to cardiac interventions stroke and all-cause death.

Secondary endpoints; death, cardiovascular death, procedure-related death, myocardial infarction, emergency revascularisation, stroke, hospitalisation with unstable angina, hospitalisation with heart failure, hospitalisation with arrhythmia, major bleeding, health-related quality of life (QoL), time off list (including number of temporary suspension and duration of each suspension), cost-effectiveness, incidence of permanent removal from list for cardiac causes; incidence of transplantation and cancellation of transplant due to CAD.

Table 2: Outcome definitions

Outcome	**Definition (**31-32)
Cardiovascular death	Cardiovascular death is defined as any death with a cardiovascular cause and includes those deaths after a cardiovascular procedure (eg, percutaneous coronary intervention), cardiac arrest, myocardial infarction, pulmonary embolus, stroke, and haemorrhage or deaths due to an unknown cause. Noncardiovascular death is defined as any death owing to a clearly documented noncardiovascular cause (eg, trauma, infection, malignancy).
Myocardial infarction	Clinical syndrome where there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. The diagnosis requires one of the following: 1. a typical increase of troponin or a typical decrease of an elevated troponin or a rapid increase and decrease of creatine kinase (CK)–MB.

	An increased troponin value (ie, higher than the decision limit for myocardial infarction) is a measurement exceeding the threshold at which the coefficient of variation equals 10%. An increased CK-MB value (ie, higher than the decision limit for myocardial infarction) is one that exceeds the 99th percentile for CK-MB values in a reference control group. One of the following must also exist for the diagnosis of myocardial infarction: ischemic symptoms (eg, chest, epigastric, arm, wrist, or jaw discomfort or shortness of breath) b. development of pathologic Q waves on the electrocardiogram (Q-wave changes must be present in any 2 contiguous leads and be z1 mm in depth; further Q waves in leads I, II, aVL, aVF, V4, V5, and V6 must be z30 milliseconds) c. electrocardiogram changes indicative of ischemia (new or presumed new ST-segment elevation or depression in at least 2 contiguous leads or new or presumed new symmetrical inversion of T waves z1 mm in at least 2 contiguous leads) d. coronary artery intervention (eg, percutaneous coronary intervention) e. new or presumed new cardiac wall motion abnormality on echocardiographic imaging or a new or presumed new fixed defect on radionuclide imaging 2. Pathologic findings of an acute myocardial infarction
Emergency revascularisation	Emergency revascularisation within 1 month of presentation of new or progressive symptoms of coronary artery disease
Hospitalisation with unstable angina	Pain or equivalent with the presence of dynamic ECG changes, that requires hospitalisation. Hospitalisation is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hr stay. This classification require that 4 separate criteria be met: a) Worsening ischaemic discomfort b) Unscheduled hospitalization c) Objective evidence of myocardial ischaemia and d) Negative cardiac biomarkers
Clinically significant atrial fibrillation	Atrial fibrillation that results in angina, congestive heart failure, or symptomatic hypotension or that requires treatment with a rate-controlling drug, antiarrhythmic drug, or electric cardioversion
Congestive heart failure	The diagnosis requires both clinical (ie, any of the following signs: elevated jugular venous pressure, respiratory rales, crepitation, or presence of S3) and radiographic (eg, vascular redistribution, interstitial pulmonary oedema, or frank alveolar pulmonary oedema) evidence
Rehospitalisation for cardiac reasons	Rehospitalisation for congestive heart failure, ischaemic symptoms with ST or T-wave changes on an electrocardiogram, arrhythmia, or heart block
Stroke	A new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting >24 hours
Major bleeding	Bleeding Academic Research Consortium (BARC) type 3 and 5. CABG-related bleeding (type 4) and bleeding 30-days post-kidney transplant are excluded.

