ISCHEMIA Trial Protocol

International **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches

Sponsor: National Heart, Lung, and Blood Institute (NHLBI)

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Statistical and Data Coordinating Center   Duke Clinical Research Institute

Protocol Version Date: January 18, 2012

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date

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: January 18, 2012

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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	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
Study Objectives	Primary objective is to determine whether an invasive (INV) strategy of routine early cardiac catheterization with intent for optimal revascularization in addition to optimal medical therapy in patients with stable ischemic heart disease (SIHD) and at least moderate ischemia on stress imaging reduces the incidence of the composite of cardiovascular death or nonfatal myocardial infarction compared with a conservative (CON) strategy of optimal medical therapy alone with cardiac catheterization and revascularization reserved for patients with refractory angina, acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest. 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 is an international comparative effectiveness study. Participants will be recruited following clinically indicated stress testing but before catheterization and randomized in a 1:1 fashion to an INV or CON strategy.
Number of Participants	Approximately 8,000 participants randomized
Trial Location	Multinational: approximately 500 sites worldwide
Inclusion Criteria	• At least moderate ischemia on a stress imaging test with nuclear myocardial perfusion (≥10% myocardium), echo or cardiac magnetic resonance wall motion (≥3/16 segments with stress-induced severe hypokinesis or akinesis), or cardiac magnetic resonance perfusion (≥12% myocardium). • Participant is willing to comply with all aspects of the protocol, including

	• adherence to 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 $\geq$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
	• Prior known 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 or CABG within the previous 12 months
	• Stroke within the previous 6 months or intracranial hemorrhage at any time
	• History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia
	• 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
	• End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min
	• Severe valvular disease or valvular disease likely to require surgery within 5 years
	• 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
	• Life expectancy less than 5 years due to non-cardiovascular comorbidity

	• Pregnancy (known to be pregnant; to be confirmed before CCTA and/or randomization, if applicable) • Patient with eGFR 30-59 ml/min 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 CCTA or cardiac catheterization at the site
Primary Endpoint	Time to first occurrence of cardiovascular 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, CCTA visit, randomization, 1.5 months, 3 months, 6 months, 12 months, and every 6 months thereafter.
Study Duration	Enrollment will occur over approximately 4 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, stroke, and transient ischemic attack.
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 8,000 randomized participants is expected to provide over 90% power to detect a 15% reduction in the primary composite event rate in participants randomized to INV as compared with CON strategy.

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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
CCTA	coronary computed tomography angiography
CEC	clinical event adjudication committee
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
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
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

Coronary artery disease (CAD) is the leading cause of death and disability worldwide and affects 17.6 million Americans, resulting in about 450,000 deaths in the United States annually.[1] Globally, 7.2 million deaths are caused by CAD each year.[2] An invasive approach to the evaluation and treatment of CAD is common, yet evidence that this approach to management favorably influences long-term clinical outcomes in patients with stable ischemic heart disease (SIHD) is outdated. In randomized clinical trials conducted in the 1970s, surgical revascularization (coronary artery bypass graft [CABG]) improved survival compared to medical therapy in SIHD patients.[3-6] The benefit was most apparent in subsets with high-risk anatomic features. The relevance of these studies to present-day patients with SIHD is unclear for many reasons. Most importantly, effective medical therapy proven in more recent trials to reduce clinical events was used minimally if at all. These therapies include aspirin, beta-blockers, statins, angiotensin-converting-enzyme (ACE) inhibitors, and lifestyle interventions.[7-17] High-dose statins, in particular, are disease and prognosis modifying agents. Moreover, in aggregate, these therapies could be expected to yield ~50% relative reduction in risk of clinical events.[9, 18-20] Thus, the continued relevance of findings from CABG vs. medicine trials conducted in an earlier era is, at best, speculative.

In the contemporary era, revascularization in addition to medical therapy vs. medical therapy alone has been studied in several patient populations. The Surgical Treatment for Ischemic Heart Failure (STICH) trial assessed all-cause mortality for CABG vs. medical therapy alone in a heart failure cohort at high risk of death: those with severe HF, an ejection fraction ≤35%, and coronary artery disease. These patients are excluded from the ISCHEMIA trial. STICH reported no significant difference in all-cause mortality (the primary end point) between the two treatment strategies ($P = 0.12$); CABG reduced the composite of CV death and hospitalization.[21] In a STICH substudy, myocardial viability did not identify patients with a differential treatment effect from CABG, as compared with medical therapy alone.[22]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[23] and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[24] trials demonstrated that in patients with SIHD, predominantly without severe LV dysfunction, a management strategy of revascularization plus optimal medical therapy (OMT) did not reduce the risk of death or MI as compared with OMT alone. Importantly, both of these trials randomized patients after cardiac catheterization (cath). Cath is an invasive diagnostic test that typically triggers a therapeutic cascade involving revascularization.[25] This phenomenon is attributed, in part, to the common attitude among patients and physicians that visualized stenoses need to be "fixed" and that a revascularization procedure will prolong their lives and/or prevent MI, not just relieve angina.[26-28] Consequently, the decision to proceed with revascularization often hinges more on anatomic feasibility than on evidence that revascularization is clinically beneficial.[26, 28] The inherent assumption of this approach is that coronary revascularization of flow-limiting stenoses will prevent or reduce clinical events. This assumption is not warranted, based on the results of modern randomized trials.

Moderate to severe ischemia is a marker of increased risk for cardiovascular events.[29] It remains unclear whether the increased risk associated with a greater magnitude of ischemia is related to the adverse effects of ischemia, occlusion of severe stenoses that cause ischemia, or if more severe ischemia is simply a marker of more extensive atherosclerosis and more vulnerable plaques. Vulnerable plaques, which may not themselves be flow-limiting, are more commonly sites of plaque rupture and thrombosis and the cause of MI than severe stenoses.[30-33] However, individual plaques with severe stenoses are more likely to occlude than less severely stenotic plaques.[34] The power of the diagnostic-therapeutic cascade poses challenges for broad translation of COURAGE and BARI 2D results into practice. In both trials, randomization of patients after coronary anatomy had been visualized raises concerns that many patients with the most severe and treatable lesions may not have been enrolled but were instead revascularized preemptively while on the cath table, thus excluding an important high risk group from rigorous, prospective study. Although the finding that prompt revascularization in stable patients did not prevent death or MI suggests that cath may not be necessary in this cohort of patients, this conclusion is not valid due to the protocol design of these two landmark trials.

