ISCHEMIA-CKD Trial Protocol

International **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches- **C**hronic **K**idney **D**isease

Sponsor:	National Heart, Lung, and Blood Institute (NHLBI)
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Statistical and Data Coordinating Center	Duke Clinical Research Institute
Protocol Version Date:	December 18, 2014

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
1.0	December 18, 2014

Protocol Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

Version Date: December 18, 2014

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator

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Name of Facility

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Location of Facility (City, Country)

CLINICAL TRIAL SUMMARY

Title	**I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches- **C**hronic **K**idney **D**isease
Study Objectives	Primary objective is to determine whether an initial invasive (INV) strategy of cardiac catheterization and optimal revascularization, if feasible, in addition to optimal medical therapy (OMT) in patients with stable ischemic heart disease (SIHD) and at least moderate ischemia on ischemia testing reduces the incidence of the composite of death or nonfatal myocardial infarction compared with a conservative (CON) strategy of optimal medical therapy alone with cardiac catheterization and revascularization reserved for failure of OMT, in participants with advanced CKD (defined as those with estimated glomerular filtration rate [eGFR] <30 or on dialysis). Secondary objective is to determine whether an INV strategy is more effective than CON strategy in improving angina control, as assessed by the Seattle Angina Questionnaire (SAQ) Angina Frequency scale, and disease-specific quality of life, as assessed by the SAQ Quality of Life scale. Other secondary objectives include comparing the incidence of the composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; individual components of this endpoint; all-cause death; stroke; as well as comparing health resource utilization, cost, and cost-effectiveness between the two randomized strategies.
Study Design	ISCHEMIA-CKD is an international comparative effectiveness study. Participants will be recruited following clinically indicated ischemia testing and randomized in a 1:1 fashion to an INV or CON strategy.
Number of Participants	Approximately 1,000 participants randomized
Trial Location	Multinational: approximately 500 sites worldwide
Inclusion Criteria	• At least moderate ischemia on an ischemia test (see definitions in protocol appendix A) • End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min • Participant is willing to comply with all aspects of the protocol, including adherence to the assigned strategy, medical therapy and follow-up visits

	• Participant is willing to give written informed consent • Age ≥ 21 years
Exclusion Criteria	• LVEF < 35% • History of unprotected left main stenosis ≥50% on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available) • Finding of "no obstructive CAD" (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months • Coronary anatomy unsuitable for either PCI or CABG • Unacceptable level of angina despite maximal medical therapy • Very dissatisfied with medical management of angina • History of noncompliance with medical therapy • Acute coronary syndrome within the previous 2 months • PCI within the previous 12 months • Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time • History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause • NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months • Non-ischemic dilated or hypertrophic cardiomyopathy • Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial • Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast • Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery) • Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity • Pregnancy (known to be pregnant; to be confirmed beforerandomization, if applicable) • Patient who, in the judgment of the patient's physician, is likely to have

	significant unprotected left main stenosis • Enrolled in a competing trial that involves a non-approved cardiac drug or device • Inability to comply with the protocol • Exceeds the weight or size limit for cardiac catheterization at the site • Canadian Cardiovascular Society Class III angina of recent onset, OR angina of **any class** with a rapidly progressive or accelerating pattern • Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina • High risk of bleeding which would contraindicate the use of dual antiplatelet therapy • Cardiac transplant recipient • Prior CABG, unless CABG was performed more than 12 months ago, and coronary anatomy has been demonstrated to be suitable for PCI or repeat CABG to accomplish complete revascularization of ischemic areas (CCC approval required)
Primary Endpoint	Time to first occurrence of death or nonfatal myocardial infarction.
Secondary Endpoints	• Angina control per SAQ Angina Frequency Scale • Disease-specific quality of life per SAQ Quality of Life Scale • Composite of cardiovascular death, nonfatal myocardial infarction, or stroke • Composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure • All-cause death • Cardiovascular death • Nonfatal MI • Resuscitated cardiac arrest • Hospitalization for unstable angina • Hospitalization for heart failure • Stroke • Composite of cardiovascular death, nonfatal myocardial infarction, stroke, resuscitated cardiac arrest, hospitalization for unstable angina

	or heart failure. • Health resource utilization, costs, and cost-effectiveness
Assessment Schedule	Pre-eligibility screening, randomization, 1.5 months, 3 months, 6 months, 12 months, and every 6 months thereafter.
Study Duration	Enrollment will occur over approximately 3.5 years with an expected minimum of 18-24 months follow-up and an average of approximately 4 years follow-up.
Clinical Event Adjudication Committee	The following events will be adjudicated by a blinded Clinical Event Adjudication Committee: death, myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the NHLBI and study leadership on safety aspects and overall progress of the study.
Statistical Considerations	A sample size of approximately 1,000 randomized participants is expected to provide ≥80-95% power to detect a 15%-19% reduction in the primary composite event rate in participants randomized to INV as compared with CON strategy.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS

ACC	American College of Cardiology
ACE-I	angiotensin converting enzyme inhibitor
ACS	acute coronary syndrome
AHA	American Heart Association
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes trial
CABG	coronary artery bypass graft
CAD	coronary artery disease
Cath	cardiac catheterization
CCC	Clinical Coordinating Center
CCS	Canadian Cardiovascular Society
CEC	clinical event adjudication committee
CI	confidence interval
CKD	Chronic kidney disease (defined as those with estimated glomerular filtration rate [eGFR] <30 or on dialysis)
CK-MB	creatinine kinase-MB
CL	Core laboratory
CMR	cardiac magnetic resonance
CON	Conservative management strategy (initial management with OMT alone, with cath and revascularization reserved for refractory symptoms or acute ischemic events)
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial
CV	Cardiovascular
DASI	Duke Activity Status Index

DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
Echo	echocardiography
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ERES	electronic signature
eGFR	estimated glomerular filtration rate
EQ-5D	self-reported generic preference-based measure of health, developed by the EuroQol Group
EQOL	economic and quality of life
EQOLCC	EQOL Coordinating Center
ESC	European Society of Cardiology
ETT	Exercise tolerance testing
EU Directive	European Union Directive on Data Privacy
FFR	fractional flow reserve
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICC	Ischemia Imaging Coordinating Center
ICH	International Conference on Harmonization
IEC	institutional ethics committee
INV	invasive management strategy (cath with intent to perform optimal

	revascularization plus optimal medical therapy)
IRB	Institutional Review Board
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial
IVRS	interactive voice response system
IVUS	intravascular ultrasound
IXRS	interactive web response system
LM CAD	left main coronary artery disease
LOT-R	Life Orientation Test – Revised
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MOE	margin of error
MOO	Manual of Operations
MPI	myocardial perfusion imaging
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NYHA	New York Heart Association
OMT	optimal medical therapy
ORT	optimal revascularization therapy
PACE	Patient-centered Assessment and Counseling for Exercise and nutrition
PCI	percutaneous coronary intervention
PET	positron emission tomography
PHI	protected health information
PHQ-8	Patient Health Questionnaire-8
PI	Principal Investigator

PIPEDA	Personal Information Protection and Electronic Documents Act
PSS	Perceived Stress Scale
REB	Research Ethics Board
RNA	ribonucleic acid
SAC	statistical analysis center
SAQ	Seattle Angina Questionnaire
SDCC	Statistical and Data Coordinating Center
SIHD	stable ischemic heart disease
SPECT	single photon emission computed tomography
WHF	World Heart Federation

2. BACKGROUND AND RATIONALE

Among patients with advanced CKD, cardiovascular disease is the leading cause of death,[1, 2] 15-30 times higher than the age-adjusted cardiovascular mortality rate in the general population.[3, 4] The projected 4-year mortality is >50% in patients with advanced CKD [5-9] and is worse than that for patients in the general population who have cancers, heart failure, stroke or MI.[10] Participants with advanced CKD are 5-10 times more likely to die than to reach end stage renal disease (ESRD).[11] Despite this, ~80% of contemporary coronary artery disease (CAD) trials exclude participants with advanced CKD. [12] Most of the treatments aimed at reducing cardiovascular events in advanced CKD are therefore extrapolated from cohorts without advanced CKD. Participants with advanced CKD and cardiovascular disease are undertreated with less frequent use of statins and revascularization therapies, and the optimal management approach to these patients is unknown. Participants with advanced CKD are notably underrepresented in contemporary trials comparing revascularization with medical therapy in SIHD patients, such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial[13] or the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[14] making any assessment about the efficacy of revascularization plus medical therapy vs. initial medical therapy alone in this cohort problematic.

Participants with advanced CKD are at increased risk for complications of the assigned invasive procedure, specifically contrast-induced acute kidney injury (AKI), [15, 16] dialysis, major bleeding and short-term risk of death. However, there is controversy in the medical literature regarding the incidence (<1% to >30%), effective treatment (saline hydration, N-acetyl cysteine, or sodium bicarbonate) and prognosis of contrast induced AKI (<0.5% to >5% requiring dialysis).[17-20] In addition although contrast induced AKI have been associated with increase in short-term mortality residual confounding in these studies makes interpretation difficult. Moreover it is unknown if these short-term increased risks are offset by long-term benefits. Limited observational study in the CKD cohort suggests a survival benefit of revascularization when compared with medical therapy alone long-term, [21-24] despite increase in short-term risks. However, the medical therapy in these trials was not optimized, drug eluting stents were rarely used and there is undoubtedly inherent selection and ascertainment bias with observational studies. The above has resulted in **substantial clinical equipoise in the management of these patients with the rates of revascularization of only around 10-45%.**[21, 23, 25] The results of ISCHEMIA-CKD will have profound implications for guidelines, health policy, and clinical practice.