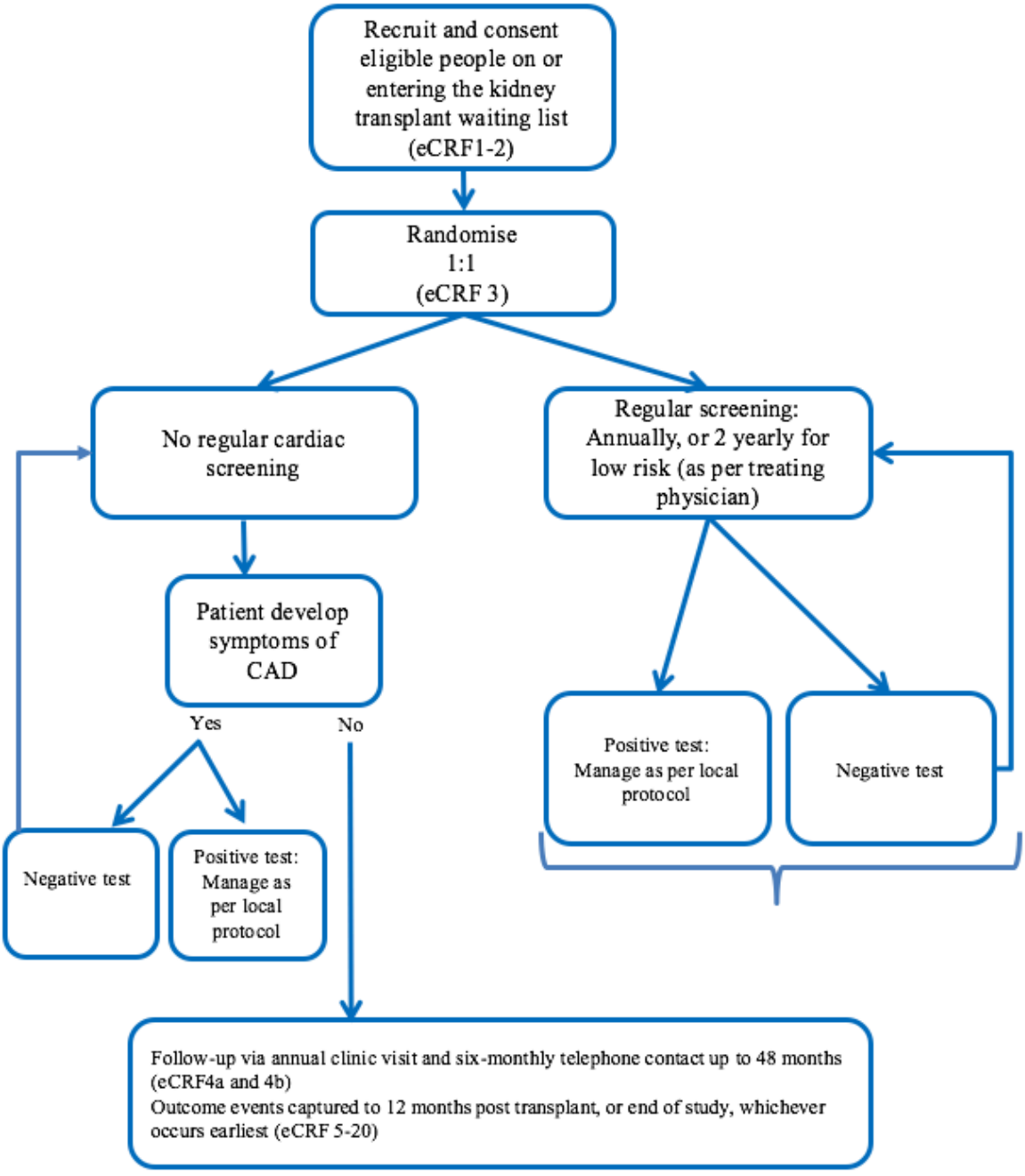
Definitions adapted from: 2014 ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials,(30) Rational, design and organization of Perioperative Ischaemic Evaluation (POISE) trial: A randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery,(31) and Standardised Bleeding Definitions for Cardiovascular Clinical Trials.(32)

Table 3: ICD codes

Outcome	**Contributing event**	**ICD-10 or procedure code**
Primary efficacy endpoints	Cardiovascular death	I46
	Myocardial infarction (MI)	I21
	Emergency revascularisation	021
	Hospitalisation with unstable angina	I20, I22
Primary safety endpoints	As above MACE	as above
	Stroke	I61-64
	Bleeding	I85.0, K29, K62.5, K92 S06.4-9, I60-62 R04 N93 T81, T82.8 T79.2 R58
	Death	I46, R96, R98-99
Secondary endpoints	All-cause death, MI, emergency revascularisation, stroke, unstable angina	as above
	Hospitalisation with heart failure	I50
	Hospitalisation with arrhythmia	I47-49
	Incidence of transplantation	0TY