Observational data suggest that early revascularization is associated with a lower likelihood of death and MI in patients with at least moderate ischemia on myocardial perfusion imaging (MPI),[35-37] but this concept has never been fully tested in a prospective, randomized clinical trial. Within a small (n=314) nuclear substudy of patients who had baseline and follow-up stress perfusion scans at 6-18 months in the COURAGE study, there were 105 patients with at least moderate ischemia at baseline, as measured by MPI in a core laboratory. Among these 105 patients, there was a significantly greater reduction in ischemia associated with PCI and OMT than OMT alone on follow-up MPI.[38] For PCI and OMT groups combined, the rate of death or MI over 3.6 years was 16% for those who experienced ischemia reduction compared with 34% for those without significant ischemia reduction on follow-up MPI. These results support the hypothesis that the benefit of an invasive strategy in SIHD patients is most likely to be observed in patients with at least moderate ischemia. In contrast, a newer, unpublished COURAGE analysis of outcomes *by treatment* in 189 patients with at least moderate ischemia on baseline core lab-measured MPI, without regard to the ascertainment of a follow-up study, showed no reduction in death/MI (PCI and OMT vs. OMT 24% vs. 21%, respectively, hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.65-2.18). The same lack of benefit for PCI was demonstrated for a larger cohort of 468 patients with *site-determined* moderate or severe ischemia at baseline.

Data from 9 reports representing 5,833 patients suggest that only 35 to 65% of patients with moderate or severe ischemia on MPI are referred for cath, reflecting equipoise in the community.[39-47] It is presently unknown whether use rates for cath and revascularization are appropriate for optimal patient management. The results of COURAGE and BARI 2D are extremely valuable to physicians caring for patients with SIHD. However, a clinical trial to determine optimal management for SIHD patients uniformly at higher risk could not have been performed before the COURAGE and BARI 2D results were available. Moderate or severe ischemia is a marker for increased risk for death, but no well-designed clinical trial of patients with this degree of ischemia has studied whether an invasive strategy improves clinical

outcomes and quality of life. Given the potential clinical benefit from revascularization on the one hand, and the significant expense of an invasive strategy on the other, this is a critically important issue to resolve. The results of ISCHEMIA will have profound implications for guidelines, health policy, and clinical practice.

3. HYPOTHESIS

An invasive (INV) approach of routine early cardiac catheterization with intent for optimal revascularization in addition to OMT will reduce the incidence of major adverse cardiovascular events over an average of approximately 4 years in participants with SIHD and at least moderate ischemia as compared with an initial conservative (CON) approach of OMT alone, with catheterization reserved for refractory angina symptoms, acute coronary syndrome, acute ischemic heart failure, or resuscitated cardiac arrest.

4. STUDY OBJECTIVES

PRIMARY AIM

The primary aim of the ISCHEMIA trial is to determine whether an invasive strategy of routine early catheterization followed by optimal revascularization, in addition to OMT, will reduce the primary composite endpoint of cardiovascular 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 refractory angina symptoms, acute coronary syndrome, acute ischemic heart failure, or resuscitated cardiac arrest.

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

5. STUDY DESIGN

The ISCHEMIA trial is an international, randomized, comparative effectiveness study. Approximately 8,000 participants at approximately 500 sites worldwide with SIHD and at least moderate ischemia on stress imaging will be randomized in a 1:1 fashion to the INV or CON strategies.
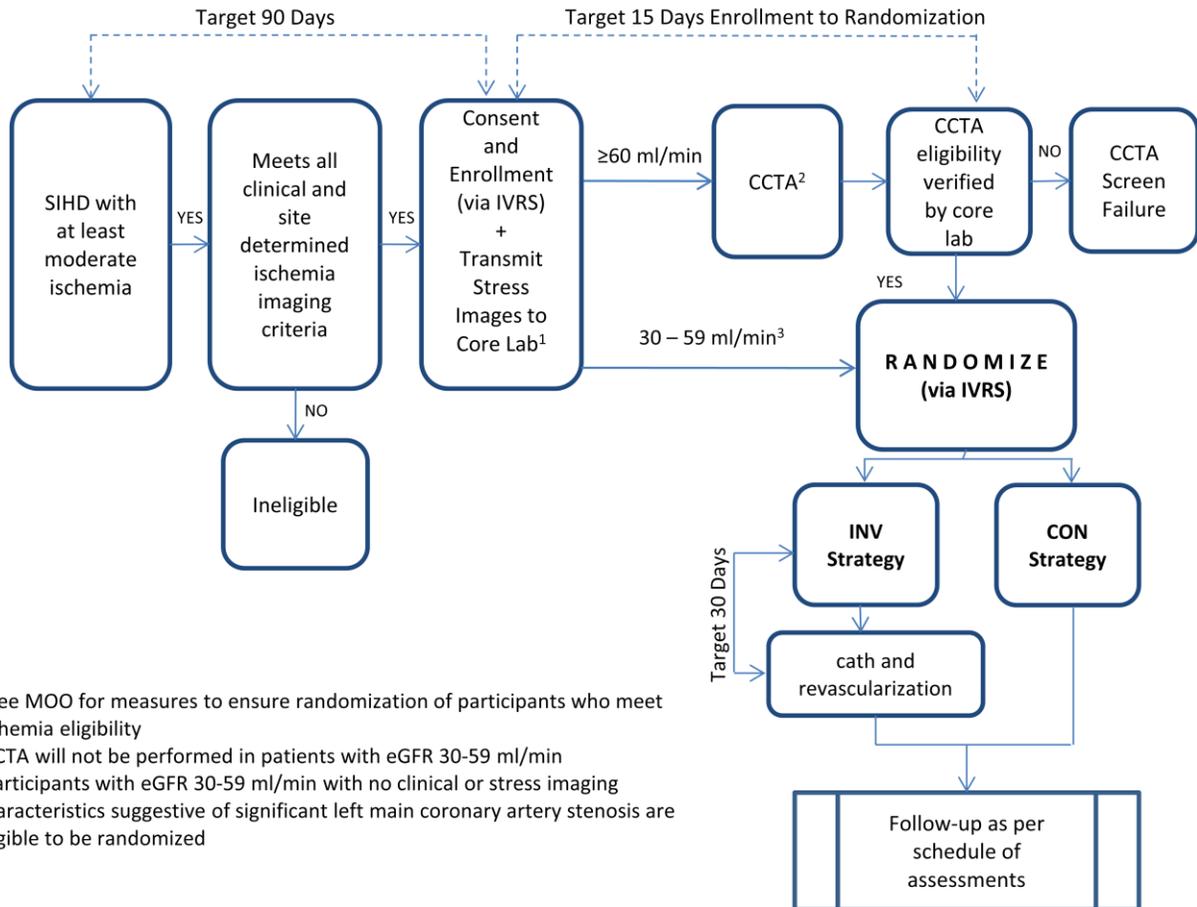
5.1 Study Flow

