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Protocol Title:

A randomized trial of screening for Coronary Artery Disease in Kidney Transplant Candidates Pilot Study

NCT02082483

A multi-center pilot study to inform the feasibility of a definitive trial to determine if a non-use of screening tests (i.e. Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo) is non-inferior to screening all asymptomatic wait-listed patients at regular intervals as described in transplant specific guidelines

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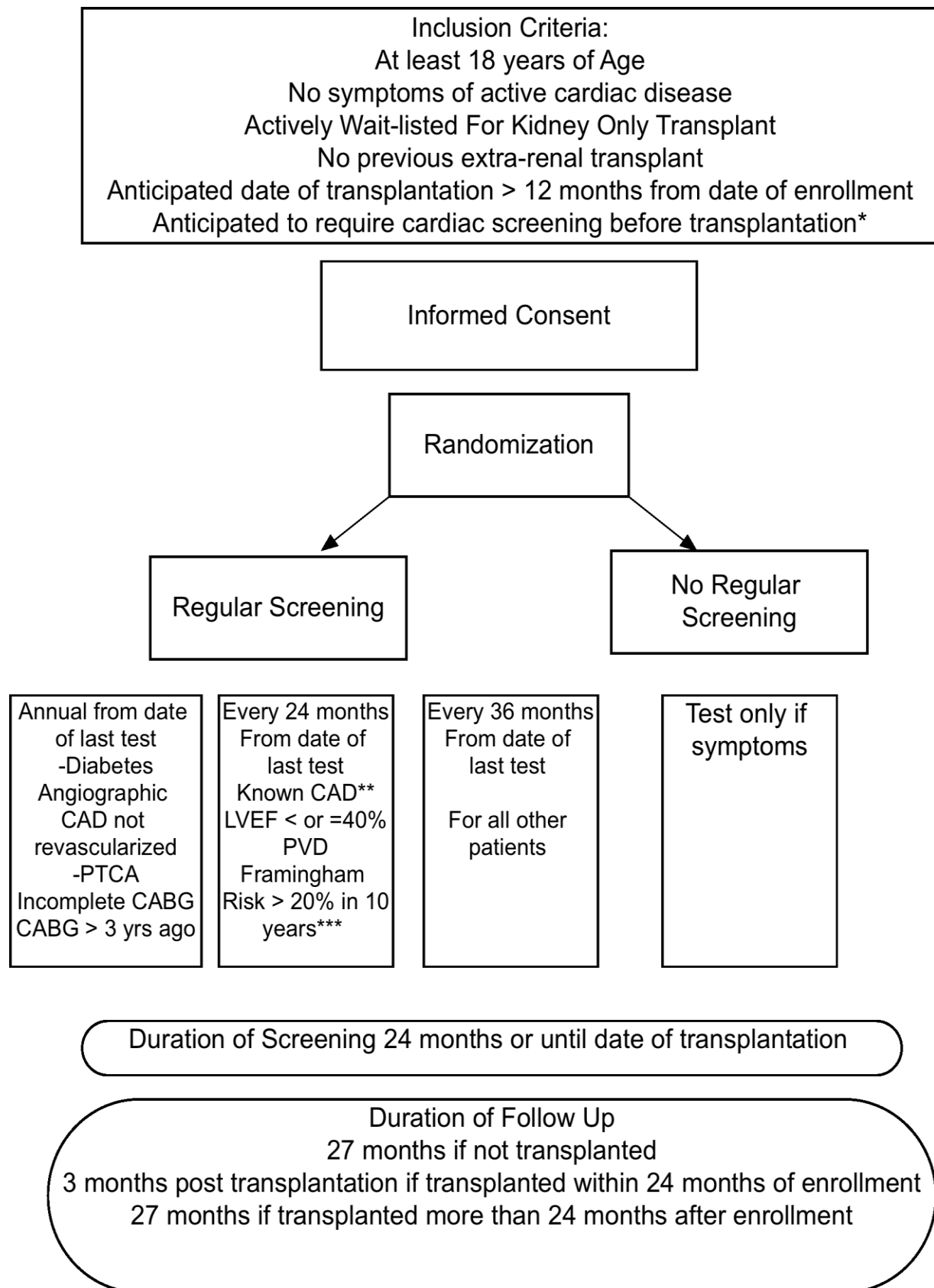
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* Each site will determine the estimated time to transplantation based on PRA and ABO blood type. The site investigator will complete Table 3 which will be used to estimate a potential participants time to transplantation. Patients who require a routine cardiac screening test (see Figure 1) to determine regular screening schedule for patients (based on cardiac history) before the estimated date of transplantation, are eligible for study participation.

Title	A randomized trial of screening for coronary artery disease in kidney transplant candidates: Pilot Study
Project Office	SPH
Study Size	144
Study Design	Multi-center, open label, randomized controlled trial of regular screening versus no-regular screening for coronary artery disease in kidney transplant candidates
Primary objective	To determine the feasibility of a definitive trial. Feasibility is determined by 1) protocol adherence 2) enrolment rates 3) consent rates. A patient will be considered adherent if they were adherent to their allocated screening strategy (regular versus no regular screening) over the 24 month treatment period. Enrolment rates will be assessed monthly during the six month enrolment period. Consent rates will be defined as the proportion of patients enrolled among eligible patients approached for enrolment and will be defined after completion of the six month enrolment period.
Secondary Objective	To record the composite outcome of cardiac death and non-fatal myocardial infarction (i.e. the proposed primary outcome in the definitive trial). These outcomes will be adjudicated by a blinded clinical endpoints committee using criteria from the POISE Trial
Tertiary Objective	To record transplant events, wait-list holds, and wait-list removals including the indication. To ascertain health care encounters related to the diagnosis and management of CAD.
Inclusion/Exclusion Criteria	Inclusion criteria: a) adult patients ≥ 18 years of age, able to provide informed consent; b) patients with dialysis-dependent renal failure and active on the deceased donor transplant waiting list; c) patients expected to require further screening for CAD prior to transplantation by the current standard of care; d) investigator consented and signed off on patient eligibility; e) patients anticipated to undergo transplantation more than 12 months from the date of enrolment. Exclusion criteria: a) patients with signs or symptoms suggestive of active cardiac disease such as unstable coronary syndromes, decompensated heart failure, uncontrolled arrhythmia, and severe valvular heart disease; b) patient who have been put "on hold" for transplantation due to a medical problem (e.g. an infection); c) prior extra-renal transplant recipients; d) multi-organ transplant candidates (e.g. kidney pancreas transplant candidates); e) patients with a planned living donor transplant; f) patients receiving dialysis in a non-local unit; g) patients with a non-approved requirement for surveillance echocardiography.
Treatment	Patients randomized to routine screening will undergo non-invasive testing for CAD according the 2005 National Kidney Foundation Guidelines (Figure 1 study manual).(7) Patients randomized to no regular screening will not undergo regular non-invasive testing for CAD in the absence of symptoms. Patients in both groups who develop symptoms of angina or an angina equivalent, will be investigated according to the local standard of care which may include the use of non-invasive or invasive cardiac testing.