7. STUDY DESIGN

7.1 STUDY DESIGN DIAGRAM



7.2 STUDY TYPE & DESIGN & SCHEDULE

This trial is a pragmatic multi-centre, randomized, parallel group definitive trial incorporating an economic evaluation and involving sites in Canada, Australia and New Zealand. Asymptomatic wait-listed patients will be randomised to no screening versus routine screening for CAD (i.e. Exercise Stress test, Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo) as per the current standard of care at each centre.

Intervention: Patients randomized to no screening will **not** undergo regular non-invasive testing for CAD while on the wait list.

Control: Patients randomized to routine screening will undergo noninvasive testing for CAD every year or second yearly as determined by local centre practice.

All: Patients in either group who develop symptoms of angina or an angina equivalent at any stage will be investigated according to the local standard of care, which may include the use of non-invasive or invasive cardiac testing.

Table 4: Study schedule

Case Report Forms (CRF)	Baseline data	6m	12m	18m	24m	30m	36m	42m	48m	54m	60m
CRF1 - Screening	✓										
CRF2 - Baseline data	✓										
CRF3 - Randomisation	✓										
CRF4a – Wait-list Follow up		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		If patient is transplanted, move to arm 2 and follow new schedule of follow-up									
QoL Survey											
KDQoL-36[1]	✓			✓		✓		✓		✓	
EQ5D	✓	✓	✓		✓		✓		✓		✓
Events & outcomes											
CRF5 – Non-Transplant hospitalisation		*	*	*	*	*	*	*	*	*	*
CRF7 - Planned CAD screening test		*	*	*	*	*	*	*	*	*	*
CRF9 - Missed CAD screening test		*	*	*	*	*	*	*	*	*	*
CRF10- Coronary angiogram		*	*	*	*	*	*	*	*	*	*
CRF11- Revascularisation		*	*	*	*	*	*	*	*	*	*
CRF12- Death		*	*	*	*	*	*	*	*	*	*
CRF13 – Non-fatal MI		*	*	*	*	*	*	*	*	*	*
CRF14 – Unstable angina		*	*	*	*	*	*	*	*	*	*
CRF15 - Stroke		*	*	*	*	*	*	*	*	*	*
CRF16 - Bleeding		*	*	*	*	*	*	*	*	*	*
CRF 17 - Wait list hold		*	*	*	*	*	*	*	*	*	*
CRF 18 - Wait list removal		*	*	*	*	*	*	*	*	*	*
CRF19 - Wait list reactivation		*	*	*	*	*	*	*	*	*	*
CRF 20 - Withdrawal		*	*	*	*	*	*	*	*	*	*
* complete if event occurs [1] Mandatory survey for Australia & NZ, *optional* for Canada											

Case Report Form	Transplant	3m	12m
CRF6 – Transplant hospitalisation	✓		
CRF4b – Post-transplant Follow up		✓	✓
QoL Survey			
KDQoL-36[1]			✓
EQ5D		✓	
Events & outcomes			
CRF5 – Non-Transplant hospitalisation		*	*
CRF10- Coronary angiogram	*	*	*
CRF11- Revascularisation	*	*	*
CRF12- Death	*	*	*
CRF13 – Non-fatal MI	*	*	*
CRF14 – Unstable angina	*	*	*
CRF15 - Stroke	*	*	*
CRF16 - Bleeding	*	*	*
CRF 20 - Withdrawal	*	*	*
* complete if event occurs			

7.3 TESTING PROCEDURES

Non-invasive cardiac screening tests: The choice of non-invasive test(s) will be according to the existing practice of each transplant centre. Although the accuracy of inotropic stress echocardiography to identify occlusive CAD is somewhat better than vasodilator stress nuclear perfusion imaging, both abnormal Myocardial Perfusion Scintigraphy and Dobutamine Stress Echo have prognostic value for cardiac events and mortality in patients with renal failure, and are used extensively in clinical practice.(11, 33) The type of test used will be documented in all instances.