See figure 1 for details. Patients will be screened following clinically-indicated stress testing, but before catheterization. Patients with at least moderate ischemia on stress imaging (see section 6.1) will be identified and screened for clinical inclusion/exclusion criteria (see section 5.3). 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 6.3). Stress testing images will be transferred to the imaging core lab electronically for all enrolled participants (see Figure 1). All participants with eGFR $\geq$60 ml/min will undergo a blinded CCTA. CCTA images will also be transferred electronically to the CCTA core lab for interpretation. CCTAs will only be interpreted by the CCTA core lab and NOT at the site. The participant, participant's physician, and site will not have access to the results of the CCTA unless the core lab determines the results reveal: 1) unprotected left main coronary artery stenosis (defined as ≥50% and not previously bypassed); 2) no obstructive lesions (≥50%) in any major coronary artery; or 3) incidental findings of clinical importance, such as an aortic aneurysm or suspected neoplasm. In the event of any of these three findings, the participant will not be eligible to continue in the study, and these results will be communicated to the site. The images will then be made available to the site for clinical use. All participants meeting CCTA eligibility criteria (see section 6.5) will then be randomized to the INV or CON strategy via the IVRS/IXRS system.

 Participants with eGFR 30-59 ml/min will not undergo a CCTA due to the increased risk of developing contrast-induced nephropathy. Participants with eGFR 30-59 ml/min who, according to the participant's physician, are unlikely to have significant unprotected left main stenosis, will proceed directly to randomization. (Patients with eGFR <30 ml/min are not eligible for the trial.) Patients with eGFR 30-59 ml/min will not be enrolled into the study if the patient's physician suspects significant left main stenosis on the basis of stress hemodynamic, ECG, and imaging results.

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 4 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 10.

Figure 1   Study Flow

¹ See MOO for measures to ensure randomization of participants who meet ischemia eligibility
²CCTA will not be performed in patients with eGFR 30-59 ml/min
³Participants with eGFR 30-59 ml/min with no clinical or stress imaging characteristics suggestive of significant left main coronary artery stenosis are eligible to be randomized

5.2   Study Population

Patients with SIHD and at least moderate ischemia on stress imaging. 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).

5.3   Inclusion/Exclusion Criteria

Screening for inclusion/exclusion criteria will be conducted in two phases. First, clinical and ischemia criteria at the local site will be used to obtain informed consent; and second, after informed consent is obtained but before randomization, criteria for CCTA eligibility will be assessed. Stress imaging core labs will work with sites to ensure randomization of participants with at least moderate ischemia.

5.3.1   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 stress imaging test (See Table 1)

2. Participant is willing to give informed consent

3. 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. Prior known 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 or CABG within the previous 12 months

10. Stroke within the previous 6 months or intracranial hemorrhage at any time

11. History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia

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. End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min

15. Severe valvular disease or valvular disease likely to require surgery within 5 years

16. Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast

17. Planned major surgery necessitating interruption of dual antiplatelet therapy

18. Life expectancy less than 5 years due to non-cardiovascular comorbidity

19. Pregnancy (known to be pregnant; to be confirmed pre-CCTA and/or randomization, if applicable)

20. Patient with eGFR 30-59 ml/min who, in the judgment of the patient's physician, is likely to have significant unprotected left main stenosis

21. Enrolled in a competing trial that involves a non-approved cardiac drug or device

22. Inability to comply with the protocol

23. Exceeds the weight or size limit for CCTA or cardiac catheterization at the site

5.3.2 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 and will undergo measurement of ischemia by the stress imaging core lab and a blinded CCTA (if eGFR $\geq$60 ml/min). Participants meeting the following exclusion criteria will not be randomized.

Exclusion (after informed consent and before randomization)

1. Pregnant (negative pregnancy test before CCTA required for premenopausal females)

2. Left main stenosis ≥50% (unprotected) on CCTA

3. Finding of "no obstructive coronary artery disease" (<50% stenosis) in all major epicardial vessels on CCTA

4. Incidental findings on CCTA of clinical importance (e.g., lung mass suspicious for malignancy; see MOO for details)

5. Interval development of a clinical exclusion criterion or a primary or secondary endpoint event.

6.   STUDY PROCEDURES

6.1   Qualifying Stress Imaging Study

The following imaging stress test modalities will be allowed for inclusion using exercise or pharmacologic stress:

- Nuclear perfusion imaging (single photon emission computed tomography [SPECT] or positron emission tomography [PET])
- Echocardiography (Echo)
- Cardiac magnetic resonance (CMR)

Non-imaging stress tests (ECG only) will not be permitted to determine eligibility. The criteria for at least moderate ischemia with each imaging modality are listed in Table 1. Stress 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 stress imaging study documenting eligibility, consistent with customary clinical practice.[36, 37] A 24-hour, 7-day helpline will be available to sites for assistance with ascertainment of eligibility, enrollment, and adherence to protocol.