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1.0 INTRODUCTION AND RATIONALE

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD) as it prolongs survival, improves quality of life, and is less costly than dialysis.(1-3) However, the demand for kidney transplantation exceeds the organ supply, and Canadians routinely wait on dialysis for 3 to 8 years for a deceased donor kidney transplant.(4) ESRD patients are at high risk for the development or progression of coronary artery disease (CAD). As such, the very risk of CAD can exclude patients from consideration of transplantation, or result in death before or after transplantation.(5, 6) CAD is difficult to diagnose in ESRD patients who may not develop the classic symptoms of angina because of uremia, diabetes and other factors.

The current standard of care described in transplant guidelines includes two phases of screening for CAD i) prior to acceptance onto the waiting list, and ii) screening at regular intervals (i.e. annually) after wait-listing.(7) The aim of screening is to identify CAD by non-invasive tests (i.e. Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo), identify critical coronary stenoses by angiography, and prophylactically revascularize diseased patients with the aim of prolonging survival before and after transplantation. Although this is the standard of care, only one randomized trial performed in 1992 involving 26 diabetic patients has ever been performed to evaluate this strategy.(8) This study was prematurely terminated because of slow recruitment and an unexpected imbalance in CAD events favoring treatment.

Ironically screening for CAD may paradoxically increase morbidity and mortality by i) exposing patients to the risk of angiography and revascularization procedures or ii) by delaying or excluding patients from life saving transplantation. Indeed, screening is not beneficial in most non-ESRD surgical candidates and is not routinely recommended. (9) However, the goals of screening transplant surgical candidates differ from those in non-ESRD surgical candidates 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. These differences and the lack of evidence in the transplant setting have led to confusion about the optimal management of transplant candidates: The two main issues of uncertainty are 1) whether to screen asymptomatic patients for occult CAD, and 2) whether the usual approach of revascularizing coronary stenoses in asymptomatic patients is of benefit.

Canadian transplant physicians are unwilling to forgo screening for CAD prior to acceptance onto the waiting list, because these tests are considered essential to determine initial transplant eligibility. However, the largest health services burden is related to screening after wait-listing, and there is clinical equipoise to determine the utility of screening after wait-listing in a clinical trial. The current application is for a pilot trial to determine the feasibility of a definitive randomized controlled trial to test the hypothesis that selective use of cardiac screening tests is non-inferior with respect to the composite endpoint of non-fatal MI and cardiac death compared to the current standard of care that involves screening all asymptomatic wait-listed patients at regular intervals. Physicians would investigate patients in both groups if they develop symptoms of CAD. With over 100,000 kidney transplant candidates in North America, Australia, and New Zealand a definitive trial is needed to inform optimal care. The definitive trial findings will either a) save valuable resources by averting needless and potentially harmful tests, or b) validate

current transplant practice and ensure optimal use of scarcely available deceased donor kidneys.

1.1 Principal Research Question

For our definitive trial, we will determine if a strategy of non-use of regular screening tests (i.e. Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo) is non-inferior with respect to the composite endpoint of non-fatal MI and cardiac death compared to screening all asymptomatic wait-listed patients at regular intervals as described in transplant specific guidelines published by the National Kidney Foundation (see Table 1 below).(7)

Table 1. Frequency of screening for CAD in patients randomized to regular screening group	
Patient characteristics	Frequency of Screening
Diabetic patients	Every 12 months
Patients with prior coronary artery disease on coronary angiogram: If not revascularized If prior percutaneous intervention (angioplasty or stent) If prior coronary artery by-pass grafting (CABG) If prior CABG but incomplete revascularization	Every 12 months Every 12 months 3 years after revascularization and then every 12 months Every 12 months
If high risk non-diabetic: More than 20% per 10 years cardiovascular event rate risk according to Framingham or known CAD (clinical, EKG, or other evidence of CAD but without angiographically visualized coronary stenosis), or PVD, or ejection fraction $\leq 40\%$	Every 24 months
Non-diabetic low risk (includes all patients not included in the above categories)	Every 36 months
https://www.cvdriskchecksecure.com/FraminghamRiskScore.aspx	

Before proceeding with a large multi-centre trial, feasibility will be assessed in a 33 month pilot trial. In the pilot trial, feasibility is the primary outcome and will be assessed by protocol adherence, patient enrolment and consent rates.

1) Protocol Adherence: A patient will be considered adherent if the observed number of screening tests performed equals the expected number of screening tests during the two year follow-up period (i.e. the expected number of tests in a diabetic patient who remains asymptomatic would be zero in the no-regular screening group, while the same patient would be expected to completed two screening tests during the 24 month treatment period in the pilot trial if randomized to regular screening). Our proposed sample size of 144 patients will 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%.

2) Enrolment of 24 patients per month during the six month enrolment period.

3) Consent of 40% of eligible patients approached for participation.

The enrolment and consent targets are informed by the planned recruitment of 2500

patients in 23 transplant centers over three years in the definitive trial. The definitive trial sample size of 2500 is based on the assumption that a no-regular screening strategy will be considered non-inferior to a regular screening strategy if there is $\leq 1\%$ absolute increase in the combined outcome of non-fatal MI and cardiac death in the no-regular screening group.

Rationale for focus on use of screening tests after wait-listing:

Although evidence for CAD screening prior to placement on the waiting list is lacking, the study will focus on the use of screening tests *after* activation to the waiting list because:

1. Physicians are unwilling to forgo initial cardiac evaluation:

In preparation for this application, we surveyed all 15 adult Canadian Transplant Centers. All centers 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. These tests are viewed as necessary to determine initial transplant eligibility.

2. In contrast, there is clinical equipoise around the use of screening AFTER wait-listing:

In a survey conducted in support of this application, all Canadian centers reported screening for CAD after wait-listing. The majority of transplant centers (11/15) had a screening protocol, while in four centers transplant physicians individually selected patients for screening. The frequency of screening reported in hypothetical patient scenarios equaled or exceeded that recommended in the Transplant Guidelines. All 15 centers were willing to randomize patients to regular or no-regular screening after wait-listing.

3. The largest health services impact is related to the use of multiple screening tests during the years of wait-listing (typically 2-8 years), rather than the one time testing prior to placement on the waiting-list.

1.2 Need for the Trial

A recent joint Scientific Statement from 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.(6) The following sections review the urgent need for a definitive trial.