3. STUDY OBJECTIVES

PRIMARY AIM

The primary aim of the ISCHEMIA-CKD trial is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization, if feasible, in addition to OMT, will reduce the primary composite endpoint of death or nonfatal myocardial infarction in participants with SIHD and at least moderate ischemia over an average follow-up of approximately 4 years compared with an initial conservative strategy of OMT alone with catheterization reserved for failure of OMT, in participants with advanced CKD.

SECONDARY AIMS

The secondary aims are to compare the following clinical and economic outcomes in participants randomized to INV or CON strategies:

- Angina control, as assessed by the Seattle Angina Questionnaire (SAQ) Angina Frequency scale
- Disease-specific quality of life, as assessed by the SAQ Quality of Life
- Composite of cardiovascular death, nonfatal myocardial infarction, or stroke
- Composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure
- All-cause death
- Cardiovascular death
- Nonfatal MI
- Resuscitated cardiac arrest
- Hospitalization for unstable angina
- Hospitalization for heart failure
- Stroke
- Composite of cardiovascular death, nonfatal myocardial infarction, stroke, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.
- Health resource utilization, costs, and cost-effectiveness

4. STUDY DESIGN

The ISCHEMIA-CKD trial is an international, randomized, comparative effectiveness study. Approximately 1,000 participants at approximately 500 sites worldwide with advanced CKD (defined as eGFR<30 or on dialysis) and at least moderate ischemia on ischemia testing will be randomized in a 1:1 fashion to the INV or CON strategies.

The design of the trial to randomize patients upstream of cath is advantageous as it will expose only 50% of participants (enrolled to INV) to contrast agent and will be the largest treatment strategy trial in advanced CKD patients with SIHD.

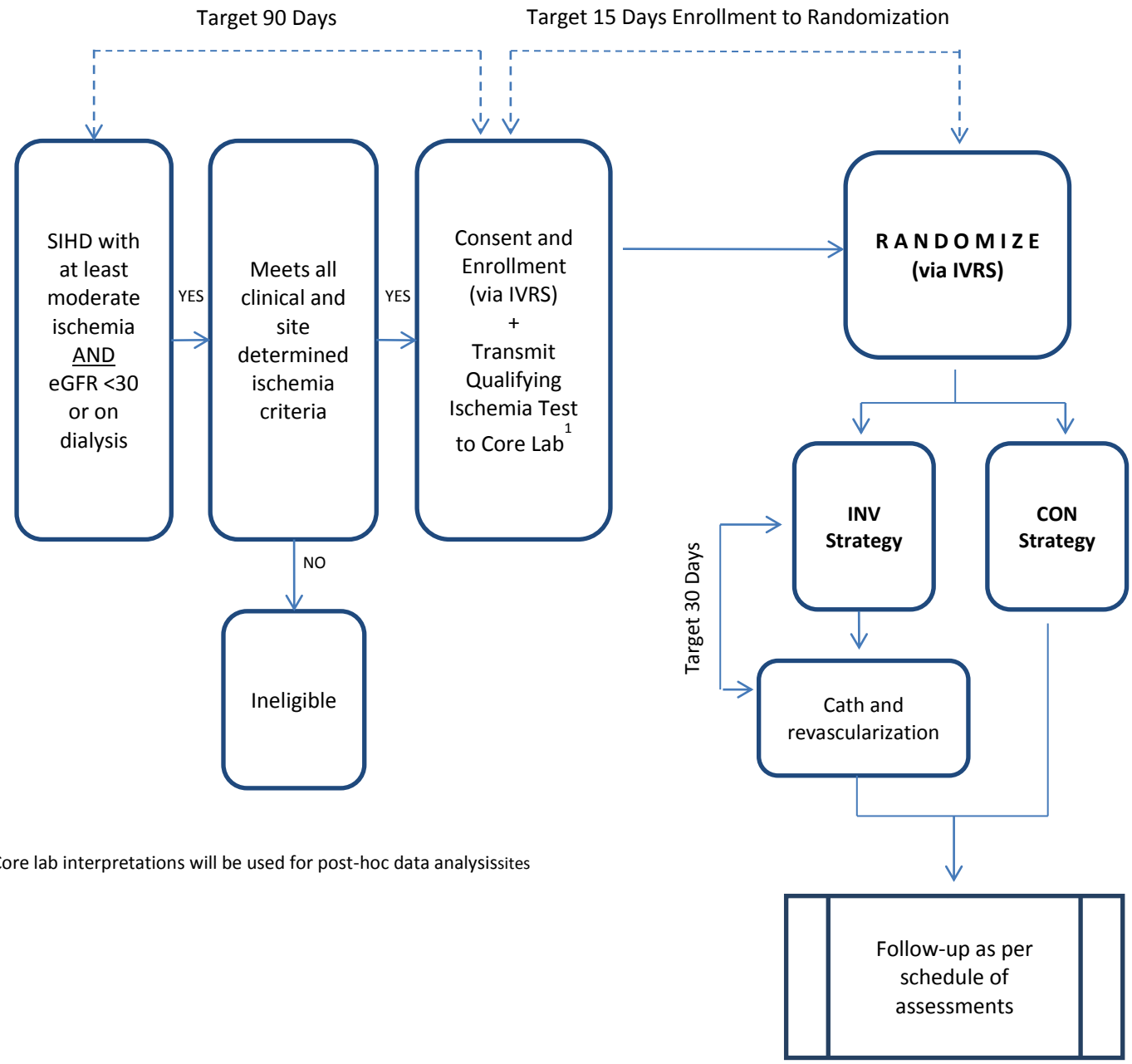
ISCHEMIA-CKD is designed to run in parallel with it's parent study, ISCHEMIA, which randomizes patients with eGFR >30, SIHD, and at least moderate ischemia in 1:1 fashion to the INV or CON strategies.

4.1 Study Flow

See figure 1 for details. Patients with advanced CKD and at least moderate ischemia (see section 5.1) will be identified and screened for clinical inclusion/exclusion criteria (see section 4.3). Patients who are suspected to be trial eligible may also be pre-screened, for example, prior to clinically indicated ischemia testing in clinical areas where SIHD patients are cared for. Patients who meet clinical and ischemia (site-interpreted) eligibility criteria and are interested in participating in the trial will be enrolled by signing an informed consent and receiving a study number via the interactive voice response system (IVRS) or interactive web response system (IXRS) (see section 5.3). Ischemia test data (e.g., images, ECG, report) will be transferred to the relevant core lab electronically for enrolled participants (see Figure 1).

Participants with known or a high likelihood of unprotected left main stenosis ≥50% will be excluded before randomization. Timing of Randomization: Participants determined to be eligible for randomization should be randomized within a target of 15 days of consent, and participants randomized to INV strategy should undergo catheterization within a target of 30 days after randomization, with optimal revascularization therapy (ORT) soon thereafter as appropriate. Participants will be enrolled over approximately 3.5 years. Randomized participants will be followed for an average of approximately 4 years. The minimum follow-up period for randomized participants will be approximately 18-24 months following randomization of the final participant. A schedule of assessments is provided in section 9.

Figure 1 Study Flow



[1] Core lab interpretations will be used for post-hoc data analysissites

4.2 Study Population

Patients with advanced CKD, SIHD and at least moderate ischemia. SIHD is synonymous with stable coronary artery disease, and refers to patients with coronary artery disease who are clinically stable (i.e., who are not in an unstable phase such as an acute coronary syndrome).

Enrollment within any subgroup, including by trial site or region, may be capped in order to ensure the trial population's representativeness.

4.3 Inclusion/Exclusion Criteria

Screening for inclusion/exclusion criteria will include assessment for clinical and ischemia criteria at the local site and ability and willingness to provide informed consent.

4.3.1 Criteria Prior to Informed Consent

Patients will be screened for the following inclusion and exclusion criteria:

Inclusion (pre informed consent)

1. At least moderate ischemia on qualifying ischemia test (See protocol appendix A)
2. End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min
3. Participant is willing to give informed consent
4. Age ≥ 21 years

Exclusion (pre informed consent)

1. LVEF <35%
2. History of unprotected left main stenosis ≥50% on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available)
3. Finding of "no obstructive CAD" (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months
4. Coronary anatomy unsuitable for either PCI or CABG
5. Unacceptable level of angina despite maximal medical therapy
6. Very dissatisfied with medical management of angina
7. History of noncompliance with medical therapy
8. Acute coronary syndrome within the previous 2 months
9. PCI within the previous 12 months
10. Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time

11. History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause
12. NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months
13. Non-ischemic dilated or hypertrophic cardiomyopathy
14. Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial
15. Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast
16. Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery)
17. Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity
18. Pregnancy (known to be pregnant; to be confirmed pre- randomization, if applicable)
19. Patient who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis
20. Enrolled in a competing trial that involves a non-approved cardiac drug or device
21. Inability to comply with the protocol
22. Exceeds the weight or size limit for cardiac catheterization at the site
23. Canadian Cardiovascular Society Class III angina of recent onset, or angina of any class with a rapidly progressive or accelerating pattern
24. Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina
25. High risk of bleeding which would contraindicate the use of dual antiplatelet therapy
26. Cardiac transplant recipient
27. Prior CABG, unless CABG was performed more than 12 months ago and coronary anatomy has been demonstrated to be suitable for PCI or CABG to accomplish complete revascularization of ischemic areas (CCC approval required)

4.3.2 Criteria After Enrollment (Informed Consent) and Prior to Randomization

Participants who provide informed consent and are clinically eligible will be registered via the IVRS/IXRS system. They are considered enrolled. Participants meeting the following exclusion criteria will not be randomized.

Exclusion (after informed consent and before randomization)

1. Pregnant (negative pregnancy test required for premenopausal females)
2. Interval development of a clinical event e.g., a primary or secondary endpoint event or interval development or discovery of an exclusion criterion

5. STUDY PROCEDURES

5.1 Qualifying Ischemia Test

The criteria for at least moderate ischemia with each test modality and the rationale for their selection are described in protocol appendix A. Ischemia tests documenting eligibility may be performed before or after medical therapy for SIHD has been initiated and adjusted. Similarly, participants already taking medical therapy for SIHD may have been on or off medications on the day of the ischemia test documenting eligibility, consistent with customary clinical practice.[26, 27] A 24-hour, 7-day helpline will be available to sites for assistance with ascertainment of eligibility, enrollment, and adherence to protocol.