Table 1: Criteria for at least Moderate Ischemia by Stress Imaging Modality

Imaging Modality	Diagnostic criterion
Nuclear perfusion via SPECT or PET	≥10% myocardium ischemic
Echo	≥3/16 segments with stress-induced severe hypokinesis or akinesis
CMR	perfusion: ≥12% myocardium ischemic and/or wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis

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

6.2   Informed Consent Process

The study will be reviewed with the prospective study participant by the investigator or his/her designee. The prospective study participant will be given adequate time to read the written consent form. 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 genetic testing (DNA). Prospective study participants will be informed that declining participation in the Biomarker or Genetic Testing 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 (including CCTA) 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.

6.3   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 stress imaging 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, site, and core lab inclusion/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.

6.4   Core Lab Ischemia Verification

Stress imaging studies for all participants will be transferred electronically to the appropriate stress imaging core lab following enrollment of the participant into the study. The core lab will review and interpret the degree of ischemia. A purpose of core lab review is to ensure that participants enrolled in this study have at least moderate ischemia. Based on performance in the interpretation of tests meeting the definition of at least moderate ischemia, stress imaging core labs will certify that sites

can continue to advance participants to the next step, CCTA (or randomization, if the eGFR is 30-59ml/min). (See MOO.)

6.5 Coronary Computed Tomography Angiography (CCTA)

Coronary computed tomography angiography (CCTA) will be performed in all participants with eGFR ≥60ml/min to identify and exclude participants with obstructive left main stenosis (defined as ≥50% unprotected stenosis) and participants without obstructive coronary stenoses (with <50% stenosis in all epicardial coronary vessels). Study staff will not view the CCTA; only the CCTA core laboratory will interpret results and sites will be blinded to the results of the scan. The scan and interpretation will not be stored in the local clinical imaging system. Participants with eGFR 30-59 ml/min will not undergo a CCTA due to the risk of developing contrast-induced nephropathy. In this subpopulation, participants can be randomized if the treating physician does not suspect significant unprotected left main stenosis based on the results of the stress test, including the imaging portion. However, if a significant left main stenosis is suspected, these participants will not be enrolled into the study.

Radiation reduction techniques will be used. We will prescribe standardized patient-specific image acquisition protocols that permit high quality CCTA with low dose radiation. Radiation reduction methods will include ECG dose modulation, weight-based tube voltage, minimization of Z-axis coverage, limiting the field of view, and automatic exposure control. Importantly, all of these dose reduction techniques are additive, can be programmed into a single default protocol, and are available in all ≥64-detector row CT scanners. The investigative group has evaluated the efficacy of combined dose reduction techniques and found a >90% reduction in biological radiation dose (1-2 mSv) without compromise of image quality or diagnostic accuracy.[48-52] Each site will be provided with a concise, easy-to-read manual and an instructional video, prepared for this trial, on how to obtain high quality CCTA images with low radiation dose. For newer scanners, we will employ further dose reduction algorithms including prospective ECG triggering, minimization of padding, and iterative reconstruction techniques.

The CCTA core laboratory will interpret the images and sites will be notified if the participant is or is not eligible because of significant unprotected left main coronary artery stenosis or the absence of obstructive stenoses. Further definition of the anatomy will not be disclosed to the participant, treating physicians, or the site unless the participant is not eligible for randomization. Participants with incidental findings of clinical importance, such as aortic aneurysm or suspected neoplasm; see MOO for details), will not be randomized and the interpretation of the CT, including coronary anatomy, will be made available to the treating physicians. In addition, there may be findings on CT of potential clinical significance that will not exclude patients from the study, such as small lung nodules. In such cases, treating physicians will be given access to and will be encouraged to review the CT images locally.

If a trial-consented participant is not randomized after CCTA, despite being confirmed eligible by the CCTA core laboratory, maintenance of investigator blinding will be investigated.

Participants meeting the clinical, ischemia, and CCTA eligibility (or physician judgment for participants with eGFR 30-59 ml/min) will be randomized to the INV or CON strategy via the

IVRS/IXRS system. The targeted time to randomize a participant after consent is obtained is 15 days (see Figure 1).

7. MANAGEMENT STRATEGIES

Table 3. Components of CON and INV management strategies

CON ([Section 7.1](#))	INV ([Section 7.2](#))
• Optimal medical therapy (OMT; includes angina management) ([Section 7.3](#)) • Provisional cardiac catheterization ([Section 7.6](#))	• Optimal medical therapy (OMT; includes angina management) ([Section 7.3](#)) • Cardiac catheterization • Optimal revascularization therapy (ORT) ([Section 7.4](#))

7.1   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.

7.2   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.**

7.3   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.

7.3.1 Management of Angina in CON Participants

Medical management of angina in CON participants will be intensified according to the ISCHEMIA 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.

7.3.2 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 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.

7.4 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.
- 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.

7.4.1 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.

7.4.2 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.

7.4.3 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.

7.5   Maximizing Adherence to CON Strategy

Adherence to the CON strategy means that all CON participants receive OMT and that none undergo cath or revascularization 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 must call the 24-hour helpline when elective cath is being considered, and they must complete a checklist.

7.6   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 (7.4) apply.

Figure 2   Cath in Participants Randomized to CON Strategy

Cath in CON Participant

Hospitalization for ACS[1]?