1.2.1 WAIT-LISTED PATIENTS ARE INCREASING IN NUMBER AND MEDICAL COMPLEXITY

There are 3500 patients active on the waiting list in Canada, with over 800 deceased donor transplants performed annually.(11) In comparison, over 92,000 patients are currently wait listed in the United States with approximately 10,600 deceased donor transplants performed annually.(12) Wait-list candidates are increasingly complex. For example, the proportion of transplant candidates ≥ 50 years increased from 29% to 62% between 1991 and 2011,(12) while the percentage with type I or type II diabetes increased from 23% to 28% between 1998 and 2008.(13)

1.2.2 LONGER WAITING TIMES AND CHANGING DONOR CHARACTERISTICS INCREASE CAD RISK

Despite efforts to increase organ donation, the demand for transplantation continues to exceed the supply of transplantable organs. The median waiting time for deceased donor transplantation increased from 2.8 to 4.6 years between 2004 to 2006, and in 2011 the median waiting times for Canadian transplant recipients ranged from 864 to 1954 days (2.3-5.3 years) (Figure 1, Appendix).(14) Exposure to dialysis is a major factor increasing the risk of cardiac events before and after transplantation.(15) As a result, the cardiac

fitness of wait-listed patients for transplant surgery must be maintained for longer time periods. Due to the organ shortage, patients are now transplanted with kidneys from older deceased donors, and donation after circulatory death donors that have more peri-operative complications, and a higher risk of peri-operative cardiac events.(12)

1.2.3 WAIT-LISTED PATIENTS ARE AT HIGH RISK FOR CAD BUT ARE COMMONLY ASYMPTOMATIC

ESRD patients are at increased risk for CAD.(16) 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 kidney transplantation.(6, 17) The risk of cardiac events is highest during the first post-transplant month but remains elevated during the first post-transplant year.(1, 18) Cardiovascular disease is the most common cause of death in both wait-listed patients (18) and patients with a functioning transplant, accounting for 30% of mortality overall.(12) However, because of physical limitations and neuropathies, ESRD patients may not develop symptoms of CAD. For example, among patients hospitalized with myocardial infarction in the third National Registry of Myocardial Infarction, chest pain at presentation was less common in dialysis (44%) compared to non-dialysis patients (68%).(19)

1.2.4 THE STANDARD OF CARE IS NOT EVIDENCE BASED AND EXPENSIVE

The current standard of care involves serial non-invasive cardiac testing of asymptomatic wait-listed patients.(7) Patients with abnormal non-invasive tests undergo coronary angiography followed by revascularization of any hemodynamically critical stenosis by coronary angioplasty with or without coronary stenting, or coronary artery by-pass grafting.(7) During this period of investigation, patients are inactivated on the waiting list and unable to receive a transplant. In 1992, Manske reported the only randomized trial examining this strategy: In a single center, 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% were randomized 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 had a cardiac end point (including 4 deaths) compared to 2/13 revascularized patients ($p < 0.01$). (8) 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) the medical therapy has changed substantially ii) the study focused on a specific high-risk population (insulin-dependent diabetics) representing < 20% of the wait-listed population(20); iii) the study evaluated one time screening in an era when transplant waiting times were dramatically shorter; iv) the trial had few events and 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 of the excess cardiovascular disease burden of ESRD is related to CAD. ESRD patients frequently die of sudden cardiac death, that is arrhythmogenic in origin and may be related to uremic cardiomyopathy.(21, 22) The rationale for screening for critical coronary stenoses also ignores evidence that the mechanism of myocardial infarction in the operative and non-operative setting is atherosclerotic plaque rupture followed by thrombosis and occlusion of the affected coronary artery.(23) The risk of plaque rupture in the peri-operative period is related to tachycardia, increased sheer stress, and a hypercoagulable state.(24, 25) The most occlusive plaques are not necessarily prone to rupture and thrombosis.(26) One third of patients with peri-operative myocardial infarction sustain damage in areas distal to

noncritical stenoses.(26) Finally, the available screening tests do not necessarily identify plaques at risk of rupture and thrombosis.

Screening for CAD is expensive. In our study, 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 \$550,000 were required by current National Kidney Foundation guidelines.(20) When the additional costs of program administration, coronary angiography, consultations and revascularization procedures in patients with abnormal screening tests are considered, the current non-evidence based strategy conservatively costs \$15 million per year in Canada.(27) The estimated cost of a single screening test for the over 90,000 wait-listed patients in the United States is \$210 million.(28) No studies have examined the cost-effectiveness of screening for CAD. *In order to ensure health care system sustainability and maximize patient outcomes given finite availability of health care resources, it is critical that the effectiveness and cost-effectiveness of screening strategies be determined.*

1.2.5 THE CURRENT STANDARD OF CARE MAY BE HARMFUL

The potential harms related to the current strategy of screening and revascularization of asymptomatic transplant candidates are summarized in Table 2 below.

Table 2. Complications of revascularization are higher in End Stage Renal Disease (ESRD) Patients			
<u>Population</u>	<u>Event Type</u>	<u>Event Rate</u>	<u>Ref</u>
U.S. Dialysis patients 1978-95	2 Yr mortality post PTCA	52%	(29)
	2 Yr mortality post CABG	44%	(29)
U.S. Transplant recipient 1995-9	2 Yr mortality post PTCA	18%	(30)
	2 Yr mortality post CABG	17-26%	(30)
Non-ESRD patients reported by Bari Investigators	5 year mortality post PTCA	14%	(31)
	5 year mortality post CABG	12%	(31)
2. Asymptomatic ESRD patients may be considered too high risk for surgery and excluded from transplantation rather than revascularized			(10)
3. Screening prolongs waiting time prior to transplantation: Audit of 130 wait-list candidates in B.C.: 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. There is increased risk of bleeding with use of anti-coagulation after revascularization in ESRD patients and some surgeons will not transplant anti-coagulated patients			(32) (6)
5. Angiography causes loss of residual kidney function. Preservation of residual kidney function is associated with increased dialysis survival			(33)

1.3 Systematic Literature review

The American College of Cardiology and American Heart Association Scientific Statement published in July, 2012 included a comprehensive systematic review of the literature between 1990-March, 2010.(6) We updated the literature review in August, 2013 and

found no further relevant trials. The publication is available (<http://content.onlinejacc.org/collection.aspx?ArticleTypeId=11552>).

Key issues most relevant to the proposed trial are reviewed in section 1.41-1.44 below:

1.3.1 NON-INVASIVE SCREENING TESTS HAVE LIMITED PREDICTIVE ABILITY FOR CAD

Noninvasive testing for CAD has imperfect sensitivity and specificity in ESRD patients. In patients with GFR ≤ 15 mL/min/1.73 m² or on dialysis, the sensitivity of Dobutamine Stress Echocardiography and Myocardial Perfusion Scintigraphy varies from 0.44 to 0.89 and 0.29 to 0.92 while the specificity varies from 0.71 to 0.94 and 0.67 to 0.89, respectively, for identifying one or more coronary stenoses $\geq 70\%$.(6, 34-36) Noninvasive tests are most predictive of significant coronary stenoses in patients with a high pre-test probability for disease.(37) Assuming a sensitivity and specificity of 0.7, and a pre-test probability of disease of 50%, the positive predictive value of a non-invasive test would only be 70%. Furthermore, a recent meta-analyses evaluating non-invasive cardiac stress tests (e.g., stress echocardiography, nuclear scintigraphy imaging) demonstrated that more than a third of the patients who suffered a major perioperative cardiovascular event had a negative test result.

1.3.2 RANDOMIZED STUDIES IN ASYMPTOMATIC NON-RENAL FAILURE SURGICAL CANDIDATES HAVE NOT DEMONSTRATED A BENEFIT OF REVASCULARIZATION PRIOR TO ELECTIVE SURGERY

The DIAD study(38) and COURAGE Trial(39) failed to demonstrate that a strategy of screening and revascularization of CAD in asymptomatic patients reduced cardiac events. These pivotal trials excluded ESRD patients and did not focus on the issue of CAD management in surgical candidates limiting the relevance of these trials for the wait-listed kidney transplant population.