5.2 Informed Consent Process

The study will be reviewed with the prospective study participant by the investigator or his/her designee. This discussion is a critical component of the consent process and the prospective study participant will be given adequate time for this discussion and to read the written consent form. Two standard clinical care strategies are being compared in this study and clinicians should enroll patients for whom there is clinical equipoise regarding their management. Prevailing practice patterns vary widely within and between regions; the discussion with prospective participants should note these local patterns. The investigator or his/her designee will be available to answer questions about the study including procedures, risks, and alternatives. The informed consent form will be signed and dated by the patient as per local regulation.

In addition, prospective study participants will be requested to consent to a biorepository sample, and to allow use of the biorepository sample for biomarkers and/or genetic analysis (DNA) in this optional study component conducted at participating sites. Prospective study participants will be informed that declining participation in the biomarker or genetic analysis portion of the study does not preclude their participation in the main study. A copy of the signed consent form will be given to the participant and the original(s) will be kept securely with each participant's research records.

Specific consent will be obtained before any protocol-mandated procedure that requires consent is performed. The consent will allow for protected health information (PHI) to be transferred to the Clinical Coordinating Center (CCC) and/or the Regional Research Organization that serves as the Coordinating Center in the country/region unless prohibited by regulations. This will make it possible for another site within that country or the CCC to follow participants if a site closes down or cannot continue follow-up for any reason, and to look up vital status. Privacy regulations in all countries will be followed, (e.g., Health Insurance Portability and Accountability Act [HIPAA] in the US; Personal Information Protection and Electronic Documents Act [PIPEDA] in Canada; European Union Directive on Data Privacy [EU Directive]). For North American participants only, PHI will also be sent to the EQOLCC.

5.3 Interactive Voice Response System (IVRS) and Interactive Web Response System (IXRS)

Enrollment and randomization will be accomplished by contact with the IVRS or IXRS. When a participant meeting site-determined clinical and ischemia test criteria has provided informed consent, the study coordinator or investigator at the site will call the IVRS or log on to the IXRS to receive a participant identification number. At this point the participant is registered as *enrolled*.

Several language options will be provided for international sites using IVRS/IXRS. To eliminate any manual transcription errors, IVRS/IXRS will be programmed to electronically transfer the participant data and study identification number to create the participant's case book within the electronic data capture (EDC) system.

In order to randomize the participant, the study coordinator or investigator will call IVRS or log in to IXRS a second time. Subjects meeting all clinical, and siteinclusion/exclusion criteria will then be randomized to either the INV or CON strategy and will be registered as *randomized*. This information will be transmitted to the participant's electronic case book within the EDC system.

Detailed information on enrollment and randomization will be provided in the MOO and in specific IVRS/IXRS materials.

5.4 Core Lab Ischemia Verification

Ischemia test data (e.g., images, ECG, reports) will be transferred electronically to the appropriate core lab for enrolled participants. The core labs will review and interpret the degree of ischemia; this data will be used for post-hoc analysis.

6. MANAGEMENT STRATEGIES

Table 1. Components of CON and INV management strategies

CON (Section 6.1)	**INV** (Section 6.2)
• Optimal medical therapy (OMT; includes angina management) (Section 6.3) • Provisional cardiac catheterization (Section 6.6)	• Optimal medical therapy (OMT; includes angina management) (Section 6.3) • Cardiac catheterization • Optimal revascularization therapy (ORT) (Section 6.4)

6.1 Conservative (CON) Strategy

In participants randomized to the CON strategy, initial management with **OMT alone will be employed** (described below). A fundamental principle of the CON strategy is to restrict cath to participants who fail OMT, i.e., those who experience an acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest or who have angina that is refractory to maximal medical therapy. In such participants who require cath during follow-up, revascularization should be performed using the principles of optimal revascularization therapy as outlined below.

6.2 Invasive (INV) Strategy

In participants randomized to INV strategy, **initial management with cath will be performed, with subsequent revascularization**, as appropriate, based upon coronary anatomy and other clinical considerations. The principles of optimal revascularization therapy will be followed (described below). In addition, **all INV participants will receive OMT as outlined below.**

6.3 Optimal Medical Therapy (OMT)

OMT will consist of intensive, comprehensive secondary prevention with lifestyle and pharmacologic intervention applied equally to both treatment groups using individualized treatment regimens based on treat-to-target algorithms under supervision by the site PI and in conjunction with the participant's primary care physician and/or cardiologist. The research team in collaboration with the participant's treating physicians will implement changes in medical therapy in keeping with guideline recommendations. The research team will obtain results of routine laboratory tests that reflect secondary prevention targets performed by the participant's physician and provide the results of any tests obtained by the study to the participant's physician. Behavioral interventions will focus on smoking cessation, nutrition, physical activity, weight control, and medication adherence. Pharmacologic interventions will include anti-atherothrombotic and anti-ischemic medications. The

minimum goals of OMT will be those recommended for SIHD patients by national/international organizations (e.g., the National Cholesterol Education Program, American College of Cardiology, American Heart Association, European Society of Cardiology, and World Health Organization). Details of this strategy are provided in the MOO and will be updated, as needed, over the course of the trial.

6.3.1 Management of Angina in CON Participants

Medical management of angina in CON participants will be intensified according to the ISCHEMIA-CKD angina treatment algorithm (see MOO). The goal for all CON participants is to control angina such that participants report a good angina-related quality of life. If the level of angina is unacceptable to the participant despite maximal medical therapy, then cath and possible revascularization is recommended, consistent with good medical care.

6.3.2 Management of Angina in INV Participants

Participants randomized to the INV strategy who experience angina following revascularization may be treated medically, as per the ISCHEMIA-CKD angina treatment algorithm (see MOO). The goal for all INV participants is to control angina such that participants report a good angina-related quality of life. Unlike the approach to CON participants with angina, repeat cath and revascularization may be performed without first maximizing medical therapy in INV participants.

6.4 Optimal Revascularization Therapy (ORT)

Optimal revascularization therapy will be performed based on findings from the diagnostic catheterization and relevant clinical information. While the selection of PCI vs. CABG (or medical therapy only in cases of normal coronary arteries, diffuse small vessel disease, etc.) will be left to the discretion of the treating team per local standards and expertise, several general principles should be followed:

- The revascularization modality selected should have the highest likelihood to safely and effectively relieve significant ischemia in all viable myocardial territories of at least moderate size.
- Decisions regarding viability testing and revascularization decisions based on such testing should be based on routine clinical practice.
- Revascularization should be performed with a goal of relieving all areas of significant ischemia, i.e., ischemia that would be detected by non-invasive imaging or FFR.
- Prior to selection of the revascularization modality, ischemic territories should be identified based on the results of noninvasive tests, angiography and, in selected cases, FFR (as outlined in the MOO).

Details of ORT are provided in the MOO and will be updated, as needed, over the course of the trial.

6.4.1 Criteria to Select PCI vs. CABG

In general, the decision between PCI and CABG will be determined according to local hospital standards and practices. Guidelines from professional societies and appropriateness criteria should be incorporated into the decision process. It is desirable for the study Heart Team (interventional cardiologist and cardiac surgeon) to discuss each case after diagnostic angiogram to reach a consensus as to the best revascularization technique.

It is recognized, however, that in some cases of non-complex coronary artery disease the performance of “ad hoc” PCI after diagnostic angiography may be preferred by participants and physicians. Whenever possible, the Heart Team should record an opinion on each participant regarding the best mode of revascularization, reaching consensus where possible and recording disagreement if not possible.

Details are provided in the MOO.

6.4.2 Guidelines for Optimal Percutaneous Coronary Intervention

PCI should be performed in a manner considered optimal by contemporary standards and guidelines. Procedural strategy, device selection, adjunctive medical therapy, pre-procedural preparation, post-procedural care and supportive services, and clinical site and operator experience are each areas where optimal performance is required. Details of this are provided in the MOO and will be updated as needed over the course of the trial.

6.4.3 Guidelines for Optimal Surgical Revascularization

The term optimal CABG is reserved for a comprehensive approach towards surgical revascularization that minimizes periprocedural risk and optimizes short- and long-term outcomes with regard to the progressive nature of atherosclerotic heart disease. This goes well beyond the intraoperative technical aspects of surgical revascularization.

The principles for optimal CABG include:

- Accurate assessment and evaluation of potential CABG participants
- Complete revascularization (anatomic and physiologic criteria)
- Optimize intraoperative management, including myocardial protection
- Minimize associated organ and system injury
- Maximize opportunity for long-term graft patency
- Optimize secondary prevention of atherosclerotic heart disease following CABG

Details of this are provided in the MOO.