No   Yes

Refractory symptoms?[2]

No   Yes

NOT consistent with CON strategy
NOT Adherent to Protocol

Consistent with CON strategy
Adherent to Protocol

[1] ACS=acute coronary syndrome, includes resuscitated cardiac arrest and hospitalization for acute ischemic heart failure
[2] According to trial definition
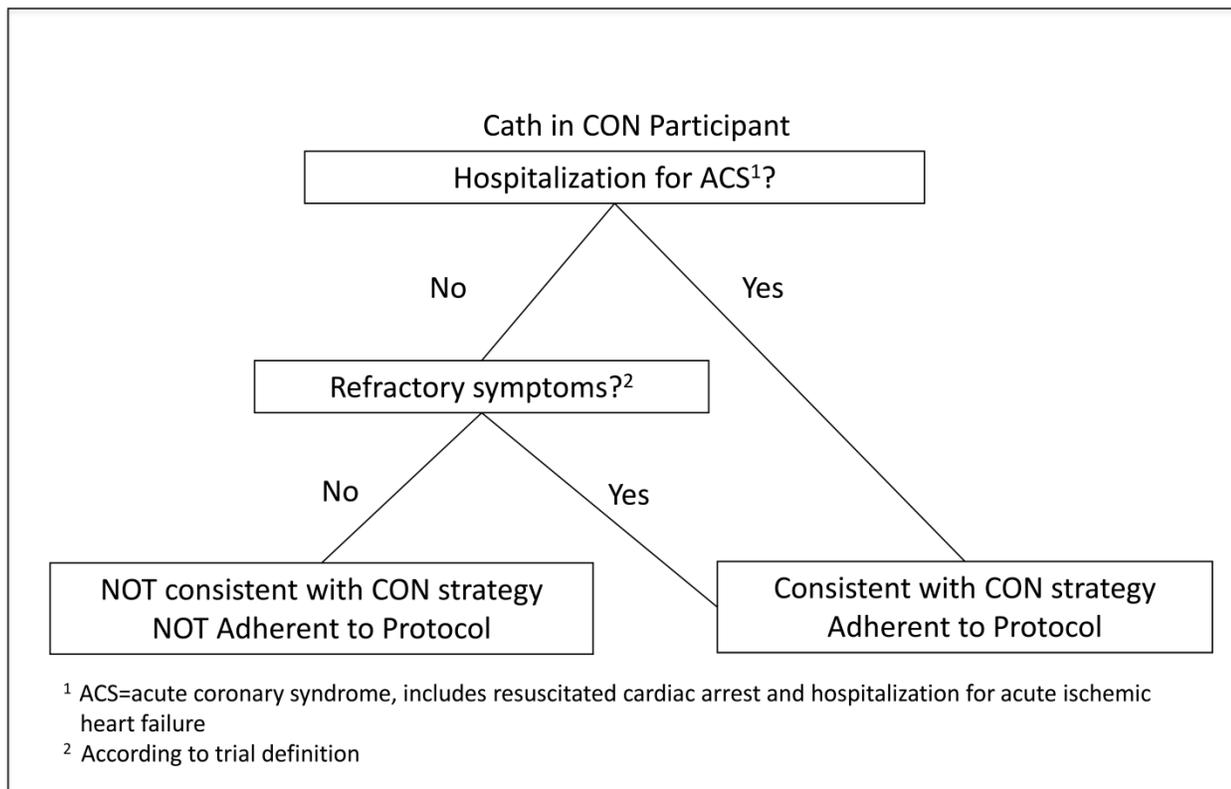
8. AUXILLIARY SCREENING LOG AND SURVEY

8.1 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 stress imaging 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).

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 stress imaging.

8.2 Screening Survey

For brief designated periods, sites will collect de-identified data on all patients with at least moderate ischemia who are screened but not enrolled by the study team. The goal of this effort will be to describe the characteristics of patients who are screened but not enrolled and to document the major reasons for exclusion. This screening survey will include the site's primary stress imaging laboratory and any other screening and referral sources. Data will be entered via a web-based EDC system which will not include patient identifiers and will be separate from the main trial EDC system. For analysis, we will compare baseline characteristics and treatment plan of patients who were screened and met inclusion criteria but were not randomized with those who were randomized. This information will provide insight into any potential bias in trial enrollment. Examples of data elements to be collected, when available, include:

- Age (excluding any age ≥90)
- Sex
- Race/ethnicity
- LVEF
- Results of the stress imaging test (ischemia severity and location)
- Basic medical history from stress imaging report (if available)
- Presence or absence of LM stenosis >50% on previous CCTA or cardiac catheterization
- History of ACS within the last 2 months
- History of PCI or CABG within the last 12 months
- History of stroke within the last 6 months or intracranial hemorrhage at any time
- End stage renal disease or eGFR 15-29 mL/min

- History of NYHA III/IV heart failure or admission to hospital in the last 6 months

- Planned non cardiac surgery within the next 12 months

- Severity of angina symptoms

- Current anti-angina medications

- Willingness to take medications

- Plan for treatment (e.g., cardiac catheterization, mode of revascularization if applicable)

- Actual treatment received (e.g., cardiac catheterization, mode of revascularization if applicable)

- Reason for not participating in the trial

Only de-identified health information will be recorded. An informed consent waiver will be obtained where applicable. There will be no follow-up of these screening survey patients.

9. Study Assessments

9.1 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.

9.2 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 they will be obtained (HbA1c required for diabetics only but recommended for all participants). 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 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.

9.3 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.

9.4 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 testing. 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.

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.

9.5   Medication Adherence

To assess medication adherence, a 4-item modified Morisky adherence survey (Likert scale responses to 4 questions)[53-56] will be completed at the randomization visit, 6 month visit, and all subsequent visits.

9.6   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.

9.7   Quality of Life Assessment

To quantify the full spectrum of patient-reported quality of life outcomes in ISCHEMIA, 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; physical function by the disease-specific Duke Activity Status Index (DASI) and angina-specific SAQ physical limitations sub-scale; a Rand general health rating; psychological well-being and depression screening symptoms by the Perceived Stress Scale (PSS) and Patient Health Questionnaire-8 (PHQ-8); a measure of optimism about the future from the Life Orientation Test-Revised (LOT-R); 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.

9.8   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 throughout the trial at each ISCHEMIA study visit or contact and entered into the main study EDC database. These data, in conjunction with billing data (collected for the US study participants only by the EQOLCC economic team and entered into a database separate from the main EDC study database), 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.