The randomized CARP trial was the first study to address the strategy of prophylactic revascularization compared with optimal medical therapy in patients with clinically stable CAD scheduled for major vascular surgery.(40) Long-term mortality was similar in patients randomized to prophylactic coronary revascularization (23%) or medical treatment only (22%) (p=0.92). This trial demonstrated a statistically significant higher incidence of perioperative myocardial infarction at 30 days after noncardiac surgery in the patients who first underwent coronary revascularization prior to their noncardiac surgery (confidential unpublished data, personal communication: Dr. Edward McFalls). If hemodynamically significant stenoses are the major cause of perioperative myocardial infarction, it is surprising that there was an increase in risk of a perioperative myocardial infarction despite coronary revascularization prior to noncardiac surgery. The trial excluded patients who had left main coronary lesions $>50\%$, a cardiac ejection fraction $< 20\%$, or severe aortic stenosis. Importantly, CARP excluded patients with renal failure.

1.3.3 TRANSPLANT SPECIFIC GUIDELINES CONTRADICT GUIDELINES FOR THE GENERAL PUBLIC

Published transplant specific guidelines recommend longitudinal screening for asymptomatic wait-listed patients and contradict recommendations for the non-ESRD population (Table C, Appendix). The most recent American College of Cardiology / American Heart Association Guidelines on Peri-operative Cardiovascular Evaluation and Care for Noncardiac Surgery suggest evaluation of symptomatic patients, but do not encourage further testing for asymptomatic patients or those with a functional capacity of ≥ 4 METS (i.e. ability to climb a flight of stairs) irrespective of diabetic status, history of CAD, or presence of cardiac risk factors.(9)

1.3.4 NO-REGULAR USE OF SCREENING TESTS MAY BE SAFE IN WAIT-LISTED PATIENTS

In our observational study of n=604 wait-listed patients in British Columbia, clinicians utilized screening tests for CAD based on ongoing clinical evaluation during wait-listing. This strategy resulted in fewer screening tests than recommended by guidelines (n = 171 versus 530 tests), and a trend toward a lower frequency of cardiovascular events (cardiovascular event rate in patients with and without the recommended frequency of investigation was 9.9 [95% CI, 7.1 to 13.7] and 6.7 [95% CI, 5.2 to 8.7] per 100 patient-years).(20) Two other observational studies also suggest that no-regular screening may be safe: In a single centre study of 514 wait-listed candidates who were screened based on clinical criteria, 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. The use of screening tests in this study was based on clinical judgment of the treating physician, and some of the tests were likely performed in patients who had symptoms suggestive of CAD. (43) 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 revascularized. Cardiac events were higher in screened patients 12/174 (6.9%) versus unscreened patients 19/426 (4.5%).(44)

1.3.5 SUMMARY WHY THE CARDIAC SCREENING TRIAL IS NEEDED

Medical advances have led to a paradigm shift away from revascularization of clinically silent coronary stenoses in non-ESRD patients. Current evidence based recommendations for CAD management in non-ESRD patients contradict the opinion-based recommendations for wait-listed kidney transplant candidates. However, non-ESRD guidelines emphasize the importance of symptoms and assume a short time course between evaluation and surgery, and may be less relevant for wait-listed ESRD transplant candidates in whom the timing of future transplant surgery cannot be precisely determined. Further, the goals of screening in transplant candidates extend beyond ensuring peri-operative safety and include maintenance of eligibility for transplantation, and ensuring that the potential long-term health benefits of transplantation are realized.

Canadian transplant physicians uniformly screen patients prior to accepting them onto the waiting list and are unwilling to randomize patients to use or non-use of screening at this stage. However, the main health services impact of screening occurs during the years of wait-listing for transplantation and there is clinical equipoise to conduct a definitive trial to determine the utility of screening for CAD after activation the waiting-list. Further if no-regular screening is shown to be non-inferior, the clinical need for future studies comparing surgical versus medical management of coronary disease in asymptomatic transplant candidates will be significantly decreased.

2.0 PLAN OF INVESTIGATION

2.1 Trial Objectives

This pilot trial will determine the feasibility of a multi-center, randomized, parallel group definitive trial.(45) Asymptomatic wait-listed patients will be randomized to routine screening for CAD (i.e. Myocardial Perfusion Scintigraphy (MPS) or Dobutamine Stress Echo (DSE)) as per the current standard of care (Table 1) versus no regular screening during wait-listing. Patients enrolled in the pilot will be included in the definitive trial analysis. The pilot trial will include six Canadian transplant centres. The definitive trial will be conducted in over 20 centers in Canada Australia and New Zealand.

2.1.1 PRIMARY OUTCOMES: In line with our primary objectives, the primary outcomes are 1) protocol adherence; 2) enrolment rates and 3) consent rates. A patient will be considered adherent if they were adherent to their allocated screening strategy (regular versus no-regular screening) over the 24 month treatment period. Enrolment rates will be assessed monthly during the six month enrolment period. Consent rates will be defined as the proportion of patients enrolled among eligible patients approached for enrolment and will be defined after completion of the six month enrolment period.

2.1.2 SECONDARY OUTCOMES: In this pilot study the secondary clinical outcome is a composite outcome of cardiac death and non-fatal myocardial infarction (i.e. the proposed primary outcome in the definitive trial) and will be adjudicated by a blinded clinical endpoints committee using criteria from the POISE Trial.(46, 47). Total mortality, cardiovascular mortality, non-fatal cardiac arrest, stroke, life-threatening bleeding and major bleeding (ie. the proposed secondary outcomes in the definitive trial) will also be defined and adjudicated as in the POISE Trial.(46, 47).

2.1.3 TERTIARY OUTCOMES: Transplant events, wait-list holds and wait-list removals including the indication will be measured. We will also ascertain health care encounters related to the diagnosis and management of CAD. This information is required to: i) determine cost, and cost effectiveness of the two screening strategies in the proposed definitive trial; ii) document concurrent management practices that may impact the incidence of outcomes in the definitive trial. The information captured will include outpatient, day care, and emergency room use (including any diagnostic testing and all medical and surgical interventions (i.e. use of thrombolytics, revascularization procedures), inpatient encounters and resource utilization (hospitalizations, CAD-related procedural costs), physician consultations. Quality of life will also be measured using the EQ-5D.

2.2 Sample Size

Adherence to screening strategies is of utmost importance to demonstrate separation between the two strategies and fidelity of our interventions. In the pilot trial, a sample size of 144 will 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%. Thus, 72 patients will be allocated to each treatment group.

In the definitive trial, randomization of 2500 patients is required to demonstrate that no-regular screening is non-inferior to regular screening, with an absolute increase in the primary outcome of cardiac death and non-fatal MI $\leq 1\%$ in the no-regular screening arm considered non-inferior.