6.5 Maximizing Adherence to CON Strategy

Adherence to the CON strategy means that all CON participants receive OMT and that none undergo cath or revascularization after randomization unless they 1) have an acute coronary syndrome, resuscitated cardiac arrest, or acute ischemic heart failure or 2) have unacceptable angina refractory to maximal medical therapy (see MOO for definition and recommended

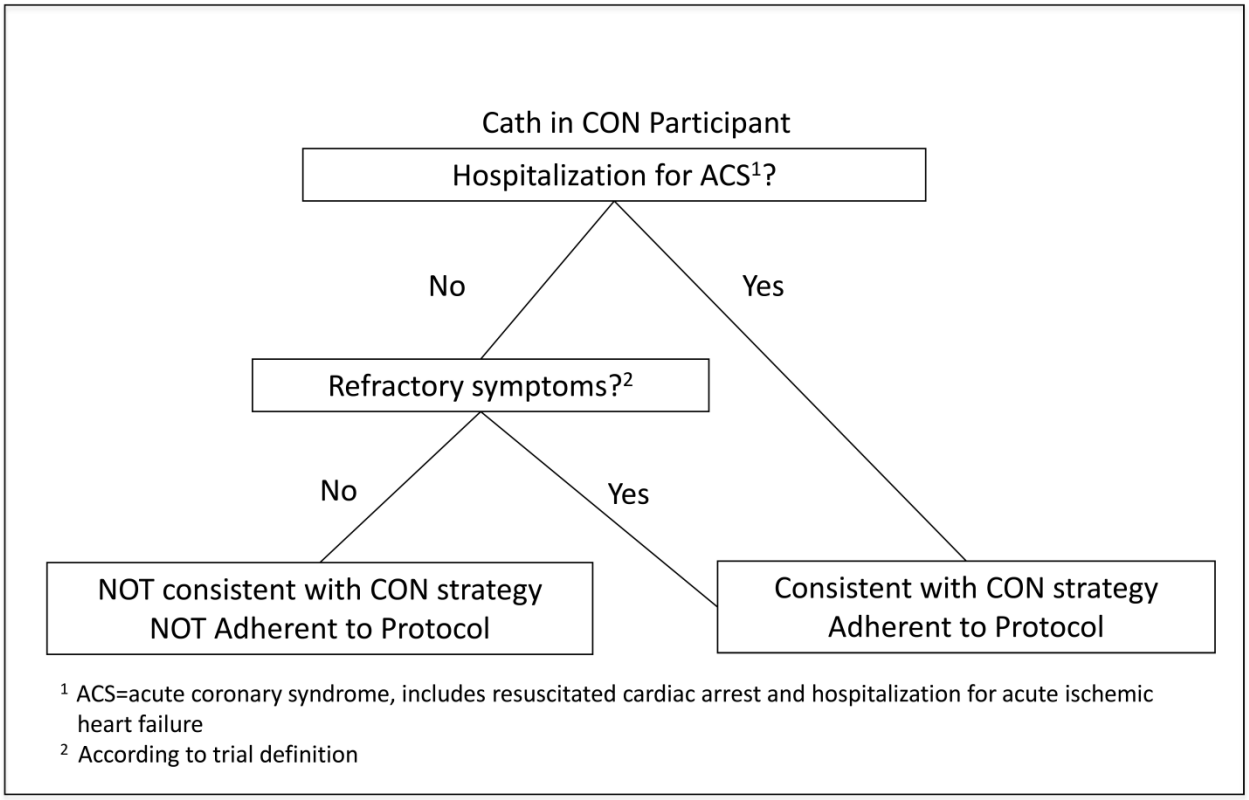
management of refractory angina). Cath performed for any other reason, including changing physician or participant preferences, is not adherent to the CON strategy and is considered a protocol violation. All protocol violations will be reported according to the guidelines provided in the MOO and may require notification of the local IRB as required by local regulations.

Investigators are discouraged from performing stress tests for the purpose of monitoring participants who are clinically stable. Guidelines for avoidance of crossover in participants with worsening symptoms in the absence of ACS may be found in the MOO. In brief, if angina worsens, medical therapy will be intensified. If symptoms are refractory to maximum medical therapy, or become unstable, participants should undergo cath. Site investigators must provide documentation, including current intensity of medical therapy, heart rate, blood pressure, and a repeat SAQ to document the appropriateness of cath. Sites are instructed to call the 24-hour helpline when elective cath is being considered, and they must complete a checklist.

6.6 Cath in Participants Randomized to CON Strategy

Cath and/or revascularization for an acute coronary syndrome, resuscitated cardiac arrest, or acute ischemic heart failure is consistent with the CON strategy. Similarly, cath for refractory symptoms (according to the trial definition) is also consistent with CON strategy. Figure 2 describes cath in participants randomized to CON and the definitions of protocol adherence and non-adherence as it relates to this. Once the decision has been made that the performance of cath in a CON participant is consistent with the CON strategy, the same principles described for optimal revascularization (6.4) apply.

Figure 2 Cath in Participants Randomized to CON Strategy



[1] ACS=acute coronary syndrome, includes resuscitated cardiac arrest and hospitalization for acute ischemic heart failure

[2] According to trial definition

7. AUXILLIARY SCREENING LOG

7.1 Screening Log

During the study enrollment period, sites will maintain a de-identified, written screening log of patients with site-determined moderate or severe ischemia who have undergone testing at the site's designated primary laboratory. Patient characteristics (age [recorded for patients <90 years of age, recorded as 90 if ≥90 years of age], sex, and, if excluded, reason(s) for exclusion will be recorded) and intended management strategy for patients who are eligible but not enrolled, if known.

The screening log will be sent to the CCC on a regular basis, where it will help identify the major reasons why patients are not enrolled, thus allowing CCC staff to develop corrective action plans for sites that are not meeting target enrollment. Depending on the site's enrollment rate over time, the CCC may decide that a given site no longer needs to submit its screening log, although the site should continue to maintain the log through the end of enrollment. In the event of poor enrollment, sites may be asked to provide comparable information about patients referred to cath without prior ischemia testing.

8. Study Assessments

8.1 Creatinine and Pregnancy Test

At the screening visit a serum creatinine test must be drawn if one is not available within the previous 90 days. In addition, a pregnancy test is required if the participant is pre-menopausal.

8.2 Standard Blood Tests

In this population with established coronary disease, as part of standard practice the following tests will typically be obtained by the participant's treating physician: complete blood count, electrolytes, creatinine, glucose, liver transaminases, lipid profile, and HbA1c. If HbA1c results are available for nondiabetics they will be recorded. If these test results are not available within specified time windows around the randomization visit (see MOO), then the following should be obtained: complete blood count, lipid profile, and HbA1c (for diabetics only). Liver transaminases should only be obtained if not available before starting statin therapy. An attempt will be made to coordinate participant follow-up visits so that they occur close in time to routine follow-up visits with their physicians when routine blood tests are performed. At 6 month follow-up visits, if lipid tests (and HbA1c at annual visits for diabetics) are not available within specified time windows they will be obtained by the study coordinator or participants will be referred to their treating physicians for the tests. Creatinine values obtained clinically for participants at the three month follow-up visit and annually will also be recorded.

8.3 Endpoint Assessments

At every visit after randomization, the study coordinator will ask participants if they have had any symptoms or a report from a healthcare provider consistent with an endpoint event since the last study visit. See MOO for detailed instructions on collection of source documents.

8.4 Blood Biomarkers and Genomics Biorepository

Randomized participants will be invited to participate in the biorepository protocol, unless precluded by local regulations. Participants who give informed consent will be asked to allow storage of samples of their blood in two biorepository protocols, one for biomarkers and one for genetic analysis. Participants who decline participation in one or both of the biorepository protocols are still eligible to participate in the main trial. The biorepositories will serve as resources for future analyses. Although no specific scientific proposals are put forth in the present protocol, we anticipate a wealth of opportunities for ancillary studies and sharing of resources with other investigators. Participants will be asked to separately consent for use of their blood samples for the biomarker biorepository and the genetic (DNA) biorepository. If a site is unable to process blood samples they may still participate in the genetic biorepository; in this case saliva samples may be collected from participants.

Blood will be drawn for the biorepository at the time of randomization, and may be drawn after 3 months of follow-up. At the time of randomization, up to a maximum of 49 mL of whole blood will be collected, which will be processed and stored as serum, plasma, RNA and, where allowable,

DNA. At the 3 month follow-up visit, up to 49 mL of blood may be drawn. (If needed, specimen collection for genetic analysis may be collected at any point during the trial.)

Measures will be taken to protect the identity of the blood sample donor by de-identifying the biospecimen samples at the enrollment site. The link between the participant's name and the numeric code will not be available to staff managing samples at the biorepository, or any investigative personnel requesting samples. Strict confidentiality and maintenance of the chain of custody will be observed in the collection and storage of biospecimens. Complete details of the biorepository protocol are provided in the MOO.

8.5 Medication Adherence

To assess medication adherence, a 4-item modified Morisky adherence survey (Likert scale responses to 4 questions)[28-31] will be completed at the randomization visit, 6 month visit, and all subsequent visits.

8.6 Lifestyle Assessment

To assess each participant's readiness to change health-related behaviors, study coordinators will use questionnaires developed by the Patient-centered Assessment and Counseling for Exercise and nutrition (PACE) program. Responses to these brief surveys will be used to tailor counseling for lifestyle change. These assessments will occur at randomization, 3 months, 12 months, annually, and at the closeout visit.

8.7 Quality of Life Assessment

To quantify patient-reported quality of life outcomes in ISCHEMIA-CKD, a battery of validated instruments will be used. Angina-related quality of life will be measured by the Seattle Angina Questionnaire (SAQ); dyspnea symptoms from the Rose Dyspnea scale; the EQ-5D as a measure of overall, generic health status; and demographic items (e.g., marital status, education, perceived income). We will use these data to analyze the health status of participants in both groups over time to quantify both the magnitude and trajectory of health status recovery as a function of randomized management strategy.

8.8 Economics Assessment

As a measure of medical utilization, resource utilization data, including hospitalizations, emergency department visits, and selected cardiac procedures and tests will be collected by the Site Coordinators at each ISCHEMIA-CKD study visit or contact and entered into the main study EDC database. These data will be used to estimate and compare medical care costs from the perspective of the US healthcare system for both management strategy groups. They will also be used, along with the clinical endpoints and quality of life data, to calculate the net incremental cost and quality-adjusted life expectancy associated with the invasive strategy and the resulting within-trial incremental cost-effectiveness ratio. Details are provided in the MOO.

9. SCHEDULE OF ASSESSMENTS

Overview of Visits

All participants will undergo eligibility screening, informed consent and randomization procedures.