10. SCHEDULE OF ASSESSMENTS

Overview of Visits

All participants will undergo eligibility screening, informed consent, CCTA (for all participants with eGFR $\geq$60 ml/min) 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 4 for complete assessment schedule). The schedule of assessments (Table 4) 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 4). 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.

Dependent on additional funding, telephone, in-person and/or email follow up may occur for participants who are enrolled and subsequently excluded from randomization due to CCTA findings of nonobstructive or LM CAD. It may include up to 5 visits over the first 18 months and up to 2 visits per year thereafter until the study ends. Participants who are excluded based on CCTA or stress test findings will be asked to provide consent for future contact for research purposes.

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

Collection of Economic and QOL data, including the follow-up Full QOL Questionnaire validated scales will be repeated at 3, 12, 24 and 36 months from randomization and at the final ISCHEMIA visit by trained telephone interviewer staff from the EQOL Coordinating Center (EQOLCC) for participants enrolled in North America and by the site coordinator in sites outside North America. A Proxy QOL questionnaire obtained from a relative, caretaker, or medical record will be used when a participant has died in the follow-up interval, is too ill, otherwise incapacitated, or unable to participate. Lastly, 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 visit. All symptom and QOL data will be data processed and analyzed by the EQOLCC quality of life team. A Hospitalization assessment as part of the main study EDC database will be collected on all randomized ISCHEMIA participants at each follow-up study interval throughout the trial to provide a measure of resource utilization. Additionally, as part of the economic data in ISCHEMIA, medical bills for participants enrolled at US sites only will be collected throughout the trial by the EQOLCC economic team from this Hospitalization assessment. The medical billing data will be obtained, extracted, data processed and analyzed by the EQOLCC.

Table 4   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	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
					Follow up								
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 Image 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
Coronary CT Angiography (CCTA)		X[F]											
Safety assessment [G]		X		X									
Vital signs, weight, height[H]			X		X	X	X	X	X	X	X	X	Q12m
Standard lab results[I]			X[J]		X	X	X	X	X	X	X	X	Q12m
Biorepository blood draw			X			X[K]							
Cardiac biomarkers[L]				X									
Electrocardiogram (ECG) [M]			X	X[N]				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	X	Q6m
Full Quality of Life (QOL) assessment [O]			X			X		X		X		X	@ closeout
Brief symptoms/QOL assessment[P]			X		X	X	X	X	X	X	X	X	Q6m
Initiate Optimal Medical Therapy (OMT)			X										
Medical Therapy Evaluation and Optimization[Q]					X	X	X	X	X	X	X	X	Q6m
Schedule catheterization for INV participants[R]			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 stress test images (immediately following enrollment and before randomization), technical worksheets, and site interpretations/local reports from qualifying stress tests to core labs.

^F CCTA not performed if estimated glomerular filtration rate < 60ml/min; Blinded CCTA images and technical worksheets will be transferred to CCTA core lab for interpretation.

^G Safety Assessment (refer to section 14.4).

^H Height is only needed at randomization, assessments only required if visit is completed in clinic.

^I Required labs include: lipids (preferably fasting), and liver transaminases (if indicated), 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.

^J Standard lab results needed at randomization include: complete blood count, electrolytes, creatinine, glucose, liver transaminases, lipid profile, HbA1c for diabetic participants. Request from participant's physician, since it is expected that routine blood work will have been done within the last 6 months; if not it will need to be done at this time.

^K May be requested.

^L For participants undergoing PCI: CK-MB at 8-16 ± 2 hours or at hospital discharge, whichever comes earlier (troponin to be measured if CK-MB not available). For participants undergoing CABG: CK-MB at 18 ± 6 hours (troponin to be measured if CK-MB not available). All biomarker measurements should be recorded on eCRF. It is recommended to obtain a biomarker measurement before all PCI and CABG procedures.

^M Send to ECG core lab; ECG required for all cardiac admissions and revascularizations; year 1 ECG optional (filed on site).

^N ECG done following procedure (60±30 mins post-PCI, 3 days post-CABG).

^O Seattle Angina Questionnaire/Duke Activity Status Index/Rand general health status item/Perceived Stress Scale/Patient Health Questionnaire/Life Orientation Test – Revised/EQ-5D/Demographic characteristics.

^P Selected Seattle Angina Questionnaire/Rose dyspnea scale/EQ-5D.

^Q At every follow-up visit the research 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.

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

Screening visit

- Patients with at least moderate ischemia by stress imaging test (see Table 1) 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 5.3

- 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 with an eGFR ≥30ml/min 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 stress testing images will be transferred electronically to the appropriate core laboratory. (see section 6.4)

CCTA visit

- For participants with eGFR ≥60ml/min, blinded CCTA will be performed

- Blinded CCTA images will be transferred to CCTA core lab for interpretation

- Participants with eGFR 30-59 ml/min do not require CCTA before randomization

- Assessment for safety (e.g., complications of CCTA)

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

- Confirm ischemia and CCTA eligibility

- 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)

- Full 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 CK-MB at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier (troponin to be measured if CK-MB not available)
    - 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
    - Blood draw for CK-MB at 18 ± 6 hours post-CABG (troponin to be measured if CK-MB not available)

- 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

- Obtain lab results from participant's treating physician for lipids (preferably fasting) and liver transaminases (when indicated). If not available these tests should be obtained by the patient'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

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

- Full QOL assessment will be collected

- Hospitalization assessment will be collected

- Biorepository blood draw will be performed

- Endpoints will be assessed

- Obtain lab results from participant's treating physician for lipids (preferably fasting) and liver transaminases (when indicated). If not available these 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

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) and liver transaminases (when indicated). If not available these 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

- Full QOL assessment will be collected (until 36 months)

- Hospitalization assessment will be collected

- Endpoints will be assessed

- Obtain lab results from participant's treating physician for lipids (preferably fasting), liver transaminases (when indicated), and HbA1c for diabetic participants. If not available these 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

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), liver transaminases (when indicated). HbA1c (only in participants with diabetes at every 12 month visit). If not available these 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

- Full QOL assessment will be collected

- 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.