3.0 ELIGIBILITY CRITERIA

Inclusion of incident wait-listed patients (i.e. patients activated to the waiting list after the start of the trial) and prevalent wait-list patients (i.e. patients already on the waiting list before the start of the trial) will enable successful enrolment, and ensure a high proportion of patients undergo transplantation during study follow-up. Only patients with an anticipated transplant date > 12 months from the date of enrolment will be included. The time to transplantation of wait-list candidates can be estimated in each center based on ABO blood type, and immunology testing for anti-HLA antibodies. Enrolment in the pilot trial will be enriched to include at least 66% prevalent wait-listed patients so that

approximately 50% of patients are expected to undergo transplantation during the 24 month pilot trial follow up period.

3.1 Inclusion criteria

- a) Adult patients ≥ 18 years of age, able to provide informed consent
- b) Patients with dialysis-dependent renal failure and active on the deceased donor transplant waiting list.
- c) Patients expected to require further screening for CAD prior to transplantation by the current standard of care. Refer to Figure 1 below to determine screening frequency. It should be noted that some prevalent patients may already be past due for their cardiac screening test according to the current standard of care at the time of study enrolment. If randomized to the regular screening arm, these patients would be scheduled for a cardiac screening test within 1 month of enrolment.
- d) Investigator consented and signed off on patient eligibility.
- e) Patients anticipated to undergo transplantation more than 12 months from the date of enrolment. Although we cannot definitively predict the timing of transplantation, we will estimate this date based on ABO blood type, and immunology testing for anti-HLA antibodies indicated by panel reactive antibodies (PRA). The time to transplantation will vary between centers in each of these groups. Therefore the site investigator will complete Table 3 below to inform the time to transplantation in each center.

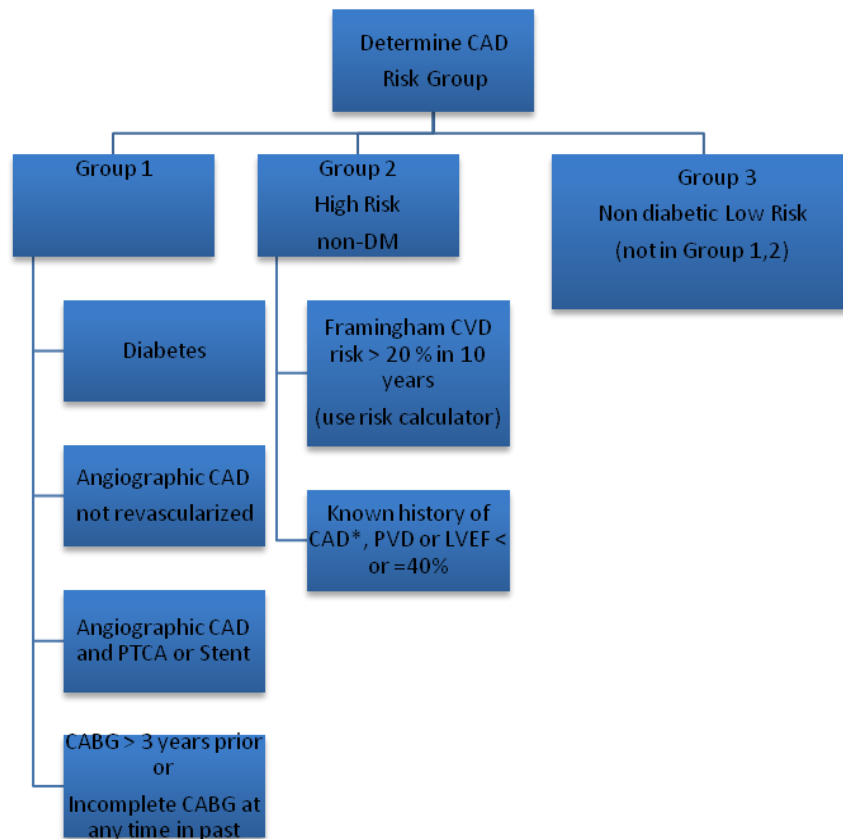
3.2 Exclusion criteria:

- a) patients with signs or symptoms suggestive of active cardiac disease such as unstable coronary syndromes, decompensated heart failure, uncontrolled arrhythmia, new arrhythmia or conduction abnormality, valvular heart disease;
- b) patients who have been put “on hold” for transplantation due to a medical problem (e.g. an infection);
- c) prior extra-renal transplant recipients;
- d) multi-organ transplant candidates (e.g. kidney pancreas transplant candidates);
- e) patients with a planned living donor transplant;
- f) patients receiving dialysis in a non-local unit
- g) patients with a non-approved requirement for surveillance echocardiography

Table 3 Estimating time to transplantation from date of first wait-listing. To be completed by Site Investigator in Each Center

Blood Group	PRA 0%	PRA 1-29%	PRA 30-79%	PRA $\geq 80\%$
A				
B				
AB				
O				

Figure 1.



Group 1 patients would be screen annually, group 2 patients would be screened every 24 months, and group 3 patients would be screened every 36 months according to the 2005 NKF Guidelines. Timing of screening tests would be determined according the date of the last screening test recorded on the transplant center chart.

The Framingham CVD risk calculator can be found at

<https://www.cvdriskchecksecure.com/FraminghamRiskScore.aspx>

* Patients with known CAD include those with clinical, EKG or other evidence of CAD, but excludes patients with angiographically proven evidence of CAD. Patients with angiographically proven CAD would be included in group 1.

4.0 PATIENT RECRUITMENT AND INFORMED CONSENT

We will enroll approximately 24 patients per month during the six month enrolment period for a total sample size of 144 patients. With 6 enrolling centres – this is equal to four patients per month X 6 months. The monthly enrolment rate is informed by the requirement to enroll approximately 70 patients per month in twenty-three centers for 36 months to complete the definitive 2500 patient trial.

We plan to consent 40% of the eligible patients approached to participate in the pilot trial. This 40% target in the pilot trial exceeds the estimated consent rate of 34% required to complete the definitive trial.

We also aim to have 50% of participants undergo transplantation within 24 months of the date of enrolment. This is important to demonstrate the risk of no-regular screening.

This will be achieved by enrolling both incident and prevalent wait-listed patients in the trial. To ensure this objective each site will enrol at least 66% prevalent wait-list patients (i.e. 16/24 patients at a given site should be prevalent patients). The data co-ordinating centre will not provide randomization if the site's enrolment of prevalent patients falls below 66% during the pilot study.

4.1 Incident patient identification and enrolment

Although incident patients could be enrolled at the time of their initial transplant evaluation, patients usually require further evaluation and multi-disciplinary team discussion before they are officially activated to the list. Therefore the study co-ordinator should receive a listing of all newly activated wait-list patients on a weekly basis (i.e. on a Friday) from the Transplant Center to be approached the following week.

Patients who reside locally should be identified for potential participation first. Note this could include patients on peritoneal or hemodialysis in the home or in-center setting. An approach to contact and consent the patient for enrolment during a routine clinical encounter or dedicated study visit should then be defined (e.g. a telephone call followed by an in person enrolment visit during a dialysis treatment or outpatient clinic visit) using institution-specific policies and procedures.

The site PI should discuss eligible patients with the treating cardiologist (if applicable) to 1) confirm the cardiologist's agreement with participation in the trial 2) determine whether the patient meets any of the requirements for screening echocardiography (see Table 4 below). Patients declined for participation by their cardiologist will be considered ineligible.