Follow-up in randomized participants will occur at 1.5, 3, 6, and 12 months following randomization during the first year and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below (See Table 2 for complete assessment schedule). The schedule of assessments (Table 2) specifies the preferred method of contact for each visit. Six-month visits may be via telephone or email, depending on participant stability, risk factor control, and the participant's distance from the clinic ("geography") (see Table 2). In the event that a scheduled clinic visit is not possible, to ensure participant follow-up other forms of contact should be used, such as telephone, email, communication from a personal physician, other allied health professional, or family member, or review of electronic health record or public records. After the first year, participants will be followed every 6 months until the end of the trial, at which time sites will be notified to perform a closeout visit.

Dependent on additional funding, telephone or email follow-up every 6 months or ascertainment of database information on vital status may continue after all clinic visits have been completed, unless prohibited by local regulations. At these long-term follow-up contacts, information on current health and medications, and interval hospitalizations will be collected.

Withdrawal from the Study: Complete and accurate follow-up is extremely important for the duration of the study**.** The participant, however, may decline to continue with their assigned management strategy at any time. This does not constitute withdrawal from the study. Participants will continue to be followed per the assessment schedule. If at any time the subject refuses to continue with study visits, every attempt will be made to continue contact by telephone, written communication, email, by proxy contact with family, friends, or allied health care providers, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. National databases that record deaths will be used to ascertain vital status, unless prohibited by local regulations. The reason for (and the level of) withdrawal will be documented for all subjects withdrawn from the study or for those having limited follow-up. The subject must specify in writing what follow-up (s)he will allow, if any, at the time of withdrawal discussion.

Quality of Life (QOL) and Economics Overview

A brief set of items capturing selected interval angina and dyspnea symptoms QOL (Brief/Symptom/QOL) will be collected by the site coordinator and entered into the EDC study database at every study visit through 36 months and then each 6 months until the final closeout ISCHEMIA-CKD visit. A Hospitalization assessment as part of the main study EDC database will be collected on all randomized ISCHEMIA-CKD participants at each follow-up study interval throughout the trial to provide a measure of resource utilization.

Table 2 Schedule of Study Assessments and Procedures (see Manual of Operations for visit windows)

	Screening visit	CCTA visit	Randomization visit (Baseline Visit)	Catheterization & PCI or CABG	Follow up								
					1.5m[A] Visit 1	3m[A] Visit 2	6m[B] Visit 3	12m[A] Visit 4	18m[B] Visit 5	24m Visit 6	30m[B] Visit 7	36m[C] Visit 8	Frequency beyond 36 months
Eligibility screen	X												
Informed consent (including biorepository consent if applicable)	X												
Creatinine and pregnancy test[D]	X												
Medical History/Medical Status	X		X		X	X	X	X	X	X	X	X	Q6m
Cardiovascular medications	X		X		X	X	X	X	X	X	X	X	Q6m
Transmit Stress Test to Core Lab[E]	X												
NYHA* and CCS class**	X		X		X	X	X	X	X	X	X	X	Q6m
Release for medical records signed			X					X		X		X	Q12m
Safety assessment [F]		X		X									
Vital signs, weight, height[G]			X		X	X	X	X	X	X	X	X	Q12m
Standard lab results[H]			X[I]			X	X	X	X	X	X	X	Q12m
Biorepository blood draw			X			X[J]							
Cardiac biomarkers[K]				X									
Electrocardiogram (ECG) [L]			X	X[M]				X		X			@ closeout
Lifestyle Assessment (PACE)***			X			X		X		X		X	Q12m
Lifestyle Counseling (PACE)***			X		X	X	X	X	X	X	X	X	Q6m
Modified Morisky Medication Adherence Survey			X				X	X	X	X	X	X	Q6m

Brief symptoms/QOL assessment[N]			X		X	X	X	X	X	X	X	X	Q6m
Initiate Optimal Medical Therapy (OMT)			X										
Medical Therapy Evaluation and Optimization[O]					X	X	X	X	X	X	X	X	Q6m
Schedule catheterization for INV participants[P]			X										
Hospitalization assessment					X	X	X	X	X	X	X	X	Q6m
Endpoint assessment				X	X	X	X	X	X	X	X	X	Q6m

Follow-up visits will be scheduled based on time since the date of randomization (baseline).

*****NYHA- New York Heart Association **CCS- Canadian Cardiovascular Society ***PACE- Patient-centered Assessment and Counseling for Exercise and nutrition (PACE) assessment and counseling

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[A] 1.5, 3, and 12 month visits should be in clinic visits, depending on participant stability, risk factor control, and geography.

[B] 6, 18, and 30 month visits may be via telephone, email, or in clinic depending on participant stability, risk factor control, and geography.

[C] Following the 36 month visit, follow-up visits should be in clinic visits at least every 12 months. Clinic visits can be replaced by email or phone depending on participant stability, risk factor control, and geography.

[D] Creatinine if not done within 90 days and pregnancy test if premenopausal.

[E] Send ischemia test images (immediately following enrollment and before randomization), technical worksheets, and site interpretations/local reports from qualifying ischemia tests to core labs.

[F] Safety Assessment (refer to section 13.4).

[G] Height is only needed at randomization, assessments only required if visit is completed in clinic.

[H] Required labs include: lipids (preferably fasting) at 3 month visit then semiannually only, and HbA1c (at visit 4, 6, 8 and annually thereafter for diabetic participants. These lab results will be requested from the participant's physician. If these results are not available they should be obtained by either the participant's treating physician or study staff. Creatinine values obtained clinically for participants with eGFR <60 at the three month follow-up visit and annually will also be recorded.

[I] Additional lab required at randomization includes complete blood count Request from participant's physician, since it is expected that routine blood work will have been done within the last 6 months

[J] May be requested.

[K] For participants undergoing PCI: troponin and CK-MB pre-procedure and at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier. For participants undergoing CABG: troponin and CK-MB pre-procedure and at 18 ± 6 hours post-CABG. All biomarker measurements should be recorded on eCRF. A biomarker measurement should be obtained before and after all PCI and CABG procedures, whenever possible.

[L] Send to ECG core lab; ECG required for all cardiac admissions and revascularizations; year 1 ECG optional (filed on site) and closeout.

[M] ECG done following procedure (60±30 mins post-PCI, 3 days post-CABG).

[N] Selected Seattle Angina Questionnaire/Rose dyspnea scale/EQ-5D.

[O] At every follow-up visit the research team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optim
guideline recommendations and study algorithms.

[P] Planned cath and revascularization only in the INV group. See MOO for time windows for performing cath and revascularization after randomizati
optimal revascularization treatment should be targeted within 30 days after randomization in the Invasive strategy group. In the Conservative group
revascularization is reserved for participants with refractory angina symptoms or acute ischemic events.

Screening visit

- Patients with advanced CKD and at least moderate ischemia (see protocol appendix A) will be assessed as potential study candidates
- General medical and cardiac history will be reviewed for eligibility according to the inclusion/exclusion criteria in section 4.3
- Willingness of both the prospective participant and their physician for participation throughout the study will be confirmed
- All screened prospective participants will be recorded in the paper screening log
- Prospective participants meeting clinical and site-based ischemia inclusion and exclusion criteria and interested in participating in the study will be consented for the study
- Consented participants will receive a study ID number via IVRS/IXRS. These participants are considered “enrolled” (not randomized).
- Creatinine testing if it has not been done within the last 90 days
- Pregnancy test if premenopausal
- For enrolled participants ischemia tests will be transferred electronically to the appropriate core laboratory. (see section 5.4)

Randomization visit (Baseline Visit) (targeted within 15 days of participant’s consent)

- Medical history including CV medications will be documented
- NYHA and CCS class (see MOO)
- Brief symptoms/QOL assessment will be collected (prior to actual randomization)
- Modified Morisky medication adherence survey (see MOO)
- Vital signs, height and weight will be measured
- 12 lead ECG will be performed and sent to ECG core lab; stress ECG, and symptom, and hemodynamic results will be sent to ECG core lab
- Results of routine laboratory tests performed within 6 months of visit will be recorded, including HbA1c for diabetic participants. If these test results are not available a blood draw for routine laboratory tests will be done at this visit (see MOO)
- Baseline blood draw for biomarker/genetics biorepositories

- Eligible participants will be randomized to INV or CON strategies via the IVRS/IXRS system. (These participants are considered randomized)
- Participants randomized to INV strategy should target to undergo catheterization, with optimal revascularization to be completed within a target of 30 days from randomization
- PACE will be implemented for all participants
- Initiate OMT in all randomized participants according to guideline recommendations and study algorithms

Cath and Revascularization for participants randomized to INV strategy (protocol assigned); also applies to all revascularization procedures for participants in both management strategies

- For protocol assigned cardiac cath and revascularization (INV strategy participants), target completion within 30 days of randomization
- Revascularization to be performed as per Optimal Revascularization Therapy (ORT) (refer to MOO)
- For participants undergoing PCI
  - 12 lead ECG to be performed post-PCI at 60 ± 30 minutes, and as needed for chest pain
  - Blood draw for both CK-MB and troponin before PCI, and at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier, whenever possible
  - All pre- and post-procedure biomarker measurements that are obtained should be recorded on eCRF
- For participants undergoing CABG
  - 12 lead ECG to be performed on day 3 post-CABG or at hospital discharge whichever comes earlier, and as needed for chest pain
  - All pre- and post-procedure operative biomarker measurements that are obtained should be recorded on eCRF

1.5 month (6 week) visit (Visit 1)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- Lifestyle counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected

- Hospitalization assessment will be collected
- Endpoints will be assessed
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

3 month visit (Visit 2)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- Lifestyle assessment and counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Biorepository blood draw may be performed if additional funding is obtained
- Endpoints will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available these tests should be obtained by the participant's treating physician or the study staff. Creatinine values obtained clinically will be recorded.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