Investigation and management of an abnormal screening test: The management of an abnormal screening test including performance of coronary angiography as well as treatment of coronary stenoses will be carried out as per the usual standard of care in individual transplant centres and will not be influenced by the investigators or study personnel in any way.

7.4 STANDARD CARE AND ADDITIONAL TO STANDARD CARE PROCEDURES

Management of patients who develop clinical symptoms of CAD: Any patient, regardless of randomised trial allocation, developing clinical symptoms of CAD (e.g. angina, congestive heart failure, or new arrhythmias) will be evaluated according to the standard of care in individual transplant centres *and may include the use of non-invasive cardiac stress testing*. Management of symptomatic CAD including revascularization will be according to the standard of care at the local transplant centre.

Other than the use of cardiac screening tests, patient management will be as per the usual standard of care in participating transplant centres. In both study groups, the frequency and content of clinical re-evaluations will be according to the existing practice of the transplant centres participating in the study. Such evaluations may include cardiology consultations. Clinical evaluations by the transplant centre during wait-listing will be recorded in both groups. Interventions to prevent cardiovascular disease events may be used. Study personnel will document all surgical and medical interventions for CAD. The use of cardio-protective medications (aspirin, beta-blockers, medications that block activation of the renin angiotensin system, lipid lowering agents) will be documented every six months in all trial participants. However, the use of lipid lowering agents, aspirin, and beta-blockers remain controversial due to the lack of definitive evidence regarding efficacy in ESKD patient, and their use is likely to vary between centres and between physicians at the same centre.(9, 34) Similarly behavioural therapies such as participation in weight loss, smoking cessation or healthy heart programs may used. Medical and behavioural treatments will not be specified in the trial but will be documented by study personnel.

7.5 RANDOMISATION

Randomisation to treatment arm will be 1:1 allocation using random permuted blocks, stratified by site and diabetes status. Block sizes of 2,4,6 and 8 will vary randomly. Randomisation will be web-based and managed by the Ottawa Hospital Research Institute, Methods Centre Data Management services.

7.6 ECONOMIC METHODOLOGY

Outline of the within-trial analysis
A cost-effectiveness and cost-utility analysis of no screening compared to usual screening will be conducted from an Australian and Canadian health system perspective.

Outcomes for the analysis
The analysis will report the cost per MACE avoided; the cost per life year gained; and the cost per quality adjusted life year (QALY) gained of no screening compared to usual screening.

Analysis methods
A cost-utility analysis rather than a cost minimization analysis will be undertaken for this non-inferiority trial, as there is no current evidence of equipoise in health outcomes (i.e. quality adjusted survival) for the no screening and screening strategies.

Censoring of costs and outcomes
Censoring of cost data may occur if: the cost event eg. hospitalization continues beyond the 4 year follow-up time; the cost data collection for some participants does not start at randomization; or if participants are lost to follow-up. A comparison of the clinical characteristics of participants with complete versus censored cost data will be tabulated. The method for addressing censored cost data will be determined after investigation of the pattern of missing data (e.g. missing completely at random, missing at random, missing not at random) using the Lin method, the Bang & Tsiatis method or multiple imputation methods.(35) Censoring of outcome data may occur if patients are lost to follow up. Survival analysis methods such as Kaplan Meier Sample Average (KMSA) or Inverse Probability Weighting (IPW) will be undertaken.

Statistical methods for analysis of economic data
Skewed cost data: Cost data are likely to be right skewed as they are bounded by zero (i.e. can't be negative); have no upper bound, and a small number of patients will likely incur very high costs, affecting the mean. The cost distribution will be plotted in a histogram and non-parametric bootstrapping will be used for analysis. (36)

Data validation
Identification of resource use in the trial case report forms and patient diaries will be validated through a cross check with treating clinicians (nephrologists and cardiologists); by comparison with the published literature; and for Australian participants through cross checks with the Admitted Patient Data Collection and Medicare data.

Missing data
It is anticipated in this trial that there may be some missing quality of life or resource use data. Investigation of the pattern of missing data (e.g. missing completely at random, missing at random, missing not at random) will determine the appropriate method for handling the missing data. For

quality of life, a weighted mean value for the group sample may be used to 'fill in' the missing items. Depending on the amount of missing data, multiple imputation will be considered.

Costs

Costs will include all CAD related health system resource use including screening and subsequent treatments, doctor's visits and in-patient hospitalisations.