4.2 Prevalent patient identification and enrolment:

At least 16/24 patients enrolled in each site will be prevalent patients.

In addition to meeting study inclusion/exclusion criteria, prevalent patients should be under chronic dialysis treatment in a location that is accessible to study co-ordinators (i.e. local patients).

The study co-ordinator should review all patients on the active transplant waiting list with the site PI, and identify eligible potential study participants who reside locally first.

The site PI should discuss eligible patients with the treating cardiologist (if applicable) to 1) confirm the cardiologist's agreement with participation in the trial 2) determine whether the patient meets any of the requirements for screening echocardiography (see Table 4). Patients declined for participation by their cardiologist will be considered ineligible.

4.3 Informed Consent: A study co-ordinator will approach eligible patients to obtain informed consent.

4.4 Randomization

A web-based randomization system will be used. A permuted blocked randomization method will be used to allocate patients. Patients will be stratified by centre and diabetic

status. A statistician, independent of the trial team, will generate the randomization scheme. The randomization process will consist of a computer-generated random listing of the treatment allocations stratified as above in variable permuted block sizes that will not be known to the investigators. The system will have backup in the form of a statistician and designated research assistant at the coordinating centre. Only the statistician and designated research assistant at the coordinating centre will have knowledge of the randomization codes. After confirming eligibility and obtaining informed consent, the study nurse will access the trial website and provide the subject's unique ID as well as a confirmation of consent and eligibility. The web site will provide the next available randomization number. The data co-ordinating centre will not provide randomization if the site's enrolment of prevalent patients falls below 66% during the pilot study.

5.0 TRIAL MANAGEMENT OF PATIENT RANDOMIZED TO REGULAR AND NO-REGULAR SCREENING

5.1 Screening test schedule: Patients randomized to regular screening will undergo non-invasive testing for CAD according the 2005 National Kidney Foundation Guidelines (Table 1 above).(7) Patients randomized to no-regular screening will not undergo regular non-invasive testing for CAD in the absence of symptoms. Patients in both groups who develop symptoms of angina or an angina equivalent, will be investigated according to the local standard of care which may include the use of non-invasive or invasive cardiac testing. Patients will remain on the pilot trial protocol (i.e. regular or no-regular screening) until death, non-fatal MI, transplantation, permanent removal from the waiting list for any reason, or 24 months after enrolment in the pilot trial.

5.2 Type of non-invasive cardiac screening test: The choice of non-invasive test(s) will be according to the existing practice of each transplant center. The National Kidney Foundation guidelines recommend that testing should be done with an exercise or pharmacological stress echocardiographic or nuclear imaging test.(7) The choice of exercise or pharmacological stress is determined by the presence of physical limitations (e.g. osteoarthritis) in transplant candidates. The high prevalence of left ventricular hypertrophy in ESRD patients may also decrease the utility of ECG treadmill testing.(6) The type of test used will be documented in all instances.

5.3 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 centers and will not be influenced by the investigators or study personnel in any way. CAD-related medical and surgical interventions will be recorded in both groups.

5.4 Management of patients who develop clinical symptoms of CAD: Any patient 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 centers 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 center. Study personnel will document all surgical and medical interventions for CAD.

5.5 Permitted investigations in randomized study patients:

The use of Myocardial Perfusion Scintigraphy or Dobutamine Stress Echo outside the study protocol will be strongly discouraged except for patients that develop signs or symptoms of active cardiac disease, and any use will be documented. Cardiac investigations (including coronary angiography) required prior to surgery for valvular heart disease are permitted. Although resting echocardiography is not indicated for detection of CAD, these tests are commonly performed in wait-listed patients and are discouraged outside the scenarios shown in Table 4 (below).

Table 4. Accepted indications for resting echocardiography
1. To follow progression of moderate or greater stenosis or regurgitant valvular disease
2. To monitor patients with bioprosthetic/mechanical heart valves or valve repair
3. To follow progression of pulmonary hypertension in patients with estimated pulmonary artery pressure (PAP) > 50 mmHg or PAP > 40 mmHg with evidence of right heart failure
4. To monitor left ventricular ejection fraction (LVEF) in patients with LVEF <40%

5.6 Other study manoeuvres :

Other than the use of cardiac screening tests, patient management will be as per the usual standard of care in participating transplant centers. Specific considerations include: (a) **FREQUENCY OF CLINICAL EVALUATIONS DURING WAIT-LISTING:** There may be variation in the follow-up of wait-listed patients by transplant centers. In both study groups, the frequency and content of clinical re-evaluations will be according to the existing practice of the participating study sites. Such evaluations may include cardiology consultations. Clinical evaluations by the study sites during wait-listing will be recorded in both groups. (b) **USE OF MEDICAL OR BEHAVIOURAL TREATMENTS TO PREVENT CAD EVENTS:** Interventions to prevent cardiovascular disease events including the use of lipid lowering agents, aspirin, and beta-blockers remain controversial due to the lack of definitive evidence regarding efficacy in ESRD patients.(6) Medical treatments will not be specified in the trial but will be documented by study personnel. Similarly behavioural therapies such as participation in weight loss, smoking cessation or healthy heart programs may used.

5.7 Methods to protect against contamination: We will minimize the use of non-invasive CAD screening tests outside of the trial protocol by:

- 1) Informing primary nephrologists and primary care physicians who oversee the care of wait-listed patients will about the trial and the need to avoid off-protocol non-invasive CAD screening tests.
- 2) Informing cardiologists affiliated with a dialysis program about the study. Eligible patients under active care of a cardiologist will be discussed to ensure agreement with participation.
- 3) Placing a Study Alert on the patient's dialysis chart.

- 4) Providing of a Wallet Card to patients containing a website with information about the trial.
- 5) Educating patients to advise health care providers of their participation and to share the information in their Wallet Card. Annual communication in the form of a Thank You Card for participation will remind participants of trial responsibilities.

6.0 FOLLOW-UP

During wait-listing, follow-up telephone interviews and chart reviews will be performed every six months, with a final follow up interview at 27 months after enrolment performed in patients who do not undergo transplantation within 24 months of the date of study enrolment.

Patients who undergo transplantation during the first 24 months after enrolment will be followed until three months after the date of transplantation. A chart review will occur at the time of discharge from hospital, and an in person or telephone interview and chart review will be performed 3 months after transplantation.

For the small number of patients who undergo transplantation ≥ 24 months after enrolment, the last follow up will be 27 months after the date of enrolment even if the 3 months of post transplant follow up are not possible. A chart review will occur at the time of discharge from hospital, and an in person or telephone interview and chart review will be performed 27 months after enrolment.

7.0 TRIAL OUTCOME ASCERTAINMENT

Standardized Case Report Forms will be used to assess all outcomes and study personnel will undergo formal orientation to these CRFs.

Primary outcomes: 1) Protocol adherence: We will define adherence by completion of the expected number of screening tests during follow up. For example, the expected number of screening tests in a diabetic patient who did not develop symptoms would be zero in the no-regular screening group, while the same patient would be expected to completed two annual screening tests if randomized to regular screening. Tests performed for clinical symptoms of CAD will be excluded from the determination of adherence.