6/18/30 month visits (Visits 3, 5, 7 respectively)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured (only if clinic visit)
- Modified Morisky medication adherence survey (see MOO)
- Lifestyle counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected

- Hospitalization assessment will be collected
- Endpoints will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available lipid tests should be obtained by the participant's treating physician or the study staff.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

12/24/36 month visits (Visits 4, 6, 8 respectively)

- Medical status assessment
- NYHA and CCS class (see MOO)
- Vital signs and weight will be measured
- 12 lead ECG will be performed and submitted to core lab only at 24 month visit. Optional ECG to be retained at site at 12 months
- Modified Morisky medication adherence survey (see MOO)
- Lifestyle assessment and counseling as per PACE will be performed
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Endpoints will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting) and HbA1c for diabetic participants. If not available lipid tests should be obtained by the participant's treating physician or the study staff. Creatinine values obtained clinically for will also be recorded.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

Continuing Follow-Up Visits (every 6 months following the 36 month visit until close out)

- Medical status assessment
- NYHA and CCS class (see MOO)

- Vital signs, and weight (only at every 12 month clinic visit)
- Modified Morisky medication adherence survey
- Lifestyle assessment as per PACE (only at every 12 month visit)
- Lifestyle counseling as per PACE
- Brief symptoms/QOL assessment will be collected
- Hospitalization assessment will be collected
- Endpoint will be assessed
- Obtain lab results from participant's treating physician for lipids (preferably fasting). If not available lipid tests should be obtained by the participant's treating physician or the study staff.
- The study team, in collaboration with the treating physician(s), will evaluate effectiveness of medical therapy and optimize as needed according to guideline recommendations and study algorithms

Close out visit (in addition to all assessments for the regularly scheduled visit)

- 12 lead ECG will be performed and submitted to core lab
- Obtain lab results from participant's treating physician for lipids (preferably fasting) and HbA1c for diabetic participants. If not available from the participant's treating physician these tests should be obtained by the participant's treating physician or the study staff.

10. ADJUDICATION OF CLINICAL EVENTS

An independent clinical event adjudication committee (CEC) will review and adjudicate all primary endpoint events and selected secondary endpoints in a blinded fashion based on study definitions. Endpoints to be adjudicated include death (including cause), myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke. Because the trial is not blinded, to mitigate bias in the ascertainment of events, several strategies will be used to identify ("trigger") all suspected endpoints in all participants including carefully constructed data collection tools that focus sites on key endpoint events, screening of ECG core lab data, site investigator and coordinator education about CEC procedures, and processing of events found by physicians during review of source documents pertaining to already identified endpoints. Care will be taken to blind reviewers to any information that could identify the participant or could reveal the randomized management strategy assignment. CEC members do not have access to management strategy assignment in order to avoid bias, which is an important process issue in this unblinded trial.

11. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

11.1 Sample Size Determination and Statistical Power

11.1.1 Summary of Power and Precision

As shown in Tables 3 and 4 below, the planned sample size of approximately 1,000 randomized participants will result in an estimate of the hazard ratio that differs from the true hazard ratio by no more than a factor of 1.19 with 95% probability and will yield power ≥80-95% for comparing the primary composite endpoint across the two randomized groups assuming the 4-year cumulative rate of the primary composite endpoint is 60% in participants randomized to CON strategy and is less by a factor of 15% to 19% (relative reduction) in participants randomized to INV strategy. Power and precision under other assumptions are summarized in Table 5 and Table 6 below.

Table 3. Estimated Power as a Function of the Anticipated Cumulative Event Rate in CON and the Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Power		
Event %	Δ = 0.15	Δ = 0.17	Δ = 0.19
45%	56	67	76
50%	64	75	84
55%	73	83	90
60%	81	90	95
65%	88	95	98
70%	94	98	99

NOTE: Δ denotes relative reduction in 4-year event rate in INV vs. CON groups. **Assumptions:** Two-sided log-rank test with alpha = 0.05; 500 participants per group; average follow-up 3.7 years; loss-to-follow-up 1% per year; survival times follow exponential distribution.

Table 4. Range of Estimated Precision (Margin of Error) as a Function of the Anticipated Cumulative Event Rate in CON and the Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Margin of Error (MOE)		
Event %	Δ = 0.15	Δ = 0.17	Δ = 0.19
45%	1.22	1.22	1.23
50%	1.21	1.21	1.21
55%	1.20	1.20	1.20
60%	1.19	1.19	1.19
65%	1.18	1.18	1.18
70%	1.17	1.18	1.18

NOTE: Margin of Error is the anti-log of the expected half-width of the 95% confidence interval for the log-hazard ratio. Assumptions: Based on a univariable Cox model with a binary treatment indicator and Wald-type 95% confidence intervals.

11.2 Statistical Analysis Plan

All major treatment comparisons between the randomized groups will be performed according to the principle of "intent-to-treat;" that is, participants will be analyzed (and endpoints attributed) according to the randomized strategy, regardless of subsequent invasive testing or treatment. Statistical comparisons will be performed using two-sided significance tests. A statistical analysis plan will be finalized before trial completion and data analysis.

11.2.1 Analysis of the Primary Endpoint

The statistical comparison of the two randomized groups with respect to the primary composite endpoint will be a “time-to-event” analysis, and will therefore be based on the time from randomization to the first occurrence of any of the components of the primary composite endpoint (death or nonfatal MI). The Cox proportional hazards will be the primary analytic tool for assessing outcome differences between the two randomized groups. To preserve power in the face of participant heterogeneity, the overall comparison may be adjusted for a selected set of prognostically important baseline covariates that will be carefully defined and pre-specified in the statistical analysis plan. The level of significance for the assessment of the primary endpoint will be α=0.05. In addition to Cox regression, event-free survival probabilities will be estimated as a function of follow-up time in each treatment group using the Kaplan-Meier method and presented with point wise 95% confidence intervals. If the data provide evidence of an overall difference in outcome between management strategy groups, we will further examine whether the therapeutic effect is similar for all participants, or whether it varies according to specific participant characteristics, which will be pre-specified in the statistical analysis plan.

11.2.2 Analysis of the Secondary Endpoints

Secondary endpoints that will be evaluated include: (1) quality of life as measured by the SAQ Angina Frequency Scale and SAQ Quality of Life Scale; (2) composite of cardiovascular death, nonfatal myocardial infarction, or stroke; (3) composite of cardiovascular death, nonfatal MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; (4) all-cause death; (5) CV death (6) MI; (7) resuscitated cardiac arrest; (8) hospitalization for unstable angina; (9) hospitalization for heart failure; (10) stroke; (11) composite of cardiovascular death, nonfatal MI, stroke, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure; and (12) health resource utilization, cost, and cost effectiveness. Plans for the analysis of the quality of life and economic endpoints are addressed below in Sections 11.2.4 and 11.2.5. For other secondary endpoints, analysis will be similar to the primary endpoint, using time from randomization until the first occurrence of the specific secondary endpoint as the response variable.

Unambiguous operational definitions of each study endpoint will be documented in the Clinical Event Committee Charter and statistical analysis plan before performing unblinded analysis. For MI we will specify a primary definition (adapted from the universal definition of MI[32]; to be used in the primary analysis of the primary and secondary endpoints). Other definitions (to be used in secondary analyses) will include the universal definition of MI and criteria to categorize large infarctions. Data collection instruments and the adjudication process will allow construction of alternative endpoint MI definitions.

11.2.3 Contingency Plan For Insufficient Primary Endpoint Events

The projected event rate of 60% at 4 years for the primary composite endpoint in CON participants was based on multiple data sources. Although we believe the projected rate is reasonably conservative, an acceptably precise estimate of the true event rate of the primary endpoint will not be known until substantial participant recruitment and follow-up have been accrued. To ensure that the primary analysis is well-powered and useful, a prospective plan to allow extending follow-up and/or changing the primary endpoint based on aggregate event rate data will be established prior to the first review of unblinded trial data. At a designated time during the trial, an analysis will be conducted to estimate the overall aggregate primary endpoint event rate and project the final number of observed events. If the estimated unconditional power (i.e. based on aggregate event rate data; not by treatment group) is less than the originally targeted 90%, then one or more of the following options will be considered:

1. Extend follow-up to allow more events to accrue.
2. Change the primary endpoint to one that occurs more frequently.
    - The current primary endpoint would become a secondary endpoint
    - The proposed new primary endpoint would be the composite of death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.
3. Follow the recommendation of an independent advisory panel.

An independent advisory panel, separate from the DSMB, will be convened for the purpose of reviewing unconditional power estimates and making a recommendation to the NHLBI Director. Members of this panel will not have access to unblinded data by treatment group or other data that may bias their recommendation.[33, 34] Additional details will be finalized in cooperation with the DSMB and recorded in the statistical analysis plan before the first unblinded interim analysis.

11.2.4 Quality of Life (QOL) Analysis

All QOL comparisons will adhere to the intention-to-treat principle. For each QOL measure examined in this study, data analysis will proceed in several stages. First, we will provide simple descriptive and comparative analyses by intention-to-treat. Statistical power estimates for this part of our analysis, based on data collected in the COURAGE trial, show that we should have in excess of 99% power to detect ¼ SD differences in our 3 principal QOL measures. Second, we will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. Since there is currently no consensus in the statistical literature about the best way to deal with the multiple comparisons problem arising from testing each individual scale separately, we propose two complementary approaches. First, we will pre-specify the angina frequency and QOL scales from the SAQ as the CAD-specific measures of primary interest and assign all other comparisons to a secondary (descriptive) status. Second, we will employ a mixed model methodology that makes use of all available QOL data at each study assessment point to model the time profile (fixed effect). Using the fitted model, we can

estimate the overall difference in the QOL measures as well as test the global hypothesis of no difference over time. We can also estimate the difference in the areas under the two QOL treatment curves (and test the hypothesis of no difference, on average). In addition, we can estimate differences in QOL at the end of the study or at intermediate points. Lastly, to address the possibility that international differences in QOL exist despite our use of extensively culturally validated instruments, we will examine interactions between key QOL outcomes, treatment, and geographic region.