Individual participant resource use

Data on resource use will be obtained in two ways. First through identification of tests, procedures and doctor's visits related to cardiac and renal management for all study participants from randomisation to study end as recorded in the patient diaries and trial case report forms. Second, Australian participants will have their records linked to the Admitted Patient Data Collection, Emergency Department Data Collection, and through Medicare for all Medicare Benefits Schedule (MBS) outpatient visits, procedures and the Pharmaceutical Benefits Scheme (PBS) for medicines.

Unit costs

Valuation of resource use will be obtained for the most recent and relevant Australian-Refined Diagnosis Related Groups (AR-DRG) and MBS or PBS costs.

Results

The mean and total volume of major categories of resource use (e.g. diagnostic tests; doctor's visits; revascularization procedures; and hospitalisations) will be reported for each group. The difference in the volume of resource use for each group and 95% confidence intervals for the difference will be reported.

Total costs

The total cost will be calculated by multiplying the arithmetic mean cost by the number of participants in each group. Mean costs with standard deviations and total costs for each group will be reported in Australian dollars for the most recent reference year, discounted at 5% per annum. The difference in total costs will be assessed using the student t test and/or analysis of variance (ANOVA). Total costs will also be adjusted for relevant baseline characteristics (e.g. age, sex).

Benefits will include: (i) quality of life, measured annually with the KDQOL-36™ and EQ-5D-5L surveys; (ii) the proportion of participants who avoid MACE; (iii) life years gained and (iv) QALY gained at year 2 (12 months post randomisation) and year 4 (study end).

Participant utilities

The EQ-5D-5L preference based instrument containing 5 domains and 5 levels within each domain will be administered to all trial participants at baseline and every 6 months throughout the trial. QALY weights (utilities with a value between 0 and 1) from self-reported data will be calculated using Australian tariffs (the value set). The 100 point visual analog scale will also be recorded. QALYs will be calculated by multiplying the utility with the time spent in that health state using an area under

the curve approach.(37) A minimally important difference in utility from the EQ-5D-5L has been reported at 0.03-0.05.(38)

Cost-effectiveness and cost-utility analyses

Using the mean discounted costs in each trial arm, and the mean discounted benefits in each arm, the incremental cost per life year gained and cost per QALY gained of the no screening group compared with regular screening group will be calculated; results will be plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate confidence intervals around incremental cost-effectiveness ratios.(39) A cost-effectiveness acceptability curve (CEAC) will be plotted, providing information about the probability that the intervention is cost-effective given a decision maker's willingness to pay for a QALY gained.(39)