11. 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, stroke, and transient ischemic attack. 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.

12. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

12.1 Sample Size Determination and Statistical Power

12.1.1 Considerations and Assumptions

The sample size of approximately 8,000 randomized participants was selected to yield high power for testing the primary superiority hypothesis under reasonable assumptions about the frequency of the primary composite endpoint, the magnitude of the difference in event rates for INV vs. CON strategies, and the pattern of accrual and dropout. Based on the distribution of coronary disease expected in this population (core-lab documentation of at least moderate ischemia; CCTA documentation of obstructive CAD) and based on unpublished data from the COURAGE trial and several observational stress imaging registries, the percent of participants experiencing the primary composite endpoint within 4 years of randomization in the CON group was projected to be 20% (range 15%-25%). In addition to the CON event rate, an additional key driver of the required sample size is the magnitude of benefit that can reasonably be expected to be achieved with the INV strategy. This determination was based on multiple factors including (i) effect size estimates from related studies; (ii) anticipated increase in effect size by using CCTA to exclude non-obstructive CAD, (iii) potential for CON participants to receive catheterization in violation of the protocol; and (iv) the investigators' assessment of the minimum effect size needed to be impactful and clinically relevant. After careful consideration of these and other factors, the sample size was formulated to provide high power to detect a 15% relative reduction (i.e., from 20% to 17% at 4 years) in the 4-year rate of the primary composite endpoint for participants randomized to INV versus CON (See Table 5 footnote for other assumptions.) Recognizing that event rates and outcome differences in ISCHEMIA may differ somewhat from these assumptions, the required sample size was also calculated for several different plausible combinations of parameter values. The final sample size was chosen to provide adequate power, even if our current assumptions prove to be optimistic. Loss of power due to protocol non-adherence was reflected in the sample size analysis by computing power with a relatively modest assumed treatment effect (20% vs.17%). Ideally, with perfect protocol adherence, a larger treatment effect would be plausible. Although the study objectives are worded in terms of testing a hypothesis (i.e. that the INV strategy is superior), another important objective is to estimate the magnitude of difference in outcomes (to within an acceptable level of statistical precision), regardless of which strategy (if either) is proven superior. Thus, the study is powered for precise parameter estimation (i.e. narrow confidence intervals) as well as hypothesis testing power.

12.1.2 Summary of Power and Precision

As shown in Tables 5 and 6 below, the planned sample size of approximately 8,000 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 1.11 with probability 95% and will yield power ≥90% for comparing the primary composite endpoint across the two randomized groups assuming the 4-year cumulative rate of the primary composite endpoint is 20% in participants randomized to CON strategy and is less by a factor of 15% (i.e. is reduced from 20% to 17%) in participants randomized to INV

strategy. Power will be ≥80% if the 4-year event rate of the primary composite endpoint is reduced by 13% instead of 15%, still assuming the 4-year rate is 20% in the CON strategy. Thus we have excellent power even with a more conservative effect size projection. Finally, power will be ≥80% if the 4-year cumulative rate of the primary composite endpoint is 15% instead of 20% in the CON strategy group, and is reduced by a factor of 15% in the INV strategy group. Thus, we have excellent power even with a more conservative estimate of the incidence of the primary endpoint. Power and precision under other assumptions are summarized in Table 5 and Table 6 below.

Table 5.   Estimated Power as a Function of the Anticipated 4-Year Cumulative Event Rate in CON and the 4-Year Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Estimated Power		
Event %	Δ = 0.13	Δ = 0.15	Δ = 0.17
10%	48%	60%	72%
15%	67%	80%	89%
20%	82%	92%	97%
25%	92%	97%	99%
30%	97%	99%	≥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; 4000 participants per group; average follow-up 3.7 years; loss-to-follow-up 0.85% per year; survival times follow exponential distribution.

Table 6.   Range of Estimated Precision (Margin of Error) as a Function of the Anticipated 4-Year Cumulative Event Rate in CON and the 4-Year Cumulative Risk Reduction in INV (Δ)

CON anticipated 4-year event rate	Margin of Error (MOE)		
Event %	Δ = 0.13	Δ = 0.15	Δ = 0.17
10%	1.16	1.16	1.16
15%	1.13	1.13	1.13
20%	1.11	1.11	1.11
25%	1.10	1.10	1.10
30%	1.09	1.09	1.09

NOTE: MOE 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. See Table 5 for additional assumptions.

12.2   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.

12.2.1 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 (CV 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 $\alpha=0.05$. 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.

12.2.2 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 12.2.4 and 12.2.5. 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[57]; 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.

12.2.3 Contingency Plan For Insufficient Primary Endpoint Events

The projected event rate of 20% at 4 years for the primary composite endpoint in CON participants was based on multiple data sources including the COURAGE nuclear substudy and several stress imaging registries. 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 <u>unconditional</u> 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 CV 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.[58, 59] Additional details will be finalized in cooperation with the DSMB and recorded in the statistical analysis plan before the first unblinded interim analysis.

12.2.4 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.

12.2.5 Health Economics Analysis

The health economic analyses for ISCHEMIA will consist of two major parts, an empirical intention-to-treat cost comparison and a cost-effectiveness analysis. Primary statistical comparisons between the two treatment groups of empirical costs will be performed by intention-to-treat. The participants enrolled outside the United States will be excluded from the primary cost intention-to-treat analyses. Confidence limits around the observed cost differences will be constructed using bootstrap methods.

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.

12.2.6 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 14.1). 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 (cardiovascular 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[60] 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 α = 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.[61] 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.[62] 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.

13. DATA HANDLING AND RECORD KEEPING

13.1 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 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.

13.2 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.

13.3 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.

Images will be stripped of identifiers present within the DICOM header during the image upload process, by a vendor which will be responsible for image transfer and storage for this trial.