Screening tests in patients randomized to the regular screening arm will be arranged by study personnel under direction of the site investigator. The study personnel will advise participants of their screening test and follow up directly with the testing facility to determine completion of the test and obtain test results. Use of cardiac screening tests and the reasons for testing, in both treatment groups will be determined using the following procedure: Patients will be interviewed in person during regular dialysis treatments or via telephone every six months. If an unscheduled test was performed the patient will be asked about the reason for test (i.e. presence of symptoms) and the identity of the organizing physician. We believe telephone interviews are feasible in this relatively healthy cohort of wait-listed patients. Patient interviews will be supplemented by review of the transplant center and dialysis patient chart or with treating physicians as necessary every six months.

2) Enrolment will be determined monthly from the Ottawa Hospital Research Institute (OHRI) which issues the randomization scheme.

3) Consent rate: Each transplant center maintains an up-to-date record of incident and prevalent active wait-listed patients. Eligibility criteria will be abstracted from the transplant center chart to a standardized case report form. The case report form will be completed by the study co-ordinator and will include the estimated time to transplantation as determined by the site investigator.

For incident wait-list patients a monthly listing of newly activated wait-list candidates will be obtained from the transplant center during the enrolment period. Eligible incident patients will be sequentially approached with a target enrolment of up to 8 incident patients in each site. Willingness to enroll in the study will be recorded on each patient's case report form along with the reason for any refusal to consent. The number of incident patients approached to complete enrolment will be determined by review of the case report forms.

Prevalent Patients will be enrolled from the local dialysis population attached to each of pilot study transplant centers. The target number of prevalent patients at each site is 18 but there is no maximum number of prevalent patients that can be enrolled. Consent will be documented as described for incident patients.

Secondary Outcomes:

Ascertainment of secondary outcomes will be enabled by the fact that primary nephrologists and family doctors are required to inform the transplant center of any significant change in the health status of actively wait-listed patients that would impact transplant candidacy. Transplant center charts will be reviewed every six months. Events not reported to the transplant center, will be captured in the direct patient interviews (medical status, health history) and chart reviews (race, gender, medical history, hospitalizations, ER visits, results of Diagnostic Imaging, other test results) conducted every six months during wait-listing (see above). Transplanted patients will have their charts reviewed at time of hospital discharge, and undergo an interview and chart review three months after transplantation. All cases will be recorded on a case report form that conceals treatment group assignment. Case report forms will be reviewed by the primary site investigator, and forwarded to the blinded CEC that will adjudicate outcomes according to the protocol used in the POISE Trial.(46, 47)

Tertiary Outcomes:

Transplant events, and wait-list holds/removals will be assessed through direct monthly communication with the transplant centers. Ascertainment of health care resource encounters related to the diagnosis and management of CAD will be obtained by patient interview supplemented by chart reviews every six months and recorded on a standardized case report form. We will verify and supplement information regarding hospitalizations, emergency room visits, use of cardiac tests and revascularization procedures obtained in the telephone interview by review of clinical and electronic health records, as required. EQ-5D will be administered at time of enrolment and at time of the final study interview (27 months in non-transplanted patients and patients transplanted after 24 months of enrolment, OR 3 months post transplantation in patients transplanted ≤24 months after enrolment).

8.0 OUTCOMES ADJUDICATION

Outcome adjudicators (a committee of clinicians with expertise in cardiology) who are blinded to treatment allocation will adjudicate the following outcomes: death (cardiac or non-cardiac) and non-fatal myocardial infarction, non-fatal cardiac arrest, stroke, life-threatening bleeding, and major bleeding.

9.0 DATA ANALYSES

For the pilot trial, descriptive analyses are planned. Feasibility will be summarized with proportions, rates, means, and medians as appropriate. Comparison of the definitive trial outcomes between treatment groups, will not be done at the end of the internal pilot as these patients will be included in the definitive trial. In the definitive trial primary and secondary outcomes will be analyzed according to the intention to treat principle.

Analyses of enrolment rates and consent rates will be done after the enrolment phase of the pilot trial in February, 2015 in support of application for the definitive trial. With a projected trial start date of Oct 1, 2014 this will allow for 5/6 months of enrolment phase data to be included in the definitive trial application.

10.0 DATA SAFETY MONITORING COMMITTEE

A data safety monitoring committee (DSMC) led by Dr. Braden Manns will oversee the pilot trial.

The Data Safety Monitoring Committee (DSMC) will have responsibility for monitoring of adverse events and will ensure the safety of patients is protected. The DSMC will receive a report of all adjudicated outcomes and any other outcomes agreed to in the DSMC charter every 6 months after randomization of the first patient. The DSMC will immediately notify the Study Chair of any safety issue. The DSMC will work independently from the trial and serve in an advisory role to the Executive Committee and Study Chair. The DSMC will consist of 3 individuals, expert in clinical trials, biostatistics, transplant cardiology, and transplant nephrology. The secondary purpose of the DSMC in the pilot study is to ensure efficient and accurate reporting of serious adverse events (SAEs) in the definitive trial. Dr. Manns will establish a DSMC Charter in conjunction with the Study Chair. Dr. Manns will identify two additional members of the DSMC and nominate a Vice Chair.

11.0 TRIAL MANAGEMENT

11.1 What are the arrangements for the Day to Day Management of the Trial?

The trial management will be through St. Paul's Hospital in Vancouver.

The Data Coordinating Centre will be located at the Clinical Epidemiology Program (CEP) of the OHRI and will be under the guidance of the Study Chair, Study Operations Director, central coordinator, senior trial methodologists and trial statistician. The CEP is currently overseeing over 40 trials and will be responsible for receiving, processing, editing, storing and analyzing all data from the sites. The Data Management will be transferred to St. Paul's hospital starting from July 2016. A detailed overview of study procedures and work plan is provided in Table 5, below.

Table 5. Overview of Study Procedures and Work Plan							
	0 m	6 m	12 m	18 m	24 m	27 m	CRF

Screening, Randomization							
Consent	X						CRF1
Randomization	X						CRF1
Screening tests for CAD							
Planned MIBI, DSE, Exercise stress							Frequency of screening varies (12,24, 36 months) depending on patient risk
Unplanned screening tests		x	x	x	x		
Patient Health Status							
Baseline Health Status	X						CRF2
Quality of Life	X					X	EQ-5D
Is patient alive?		X	X	X	X	X	CRF2,12
Did patient have Myocardial infarction, nonfatal cardiac arrest, stroke, bleeding?		X	X	X	X	X	CRF2,13, 14,15,16
Did patient have coronary angiography?		X	X	X	X	X	CRF2,10
Did patient have coronary revascularization		X	X	X	X	X	CRF2,11
Is patient on hold on WL?		X	X	X	X	X	CRF2,17
Is patient removed from WL?		X	X	X	X	X	CRF2,18
Is patient transplanted?		X	X	X	X	X	CRF2,5
Was patient unable to proceed with an offer for transplantation?		X	X	X	X	X	CRF2,5
B. Clinical Encounters							
Hospitalizations, ER visits, Cardiac Day Procedures		X	X	X	X		CRF2, 4
Outpatient cardiology consults		X	X	X	X		CRF2
Transplant center evaluations		X	X	X	X		CRF2
D. Medications							
Medication Review	X	X	X	X	X	X	CRF1, CRF2