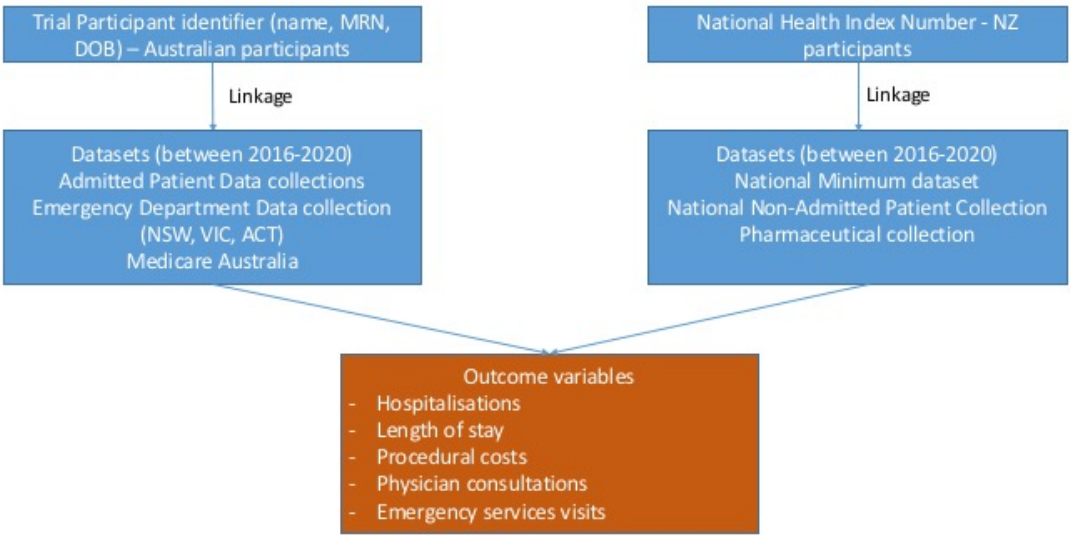
Sensitivity analysis

One-way sensitivity analyses will be conducted around key variables, including the most expensive items of resource use, and the frequency of cardiac screening in the usual care arm: i.e. every year versus every 2 years. Sensitivity analysis will be undertaken using an alternative QALY weight obtained from the SF-6D a component of the KDQOL-36™ questionnaire using country-appropriate tariffs. In addition, sensitivity analyses will vary the discount rate from 0-6%.

7.7 DATA LINKAGE

To obtain additional data for economic evaluation, we will use data linkage to link Australian and New Zealand participant records to available national data sets. Figure 1 summarises this procedure. The period of interest will be from the beginning of the recruitment period to the end of the study period (2016-2020). In Australia, we will apply probabilistic linkage procedures to link data based on patient name, date of birth, sex and postcode. We will link their records to the Admitted Patient Data Collections and the Emergency Department Data Collections for NSW, Victoria and the ACT, and Medicare Australia for outpatient visits, diagnostic tests and medicines prescribed under the Pharmaceutical Benefits Scheme (PBS) for all jurisdictions. In New Zealand, the benefit of a unique National Health Index (NHI) number will allow deterministic record linkage. We will link New Zealand participants to the National Minimum Dataset, National Non-Admitted Patient Collection and the Pharmaceutical Collection. We will capture inpatient encounters, the length of stay and resource utilisation (hospitalisations, procedural costs), physician consultations and emergency services use from these databases.

Figure 1: Data linkage method for Australia and New Zealand



8. STUDY POPULATION

8.1 RECRUITMENT PROCEDURE

Participants will be recruited through any participating centres. Patients will be identified from site kidney transplant waiting lists, and approached when attending routine waiting list review appointments. Patients will also be approached immediately after they are waitlisted for the first time.

8.2 INCLUSION CRITERIA

1) adults aged 18 years of age or older;
2) dialysis-dependent kidney failure and currently being assessed for or active on the kidney transplant waiting list;
3) expected to require further screening for CAD prior to transplantation (by current standard of care);
4) able to give consent;
5) anticipated to undergo transplantation more than 12 months from date of enrolment

8.3 EXCLUSION CRITERIA

1) patients with signs or symptoms suggestive of uncontrolled cardiac disease such as unstable coronary syndromes, decompensated heart failure, uncontrolled arrhythmia, and severe valvular heart disease;
2) patients who “on-hold” for transplantation due to a medical problem;
3) patients with other solid organ transplants;

4) multi-organ transplant candidates (e.g. kidney-pancreas transplant candidates);
5) patients with planned living donor transplant.

8.4 CONSENT

Informed written consent will be requested using the approved patient information and consent form as per the conduct of Good Clinical Practice. Consent will be sought from Australian participants for linkage of trial records to Medicare data for identification of health system resource use. To enable capture of longer term data for this cohort, permission to undertake linkage to the ANZDATA registry will be sought. In an effort to enhance fidelity of the study, permission to contact a treating cardiologist, if present, will be sought.

9. PARTICIPANT SAFETY AND WITHDRAWAL

9.1 RISK MANAGEMENT AND SAFETY

Data will be formally reviewed on a 6 monthly basis by the data safety monitoring board (DSMB) who will receive appropriate data reports derived from Research Electronic Data Capture (REDCap). Any safety issues identified will be reported to the trial committee who will inform investigators via a regular newsletter.

9.2 HANDLING OF WITHDRAWALS

Provision for withdrawals and drop outs has been made in determining trial size, therefore replacements will not be required.

10. STATISTICAL METHODS

10.1 SAMPLE SIZE ESTIMATION & JUSTIFICATION

The target total sample size is 3306 patients from 23 sites (7 from Australia, 1 from NZ, 15 from Canada). This number of sites will provide a target number of 1000 patients from Australia, 100 from New Zealand and 2206 from Canada. This equates to recruitment of ≤ 4 patients per month per centre. This rate is feasible given current wait-list and transplant volumes from all countries.