11.2.5 Health Economics Analysis

The health economic analyses for ISCHEMIA-CKD will consist of a cost-effectiveness analysis.

The cost-effectiveness analyses will estimate the incremental cost required to add an extra life year with the INV strategy group relative to CON strategy group. In secondary analyses, we will incorporate utility weights to estimate the incremental cost per quality adjusted life year gained with the INV strategy relative to CON strategy. These analyses will be conducted from a societal perspective and will use a lifetime horizon so that the estimated incremental cost-effectiveness and cost-utility ratios can be compared with societal benchmarks. We will also calculate within-trial cost-effectiveness/cost-utility ratios, although these ratios are limited in their value due to their failure to account for long-term benefits and costs and the absence of comparative benchmarks. Cost will be adjusted for inflation, and both costs and life expectancy will be discounted to present value at a 3% annual discount rate. Plots of cost-effectiveness acceptability curves indicating the probability that the intervention is cost-effective for a range of willingness-to-pay thresholds will be done. Extensive sensitivity analyses will be performed.

11.2.6 Interim Analysis

For ethical reasons, interim examination of clinical endpoints and key safety events will be performed at regular intervals during the course of the trial. An independent Data and Safety Monitoring Board (DSMB) appointed by the NHLBI will monitor participant safety and to review performance of the trial (see 13.1). The primary objective of these interim analyses is to ensure the safety of the participants enrolled in the trial and evaluate the accumulating endpoint data by treatment group to test for possible differences favoring either of the two randomized management strategies. In addition, interim monitoring will involve a review of participant recruitment, compliance with the study protocol, status of data collection, an assessment of whether control group event rates are consistent with the rates hypothesized in the sample size calculations, and other factors which reflect the overall progress and integrity of the study. Because interim analyses may occur when adjudication of an event is in progress, the interim analyses will be based primarily on adjudicated events and secondarily on all best available events, i.e., as adjudicated by CEC if present or as eCRF/Investigator defined if the event has not yet been adjudicated by CEC. The results of the interim analyses and status reports will be carefully and confidentially reviewed by the DSMB. Detailed plans for interim monitoring will be documented in a separate DSMB analysis plan.

Interim comparisons by management strategy will focus on all-cause mortality and the primary composite endpoint (death and MI). Cox-proportional hazard models with treatment as the

covariate will be used for the analysis. Estimates of hazard ratios and 95% confidence intervals comparing the INV and CON strategies will be reported. To account for repeated significance testing of the accumulating data, the group sequential method of Lan and DeMets[35] will be used as a guide for interpreting these interim analyses. Monitoring boundaries for each endpoint will be based on a two-sided symmetric O'Brien-Fleming type spending function with an overall two-sided significance level of $\alpha = 0.05$. The O'Brien-Fleming approach requires large critical values early in the study but relaxes (i.e., decreases) the critical value as the trial progresses.[36] These proposed monitoring boundaries are intended as a guide for interpreting the interim analyses and not as a rule for early termination.

An additional key parameter for interim monitoring will be the frequency of early catheterization among participants randomized to the CON strategy. Such catheterizations will be classified according to (1) whether the catheterization was allowed by the protocol (e.g. for documented refractory symptoms) and (2) whether the catheterization was preceded by a nonfatal primary endpoint event (i.e., MI). A pattern of frequent early catheterization in CON participants without prior endpoint events would suggest that the study may have difficulty achieving high statistical power. Moreover, if this was due to frequent protocol violations, then a finding of no treatment effect may be challenging to interpret. To address these concerns, rates of early catheterization in the CON group will be analyzed and reported, with a focus on estimating the probability that a CON participant will undergo catheterization within a specified time interval and before an endpoint event. To obtain this probability, the distribution of "time from randomization to catheterization" for CON participants will be estimated using the cumulative incidence function method for competing risks.[37] For this latter analysis participant follow-up will be censored at the last contact date or terminated after the participant's first primary endpoint event, whichever occurs first.

Judgment concerning the continuation of the study will involve not only the magnitude of observed differences between randomized strategies and degree of statistical significance, but also careful consideration of many other important factors including the need for precise parameter estimation, the overall progress and integrity of the trial (including the frequency of catheterization in the CON group, as discussed above), and information available from other studies at the time of DSMB deliberations. If a stopping boundary is crossed early in the trial, this result should be tempered by the knowledge that revascularization may result in early hazard, but long-term benefit. Although we hypothesize that outcomes will be improved by the INV strategy, it should be emphasized that a small treatment effect for the primary endpoint is not necessarily a negative result for the study. Indeed, evidence suggesting absence of a large benefit from the invasive strategy would be highly important to future guidelines and clinical practice. However, a large sample size is required in order to derive such evidence. If the study were to be stopped early with less than the full sample size, the lack of statistically significant difference may be accompanied by wide confidence intervals and no clear conclusion might be possible. The DSMB will incorporate this perspective along with other considerations when making recommendations about continuation.

12. DATA HANDLING AND RECORD KEEPING

12.1 Electronic Data Capture (EDC) System

The full study dataset will be collected for participants who enter the randomized phase of the study. The primary data collection system for ISCHEMIA-CKD will use a web-based electronic data capture (EDC) system, a validated Electronic Record, Electronic Signatures (ERES) compliant platform (21 CFR Part 11). All these data collected at any point in the trial except the economic and quality of life information, are entered into this EDC system.

12.2 Data Management and Quality

Any out-of-range values and missing or inconsistent key variables will be flagged and addressed at the site in real time during the data entry process. When a query is generated on a particular variable, a flag will be set in a field in the database enabling the system to track the queries and produce reports of outstanding queries. Queries can also be generated from manual review of the data forms. These queries will be entered into the database and tracked in the same manner as the computer-generated queries. At regular intervals, all data will be transferred from the EDC database to SAS for statistical summarization, data description, and data analysis. Further cross-checking of the data will be performed in SAS, and discrepant observations flagged and appropriately resolved through a data query system. The Statistical and Data Coordinating Center (SDCC) will perform internal database quality-control checks, and data audits throughout the course of the trial.

12.3 Data Confidentiality and Security

Computerized data will be accessible only by password, and a centralized monitoring system will record and report all access to data. The DCRI computer network is protected by a firewall. Electronic CRFs (eCRFs) will be identified by study number only, to ensure participant anonymity. No participant identifiers will be used in the presentation of data. Study records that might identify participants will be kept confidential as required by law. Except when required by law, participants will not be identified by name, personal identification number (e.g. social security number, social insurance number), address, telephone number, or any other direct personal identifier in study records. This information will be retained by each individual center and will not be disclosed to the Coordinating Center except as needed for centralized clinical, quality of life and economic follow-up of the participants. Participants will be informed that the study physician and his/her study team will report the results of study-related tests to the Coordinating Center and to the NIH. Participants will be informed that their records may be reviewed in order to meet federal, state or regional/local regulations. Reviewers may include the CCC/SDCC monitors, IRBs/ECs, the NIH, other government regulators as dictated by local law, or their delegates.

Ischemia tests will be stripped of identifiers during the upload process, with the exception of date of study in DICOM headers, by a vendor which will be responsible for ischemia test transfer and storage for this trial.

12.4 Training

All investigational site and core lab staff authorized to enter ISCHEMIA-CKD study data will receive training on the EDC system. Training records will be retained by the EDC Helpdesk at the SDCC.

12.5 Records Retention

Study records will be maintained by the site investigators for a period of three (3) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

13. SAFETY MONITORING PLAN

13.1 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed by the NHLBI to monitor participant safety and to review performance of the trial. The DSMB will include on its roster a nephrologist. A DSMB charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the NHLBI and agreed upon by the DSMB. Reports will be prepared regularly by the SDCC in accordance with the plan outlined in the charter and as requested by the DSMB chair, and will include interim analyses of primary and secondary endpoints; additional safety events; and other information as requested by the committee. After each meeting, the DSMB will make recommendations to the NHLBI and the trial leadership about the continuation of the study. After approval by the NHLBI director, a summary of the DSMB report and recommendations will be forwarded by the CCC to investigators for submission to their local, regional and national IRB/Ethics Committees, as applicable. DSMB reports will be the primary mechanism for reporting safety concerns to NIH and IRBs.

13.2 Risks and Benefits

All procedures and tests performed in this study are commonly performed in clinical practice and have well defined safety profiles. Furthermore, all procedures performed in this study, are commonly performed for the patient population enrolled in the study, i.e., those with advanced CKD, SIHD and at least moderate ischemia. The risk of cath and revascularization will be minimized by the selection of experienced operators who meet study certification criteria. These risks are justified by the potential benefit (long-term reduction in events resulting from revascularization, as discussed in the background section).

Risks:

Cath/PCI/CABG Risks: Each of these procedures is performed in clinical practice for patients who meet eligibility criteria for the CKD trial. The major risks of these procedures include death, myocardial infarction and stroke. Other risks of catheterization and PCI include severe contrast reaction such as anaphylaxis, emergency CABG, bleeding, need for blood transfusion, contrast-induced AKI, AKI requiring dialysis and vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed or infection. Other risks of CABG include return to operating room for bleeding, need for blood transfusion, infection, prolonged intubation, mediastinitis, AKI, AKI requiring dialysis and atrial fibrillation. Risks of these procedures vary in likelihood based on the patient's risk profile and are generally higher in the CKD cohort than in participants without CKD.

