Detailed Summary of Protocol Changes and Rationale

Protocol Number:
ISCHEMIA Protocol Amendment, Version 2.0
Protocol Title:
International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

	Version Number	Version Date
Current Approved Protocol	1.0	Jan.18.2012
Amended Protocol	2.0	Jan.06.2014

General Changes:

Old Text:
All references to *"Stress Imaging"*

New Text:
"Ischemia testing"

Rationale for Change:
To permit the use of alternative testing modalities to assess ischemia without imaging such as exercise tolerance testing (ETT) to determine patient eligibility. Specifically, ETT with treadmill or bicycle ergometry will be included as qualifying stress test modalities to improve generalizability, as ETT is recommended by major national and international guidelines and is the prevailing local practice in many countries.

Specific Changes:
Section numbers are references to the amended protocol.

1. ***Section 2. Background and Rationale***
   New Text:
   Background section updated.

   Rationale for Change:
   Recent relevant additions to the literature such as the FAME 2 trial, STICH ischemia subset analysis, and COURAGE nuclear baseline study.

2. ***Section 3: Hypothesis***
   Deleted Section

   Rationale for Change:
   The trial primary aim states the objective of determining whether an invasive strategy is superior to an initial conservative strategy. The study hypothesis has been construed by some readers as implying a belief or expectation that this assertion is true. Because there is clinical equipoise among participating physicians as well as study leadership we believe that the primary aim as a statement of the trial objective is accurate and sufficient.

3. ***Section 3. Primary Aim***

New Text

PRIMARY AIM

The primary aim of the ISCHEMIA trial is to determine whether an initial invasive strategy of ~~routine early~~ cardiac catheterization and ~~followed by~~ optimal revascularization, if feasible, 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 failure of OMT. ~~refractory angina symptoms, acute coronary syndrome, acute ischemic heart failure, or resuscitated cardiac arrest~~.

Rationale for Change:

Clarification and simplification of the primary aim.

4. ***Section 4. Study Design***

New Text:

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~~ ischemia testing ~~imaging~~ will be randomized in a 1:1 fashion to the INV or CON strategies in the main trial. In addition, approximately 1,000 participants with advanced CKD (defined as eGFR <30 or on dialysis) and at least moderate ischemia on ischemia testing will be randomized in a 1:1 fashion to the INV or CON strategies in an optional CKD ancillary trial (see section 18). Additionally, other optional ancillary studies will be conducted (see section 19).

Rationale for Change:

Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

4.1 Study Flow

New Text:

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

Rationale for Change:

To clarify that pre-screening activities may occur in areas other than ischemia testing facilities; the process of screening at sites may vary. In addition, exercise testing will be included as a qualifying ischemia test modality as described above.

New Text:

CCTA step: ~~All p~~Participants with eGFR ≥60 ml/min will undergo a blinded CCTA unless they had visualization of the coronary arteries by CCTA or invasive angiography within 12 months with a stable subsequent clinical course, or unless CCTA is deemed clinically unnecessary by

the site based on an exception as indicated in the MOO and approved by the CCC. Such examples might include variation in eGFR calculation based on local lab policies, or local rules for performance of CCTA which vary from the study protocol. CCTA images will also be transferred electronically to the CCTA core lab for interpretation.

Rationale for Change:

CCTA is not required in clinically stable patients with coronary anatomy defined within 12 months since such patients are already known to have obstructive CAD without unprotected ≥50% left main disease. Flexibility in the protocol description for CCTA requirements is necessary to permit exceptions where applicable without compromising participant safety or integrity of the trial.

New Text:

~~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~~ Coronary ~~results of the~~ CCTA images will not be interpreted at the sites unless ~~the core lab determines the results reveal~~: 1) the participant is excluded due to CCTA findings, including ~~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. In the event of any of these exclusionary findings, the participant will not be eligible to continue in the study, and these results will be communicated to the site; 2) ~~of clinical importance, such as an aortic aneurysm or suspected neoplasm.~~ the participant is excluded from randomization for any other reason; 3) the participant undergoes protocol-assigned or non-protocol assigned catheterization and review of CCTA findings is desirable for planning of revascularization. ~~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.~~ Sites may interpret non-coronary CT images locally to evaluate for any non-coronary incidental findings; this review will be encouraged if the core lab identifies an incidental finding on CCTA which does not disqualify the patient, e.g., smaller lung nodules. A list of incidental findings for which the CCTA core lab routinely screens may be found in the MOO. All participants meeting CCTA eligibility criteria ~~(see section 6.5) will~~ should then be randomized to the INV or CON strategy via the IVRS/IXRS system.