11.2 Methods for protecting against sources of bias:

Blinding of patients and health care providers is not possible because the results of non-invasive cardiac tests are required for patient management as per the existing standard of care in participating transplant centers. The likelihood that co-interventions that may impact cardiovascular events will be differentially utilized in the two trial groups is

minimized by the fact that study patients are not under the direct care of a transplant physician while they are wait-listed on dialysis. We will mask allocation to ensure concealment of randomization. A web-based randomization system will prevent study personnel from tampering with allocation (e.g. will not be able to read allocation assignment through an envelope). In addition, random variation of block sizes will prevent sites from “gaming” the allocation by guessing the next treatment assignment. The reasons for use of CAD screening tests will be documented in all cases. The following additional methods will be used to protect against bias:

- ASSESSMENT OF OUTCOMES BY AN EXPERT CLINICAL OUTCOMES EVALUATION COMMITTEE (CEC)

BLINDED TO THE TREATMENT GROUP ASSIGNMENT: All the proposed primary and secondary outcomes for the definitive trial (death, non-fatal MI, non-fatal cardiac arrest, stroke, bleeding) will be reviewed by the independent CEC blinded to group assignment as well as patient and transplant centre identity.

- METHODS TO PROTECT AGAINST CONTAMINATION: We will minimize the use of non-invasive CAD screening tests outside of the trial protocol by:

- 1) Informing primary nephrologists and primary care physicians who oversee the care of wait-listed patients will about the trial and the need to avoid off-protocol non-invasive CAD screening tests.
- 2) Informing cardiologists affiliated with a dialysis program about the study. Eligible patients under active care of a cardiologist will be discussed to ensure agreement with participation.
- 3) Placing a Study Alert on the patient’s dialysis chart.
- 4) Providing of a Wallet Card to patients containing a website with information about the trial.
- 5) Educating patients to advise health care providers of their participation and to share the information in their Wallet Card. Annual communication in the form of a Thank You Card for participation will remind participants of trial responsibilities.

- RIGOROUS DOCUMENTATION OF ALL MEDICAL CO-INTERVENTIONS: 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. The use of these medications in dialysis patients varies between centers and between physicians at the same center. Given that we are stratifying by site, it is expected that use of such interventions will be balanced between the treatment arms.

11.3 Trial Oversight

Dr. Gill (nominated principal applicant) will serve as Study Chair, and Dr. Kim (principal applicant) will serve as Study Vice-Chair; Dr. Devereaux (principal applicant) will serve as a senior trial methodologist and oversee all issues regarding cardiac testing and adjudication; Dr Knoll (principal applicant) will serve as study Operations Director overseeing data management and central data coordination at OHRI; From July 2016 Dr. Gill will take over the position of study Operations Director overseeing data management and central data coordination at St. Paul’s Hospital; Dr. Fergusson (co-applicant) and will serve as a senior trial methodologist; Dr Ramsay (co-applicant) will serve as the trial statistician; Dr. Tonelli (co-applicant) and Chair of the Canadian Task Force on Preventative Healthcare, will provide dialysis content expertise. Drs. Gill, Kim, Knoll, Devereaux, Fergusson, Ramsay, Cantarovich (co-applicant) and Tonelli will sit on the study Executive

Committee. Dr Ramanathan a cardiologist (co-applicant), Dr. Ribic a transplant nephrologist (co-applicant), and Dr Tonelli will assist Dr Devereaux with event adjudication. Dr. Klarenbach (co-applicant) will oversee the data collection required for the health economic analyses in the definitive trial.

11.4 Trial Steering Committee

The Steering Committee will consist of members of the Executive Committee as well as central and site-specific research staff. The committee will have two organizational teleconferences before study initiation and teleconferences quarterly during study recruitment and follow-up. The committee will review and implement all aspects of this trial. Clinical events will be adjudicated at six month intervals during the pilot trial.

11.5 Monitoring

11.5.1 SITE MONITORING

The trial data, compliance, adverse events will be rigorously monitored using remote methods of surveillance. This ensures that trial-related data are accurate, complete and verifiable from source documents and that participant rights and safety are protected. This process will ensure compliance with the regulatory requirements, protocol, GCP, study-specific procedures and participant eligibility. In addition to evaluating the reported data for accuracy and completeness, trends indicative of insufficient documentation or protocol deviations will be identified.

Discrepancies noted in the data will be recorded and the site will be informed of all observations in subsequent monitoring reports.

A representative of the steering committee or delegate will review deficiencies with the appropriate study team member in order to implement corrective actions or to recommend follow-up procedures. Documentation of all deficiencies will be recorded and appear in the site monitoring report.

11.5.2 TIMING AND FREQUENCY OF MONITORING VISITS

Interim Monitoring Visit:

Remote monitoring will be performed for this pilot study. To ensure patient safety and data integrity, on-site monitoring may be required at the discretion of the Steering Committee if remote monitoring shows discrepancies in data, lack of compliance with regulations or if requested by the DSMC or the site Investigator.

If an onsite monitoring visit is required, the study monitor will assess:

- CRF source data verification
- Patient eligibility and consent
- Study specific SOPs
- Delegation logs
- SAEs for recording and reporting completeness
- Regulatory documentation (for site and/or sponsor)
- Training documents

- Protocol defined endpoints
- Essential document maintenance
- Deviation/violation recording and reporting
- Privacy considerations
- Any protocol-specific procedures

After completion of the enrolment phase, the data co-ordinating center will contact each site to resolve any queries regarding missing or inaccurate data. De-identified data from each site may be requested and will be sent via secured courier. Documentation to be sent to the monitor for remote Source Data Verification will be specified by the data co-ordinating center and may include:

- Copies of signed and dated de-identified patient assessment forms (CRFs) with corresponding de-identified source documents
- Copies of de-identified source documentation that supports subjects eligibility to be enrolled into the study
- Copies of de-identified Investigator progress notes regarding patient-related decisions
- Signed and dated training logs as well as copies of materials used to train study staff (slide presentations, hand-outs)

All data to be couriered will be checked by the site coordinator prior to sending in order to ensure patient privacy and confidentiality is maintained. No identifying materials will be sent off-site.

11.5.3 MONITORING PROCEDURES

Study monitoring is a Sponsor responsibility as outlined in ICH-GCP.

11.6 Ensuring Data Quality:

1. all research personnel will undergo a training session prior to trial start
2. all centres will have a detailed trail manual outlining all steps in the protocol
3. all investigators have direct access to the study PI via cell phone contact
4. the data co-ordinating center will evaluate all data as soon as it is received and quality control checks will identify any errors or omissions;
5. The programmer will create internal validity and range checks for all data
6. data management assistants will undertake multi-level regular quality control report
7. the data-co-ordinating office will contact the site to rectify any errors or omissions and this will be done by secure internet correspondence. Issues not rectified in a suitable time frame will be advanced to the attention of the Steering Committee.
8. detailed monthly reports on patient follow-up, data transmission, consistency, thoroughness, and completeness of data collection, and event rates will be compiled by the data co-ordinating center and submitted to the trial Steering Committee on a monthly basis