13.4 Training

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

13.5 Records Retention

Study records will be maintained by the site investigators for a period of six (6) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

13.6 Management of Economic and Quality of Life (EQOL) Data

The economic and quality of life studies will be fully integrated into the clinical trial and will be covered by the main trial Informed Consent Form. Interviewers will be blinded to the study group. Data processing, quality control, and analysis of EQOL data will be performed by the EQOLCCs. Although the EQOL computer network is not a regulated environment as are the clinical databases, EQOL follows the same network security protocols including password protection, expiring logons, and restricted access. Participant information records will be kept confidential in a separate, secured SQL Server database, and the participant's name will never be released. Even though the interviewers must be unblinded to participant identity in order to collect the EQOL data, unblinded information is locked with restricted access, and none of the electronic databases or analysis files include direct participant identifiers. The electronic databases have (coded) study identifiers. In addition to participant identifiers never being linked to the clinical database, they are never passed on to the sponsor or third party. The interviewers obtain an approved Duke University IRB required consent from the participant on the telephone before a questionnaire may be administered. All of the EQOL data are analyzed in aggregate with only coded study identifiers (no direct participant identifiers), and no individual data/participant identifier will ever be presented in any oral or written form. No name or other identifiable information ever appears on the data or reports about the study.

14. SAFETY MONITORING PLAN

14.1 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. 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.

14.2 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, except CCTA, are commonly performed for the patient population enrolled in the study, i.e., those with SIHD and at least moderate ischemia. The only procedure being done for study purposes is CCTA. Although CCTA has increasingly been used to evaluate the presence and extent of coronary artery disease, it is not considered standard of care when used in the testing sequence in the trial. 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:

CCTA Risks: The primary risk is an increased exposure to radiation from the CCTA scan. On average, the estimated total radiation dose from this study (one CCTA scan) will range from 4-8 mSv. In comparison, other estimated doses of medical radiation include: chest X-ray (0.05 mSv); invasive cardiac catheterization (5-7 mSv); PCI (10-16 mSv); nuclear stress test (12-30 mSv). In 1 year a person living at sea level is exposed to natural radiation of about 3 mSv, so the expected radiation dose from CCTA is around 1-3 times that amount.

Other known risks of CCTA include allergy. Participants with known contrast allergy will be premedicated and participants with prior anaphylaxis to contrast will not be included in the study. As noted above participants with eGFR 30-59 ml/min will not undergo CCTA to minimize risk from this procedure in the trial. Patients with eGFR<30 ml/min will be excluded. Beta blockade, which is routinely used during CCTA, may cause bradycardia, hypotension or

bronchospasm, and nitroglycerin can lower blood pressure and may cause headache. Participants will be monitored throughout the procedure for these effects and treated if necessary.

All females who are premenopausal must have a negative pregnancy test documented before undergoing the CCTA or being placed into either of the two study groups.

Cath/PCI/CABG Risks: Each of these procedures is commonly performed in clinical practice for patients who meet eligibility criteria for the study. 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 nephropathy 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 and atrial fibrillation. Risks of these procedures vary in likelihood based on the patient's risk profile.

Risk Lowering Measures:

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 14.1)

Benefits:

The ISCHEMIA trial results should provide evidence based data to support management of patients with SIHD.

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. It is hoped the knowledge gained will be of benefit to others with a similar medical condition in the future.

14.3   Safety Monitoring Objectives and Rationale

The main safety objectives in ISCHEMIA 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.

14.4　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.

14.5　Events to be Monitored

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

1. Complications of cardiovascular tests (e.g. CT coronary angiogram, 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:

CT coronary angiography:

1. Severe contrast reaction such as anaphylaxis
2. Hemodynamic instability, including symptomatic bradycardia or hypotension, due to the beta blockade or nitrates given for the CCTA scan acquisition
3. Acute bronchospasm due to the beta blockade given for the CCTA scan
4. Contrast induced nephropathy
5. Radiation dose exposure

In addition the incidence of finding significant LM stenosis ($\geq$50%) on cardiac catheterization not reported on CT coronary angiogram will be monitored and reported to the DSMB. Incidental findings on CCTA that are of clinical importance (e.g., aortic aneurysm or suspected neoplasm) will be reported to the site and the participant may be excluded from the study.

Cardiac catheterization and PCI:

1. Severe contrast reaction such as anaphylaxis
2. Periprocedural stroke
3. Emergency CABG
4. Contrast-induced nephropathy

5. 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

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 and blinded CCTA). 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 12.2.6).

15. ETHICAL CONSIDERATIONS

15.1 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.

15.2 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, including informed consent for any screening procedures conducted to establish participant eligibility for the study (e.g. CCTA). 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. CCTA and 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.

15.3 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. A separate IRB/IEC/REB waiver of consent may also be required for the screening survey, according to local regulations. 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.

15.4   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.

15.5   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.

16. STUDY ORGANIZATION

ISCHEMIA is sponsored by the US National Heart, Lung, and Blood Institute (NHLBI). The Clinical Coordinating Center (CCC), 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 Ischemia Imaging Coordinating Center (ICC) will organize and oversee the stress imaging core laboratories, coordinate and implement educational systems for sites and monitor site stress imaging performance. The Economics and Quality of Life Coordinating Center (EQOLCC) is responsible for the conduct of the quality of life and the economics and cost effectiveness portions of this study. The Computed Tomography Coronary Angiography Core Laboratory (CCTA CL) will interpret all CCTA scans and will provide technical support. 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.

Details of the Committees, their charge and membership may be found in the MOO. These Committees include Leadership, Executive and Steering Committees, optimal medical therapy and optimal revascularization committees, committee on recruitment of women and minorities, biorepository, statistics, ancillary studies and publications committees.

17. DATA ACCESS AND SHARING

The Publication Committee will authorize access to study data and biospecimens. Investigators must submit a proposal requesting approval to access ISCHEMIA trial data/specimens. The ISCHEMIA 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.

18. 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 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-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.

19. REFERENCE LIST

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