Feasibility in Australia and New Zealand: We anticipate enrolling >40% of the eligible patients approached to participate. Based on incident and prevalent wait-list counts between 2010-12 in Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), 2400 incident and 1200 prevalent wait-list patients will be available during the planned three year enrolment period of the definitive trial.(6) In a random chart audit of 73 incident and prevalent waitlisted patients in British Columbia, undertaken in 2012 in preparation for this application, 90% of incident patients and 60% of prevalent patients met study eligibility criteria. Therefore we conservatively estimate that 2500 wait-list candidates (including 90% of 2400 incident patients (n=2160), and 60% of 1200 prevalent patients (n=720) will be eligible to participate in the definitive trial. Randomisation of 1100 Australian and New Zealand patients will be achieved if 29% of the estimated 2880 available eligible wait-listed patients consent to participate. We believe this is a feasible target based on published

information from a recent survey in which 73% of 241 wait-list candidates indicated a willingness to participated in a CAD screening study.(40) If enrolment targets are not met, extension of the enrolment period or recruitment of additional sites will occur (there are 16 centres performing kidney transplantation in adults in Australia).

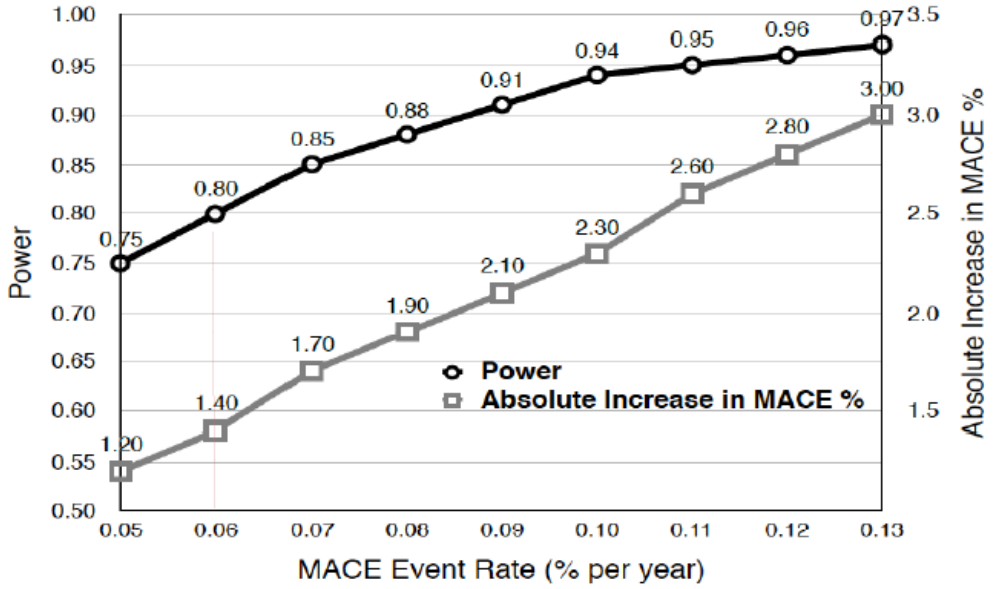
10.2 POWER CALCULATIONS

We conservatively estimate an average MACE rate of 6%: MACE rates in the U.S. range from 8.7 % in the first year after a kidney transplant to 13.2 % per year on the waiting list.(41) Unpublished data in Australia and Canada show lower rates of 3% and 8% respectively. The lowest MACE rate would be observed if *all* patients underwent transplantation rapidly (i.e. one year wait-listing (MACE 8%), followed by one year of post transplant follow up (MACE 3%)). In this hypothetical scenario, the average MACE rate would be 5.5%. We estimate that 50% of participants will receive a kidney transplant during the study - therefore the majority of patient follow up time will be accrued on the waiting list (when the MACE rate is high) rather than after a KTX justifying our estimated average MACE rate of 6%.

Using a MACE rate of 6% per year and non-inferiority defined as a Hazard Ratio (HR) of MACE < 1.25, randomization of **3306 patients** will give us 80% power using a two-sided 5% significance level. An HR of 1.25 equates to an absolute difference in MACE being <1.4% higher in the non-screening group compared to the regular screening group (i.e. 7.4% versus 6.0 %).