Risk Lowering Measures:

The risk of cath and revascularization will be minimized by the selection of experienced operators who meet study certification criteria. Strategies to minimize the volume of contrast used and reduce the risk of contrast-induced AKI are outlined in the MOO. These risks are

justified by the potential benefit (long-term reduction in events resulting from revascularization, as discussed in the background section). Study procedures are designed to manage and minimize risks through careful selection of the patients who participate in the trial. Participants will be monitored closely through the trial at many time points to check on their health. In addition, an independent DSMB will monitor safety of the participants throughout the study (see section 13.1)

Benefits:

The ISCHEMIA-CKD trial results should provide evidence based data to support management of participants with CKD and SIHD. It is hoped the knowledge gained will be of benefit to others with a similar medical condition in the future.

There may be benefit from participation in this study by receiving the medications and lifestyle counseling that are proven to improve outcomes in patients as well as involvement of an additional team following the participants' health status. Participants may receive some medications and stents free of cost, as available.

13.3 Safety Monitoring Objectives and Rationale

The main safety objectives in ISCHEMIA-CKD are to characterize the risk profiles of the two randomized management strategies and to monitor for unanticipated risks to study participants. All medications and procedures to be used/performed in this study are commonly used/performed for clinical indications as part of standard of care and have well-defined safety profiles. Because no investigational device, drug, diagnostic test or therapeutic intervention is being tested in this comparative effectiveness trial, reporting is primarily governed by the Common Rule (45 CFR Part 46, Subpart A), as well as ICH Guidelines, IRBs and local regulations.

13.4 Adverse Events Reporting by Investigators

Data for monitoring participants' safety will be captured within the EDC database as part of the required study data. There are no additional study-specific reporting requirements. Site investigators should follow usual clinical practices at their institutions for reporting serious, unexpected events related to standard of care medications and devices to regulatory agencies.

13.5 Events to be Monitored

Safety monitoring in ISCHEMIA-CKD will be concerned with estimating event rates for the following types of clinical events:

1. Complications of cardiovascular tests (e.g. cardiac catheterization) and therapeutic procedures (e.g. PCI, CABG)
2. Events occurring in the time period between consenting to participate in the trial and being randomized.
3. Study endpoints.

1. Complications of cardiovascular tests and therapeutic procedures

All drugs, diagnostic tests and therapeutic procedures to be used in this trial have been extensively evaluated previously, have established safety profiles with known risks and benefits and are routinely used in clinical practice. Events listed below occurring within 72 hours of the procedure will be considered as a complication of the procedure. Some safety events related to specific tests and procedures captured within EDC, in addition to death and MI, include:

Cardiac catheterization and PCI:

1. Severe contrast reaction such as anaphylaxis
2. Periprocedural stroke
3. Emergency CABG
4. AKI
5. AKI requiring dialysis
6. Vascular access site complications including pseudoaneurysm, AV fistula, retroperitoneal bleed

CABG:

1. Return to operating room for bleeding
2. Prolonged intubation
3. Mediastinitis
4. Atrial fibrillation
5. AKI requiring dialysis

In addition the incidence of finding significant LM stenosis (≥50%) on cardiac catheterization will be monitored and reported to the DSMB.

2. Events occurring in the time period between consent and randomization

In general, eligibility for randomization will not be known at the time of enrollment but will need to be confirmed after performing additional screening procedures (e.g. pregnancy test). As a result, several days may elapse before the participant is randomized. Frequency of clinical events (e.g. death, MI) occurring during this time period, prior to randomization, will be monitored and reported to the DSMB.

3. Events that are trial endpoints

Selected trial endpoints (e.g. all-cause mortality) will be monitored at regular intervals during the course of the trial for the purpose of protecting participants' safety. Event rates in each treatment group will be confidentially reviewed by the DSMB. These analyses will inform the DSMB's recommendation to stop or continue the study or modify the protocol (see **section 11.2.6**).

14. ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the international conference on harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 45 and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

14.2 Informed Consent Process

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every participant or, in those situations where consent cannot be given by participants, their legally acceptable representative, prior to clinical study participation. The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society. Women of child bearing potential will be informed that there may be unknown risks to the fetus if pregnancy were to occur during the study and they were exposed to radiation (e.g. cardiac catheterization and revascularization if randomized to the INV strategy group) and agree that in order to participate in the study they must adhere to the contraception requirement during this period of the study. If there is any question that the prospective participant will not reliably comply with study procedures and/or follow-up, they should not be entered in the study.

14.3 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent forms (main consent form and genetics testing consent form) will be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) at each site. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB is required before site initiation. Prior to study start, the site principal investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, Clinical Quality Assurance representatives, designated agents of CCC, IRBs/IECs/REBs, and regulatory authorities as required. Investigators must agree to apply due diligence to avoid protocol deviations.

14.4 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by CCC, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for participant safety may be implemented prior to IRB/IEC/REB approval. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment(s) will be submitted: (a) to the IRB/IEC/REB for

review and approval/favorable opinion; (b) to the sponsor, NIH/NHLBI for agreement; and, if required, (c) to the regulatory authority(ies). Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, CCC should be notified of this action and the IRB/IEC/REB at the study site should be informed.

14.5 Early Termination of the Study

The CCC and NHLBI retain the right to terminate the study, a study site or an investigator at any time. The CCC will monitor the progress of the study. If warranted, the study may be suspended or discontinued early if there is an observation of safety concerns posing an unreasonable risk to the study population. If the study is terminated early, the CCC will provide a written statement to the site Principal Investigators to enable notification to site IRBs/IECs/REBs and study participants. The CCC will also inform the appropriate Competent Authorities. The CCC may terminate enrollment activity at a site, or participation in the study by the investigator and site if there is evidence of an investigator's failure to maintain adequate clinical standards or failure to comply with the protocol. Notification of enrollment suspension or termination of the study or study site/investigator will be sent to the investigator and the IRBs/IECs/REBs.

15. STUDY ORGANIZATION

ISCHEMIA-CKD is sponsored by the US National Heart, Lung, and Blood Institute (NHLBI). The Clinical Coordinating Center (CCC), Principal investigator, Study Chair, and Study Co-Chair maintain responsibility for the overall conduct of the study, including site management and site monitoring in participating countries, analysis and reporting. The Statistical and Data Coordinating Center (SDCC) is responsible for the treatment allocations of eligible participants, receipt and processing of data collected by the clinical sites, core laboratories and coordinating centers, quality control programs, and statistical analysis and reporting. The angiographic core laboratories (ACL) will characterize coronary anatomy for participants undergoing coronary angiography and procedural outcomes for those undergoing PCI. Members of the NHLBI will participate in the study leadership. Details regarding the Cores and Coordinating Centers may be found in the MOO.

16. DATA ACCESS AND SHARING

The Publication Committee will authorize access to study data and biospecimens (in conjunction with the Biorepository Committee). Investigators must submit a proposal requesting approval to access ISCHEMIA-CKD trial data/specimens. The ISCHEMIA-CKD trial will participate in the NHLBI Central Repository for study data and specimens.

All data access will follow guidelines described in the NHLBI Limited Access Data Policy (www.nhlbi.nih.gov/resources/deca/policy_new.htm), the NIH Data Sharing Policy (http://grants.nih.gov/grants/gwas/index.htm), and the Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS) http://grants.nih.gov/grants/gwas/index.htm) with regard to documentation, content, storage and timing.

17. PUBLICATIONS POLICY: OVERVIEW

Primary and secondary reports of study findings will be published in peer-reviewed journals. Proposals for presentations and publications incorporating data obtained from participants involved in the ISCHEMIA-CKD trial must be submitted for review by the publications committee. The primary publication will be authored by the trial's writing committee. No site is permitted to present or publish data obtained during the conduct of this trial without prior approval from the publications committee. Authorship for ISCHEMIA-CKD-related publications will be determined by the publications committee taking into account contribution to the trial and the relevant analyses. The full publications policy may be found in the MOO.

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19. APPENDIX A

Ischemia Test Eligibility Criteria

Specific criteria for each modality were developed and refined based on data indicating that the risk of cardiovascular events based on inducible ischemia is consistent with that targeted in this trial. Criteria were harmonized across modalities in order to yield a similar risk of cardiovascular death or MI regardless of the type of stress test performed.[1]

Table: Criteria for at least Moderate Ischemia by Stress Test Modality[2]

Test Modality	Diagnostic criterion
Nuclear perfusion via SPECT or PET[3]	≥10% myocardium ischemic
Echo[3]	≥3/16 segments with stress-induced severe hypokinesis or akinesis
CMR[3]	Perfusion: ≥12% myocardium ischemic and/or Wall motion: • ≥3/16 segments with stress-induced severe hypokinesis or akinesis
Exercise Test without Imaging (Criteria 1-3 must all be met)	1. Absence of resting ST segment depression ≥1.0 mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.) 2. As compared to the baseline tracing, additional exercise-induced horizontal or downsloping ST segment depression ≥1.5 mm in 2 leads *or* ≥2.0 mm in any lead; ST segment elevation ≥1mm in a non-infarct territory. Both the J-point and the ST segment at 80 msec. need to meet criteria. When the HR is >130/min, the ST segment at 60 msec. may be used if the segment at 80 msec. cannot be determined. 3. Either of the following: a. Peak workload not to exceed completion of stage 2 of a standard Bruce protocol or ≤7 METS if a non-Bruce protocol is used *or* b. ST segment criteria are met at <75% of the maximum predicted HR

SPECT=single photon emission computed tomography, PET=positron emission tomography; Echo= echocardiography; CMR=cardiac magnetic resonance

[1] Shaw L, Berman D, Stone G, Picard M, Friedrich M, Kwong R, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. JACC Cardiovasc Imaging (in press).

[2]Additional criteria may be required for confirmation of obstructive coronary artery disease, depending on eGFR and type of ischemia test. See Section 5.5.

[3]Ancillary findings may also be included in the determination of severity of ischemia by imaging (see MOO).

Note the exclusion criterion: Patient who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis will be excluded (see Section 4.3.1).