Figure 2 shows the study power for MACE rates between 5 -13% per year. These calculations have assumed the true HR=1 and that event rate will follow an exponential distribution. They also take into account the different study follow-up in Canada (5 years) and Australia/NZ (4 years), and allow for a 10% drop-out rate. Power calculations were performed using the **Non-inferiority Logrank Tests** in PASS 12 (NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Figure 2: Study power for MACE rates



- For all power calculations, non-inferiority is defined as an absolute increase in the **Hazard Ratio (HR) of MACE <1.25**, Two-sided **alpha is 5%**, and the total sample size is fixed at **N=3306**
- Using a MACE rate of 6% per year and non-inferiority as defined above, randomization of **3306 patients** will give us 80% power using a two-sided 5% significance level to claim no screening is non-inferior to regular screening if the absolute difference in MACE in the no screening group is <1.4% higher (i.e. 7.4% versus 6.0 %) than in the regular screening group.

10.3 Statistical Methods To Be Undertaken

Efficacy outcomes will be analysed using intention to treat. A significance level of 5% shall be used for all analyses, unless otherwise specified. All analyses will be adjusted for site.

The primary analysis will be an analysis of the time to first occurrence of the primary outcome MACE, using a Cox model with treatment arm as a covariate and stratified by site. This analysis will provide an estimate of the HR, a p-value and CI. Non-inferiority will be claimed if the 95%CI of the HR lies entirely lower than an HR value of 1.25, with the screening arm being the referent group. Superiority will be claimed if the 95%CI lies entirely lower than 1. Proportional hazards assumption will be assessed using log-log survival plots and Schoenfeld residuals.

The outcome of all-cause mortality will also be analyse using a Cox model. The time to all other outcomes will be analysed using a competing risk model, with the competing risk being death. Outcomes which can occur more than once will also be analysed using an Andersen and Gill model (42). This model is a natural extension of the Cox model and unlike the Poisson or Negative Binomial models for count data, does not require the assumption of a constant event rate over time. Robust standard errors using the Sandwich estimator will be applied to ensure the correct p-value and CIs are calculated.

All time to event data will also be graphically summarised using a Kaplan Meier or cumulative incidence curves comparing the two treatment arms.

For all time to event outcomes, a subgroup analysis will conducted to test for a statistical interaction (effect modification) between treatment arm and transplantation. This will be performed by stratifying the survival models by transplant date and testing the HRs between the two strata.

Time off waiting list will be analysed using a negative binomial model, with an offset for total time in study.

Safety outcomes will also be analysed using both intention to treat and per-protocol approaches.

Balance between treatment arms will be assessed by comparing means for continuous variable characteristics, such as age, or by comparing proportion for categorical characteristics, such as sex. If there is any imbalance, then an adjusted analysis for any unbalanced characteristics will be conducted in addition to the analyses stated above, which only account for site.

11. DATA SECURITY & HANDLING

11.1 DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Data will be captured using REDCap and stored on servers at the Sydney Local Heath District (SLHD) Royal Prince Alfred data centre. Participating sites will enter data into electronic case report forms (eCRF) via a secure web-based data capture software tool. REDCap allows data to be inputted at multiple sites with web authentication, data logging and Secure Sockets Layer encryption. Records will be kept for a minimum of 15 years.

The coordinating site will generate periodic data audit for quality and accuracy and provide data reports required for progress reports, data safety monitoring board meetings and event adjudication committee meetings.

11.2 CONFIDENTIALITY AND SECURITY

The coordinating site will monitor data inputted by contributing sites. Users are given individual usernames and passwords and are granted access to the project with certain privileges. Data collected from individual sites will be anonymous and de-identified. Confidential data such as patient details will also be de-identified during the export mechanism to allow data to be analysed. The backup process is maintained by SLHD Information Management and Technology Division and are performed daily to a separate server.

11.3 ANCILLARY DATA

Ancillary data such as test reports will be uploaded onto the eCRF and will stored electronically via the mechanism outlined above

1. APPENDIX

List of Attachments included:

Document Name	Version Number	Date (e.g., 18 January 2012)
QOL-Health Questionnaire - EQ-5D-5L	1.0	June, 2015
Kidney Disease and Quality of Life – KDQOL-36	1.0	2000

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