Rationale for Change:

The revised language provides clarification as to when study CCTA results will be provided to a site, and when and how the study CCTA may be interpreted locally, specifically in reference to incidental findings. Sites are expected to obtain formal local clinical interpretation of the non-cardiac images of the study CCTA scans whenever incidental findings have been reported by the core lab and to act on those findings in accordance with local clinical judgment. This is not a change from the previous process. If a clinical report is generated for the chest interpretation, sites may wish to include a statement about coronary interpretation by the core lab. Sites are permitted to review the non-cardiac portions of all CCTA scans if this is consistent with local practice standards (i.e., if site requirements indicate that all incidental findings, even very low risk findings, must be reported). Coronary images are not to be reviewed in such cases, to maintain blinding.

The rationale for blinding coronary anatomy from CCTA is to prevent crossovers based on the knowledge of anatomy. However, this is not applicable for participants randomized to INV as they will undergo cardiac catheterization and anatomy will be known. It was also felt that knowledge of anatomy from CCTA in patients randomized to INV may permit more optimal revascularization for certain subsets such as those with chronic total occlusions. Therefore,

sites are permitted to review coronary anatomy to facilitate revascularization, when participants are assigned to INV or if a participant assigned to CON undergoes a non-protocol-assigned cardiac catheterization.

New Text:

Participants with known or a high likelihood of unprotected left main stenosis ≥50% will be excluded before randomization. The primary method to identify such patients is CCTA. Participants with eGFR ~~30-59~~ <60 ml/min will not undergo a CCTA due to the increased risk of developing contrast-induced nephropathy, unless the site investigator and participant's personal physician believe the benefits outweigh the risks. Some participants with eGFR ≥ 60 may not undergo CCTA (see section 5.5 and MOO). Local practices vary regarding calculation of eGFR and cut points of eGFR used for performance of CCTA. Participants ~~with eGFR 30-59 ml/min~~ who do not undergo CCTA 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.~~

Rationale for Change:

Since the CCTA helps exclude participants not appropriate for randomization, certain situations may arise that make a CCTA applicable despite low eGFR at the discretion of the PI and participant's personal physician (e.g., patients with borderline low eGFR). In addition, as described above, in other patients with eGFR ≥60 with recently defined coronary anatomy, the potential benefits of CCTA do not outweigh the risks. Flexibility in the protocol description for when CCTA is a required study procedure is necessary to provide exceptions where appropriate, with examples noted in the new text.

Revisions have been made such that all text is consistent with this language for review of incidental findings at sites and the noted flexibility in the protocol description for exceptions to CCTA where appropriate.

New Text:

Patients who qualify through exercise tolerance testing (ETT) alone without imaging (e.g. exercise treadmill and bicycle ergometer testing) will be required to be eligible for and to have a CCTA prior to randomization unless they meet a specified exception, e.g., patients who have had CCTA or invasive angiography within 12 months (see MOO for other exceptions).

Rationale for Change:

In addition to stress imaging, exercise testing without imaging will be included as a qualifying ischemia test modality to improve enrollment and generalizability of trial findings. Exercise testing has limited sensitivity and specificity for detection of obstructive CAD. In order to reduce false positive rates, these participants will be required to be eligible for and to undergo a CCTA to confirm that they have obstructive CAD, unless otherwise indicated in the MOO.

New Text:

Timing of Randomization: Participants determined to be eligible for randomization should be randomized within a target of 15 days of consent, and participants randomized to INV strategy should undergo catheterization within a target of 30 days after randomization, with optimal revascularization therapy (ORT) soon thereafter as appropriate.

Rationale for Change:
Point of reference added for clarification.

Figure 1. Study Flow Diagram
New Text:
Flow diagram updated.

Rationale for Change:
To incorporate ISCHEMIA-CKD ancillary trial in the study protocol, to include the possibility of alternative ischemia test modalities to determine patient eligibility, and to permit flexibility in the protocol description for exceptions to CCTA where appropriate.

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

Rationale for Change:
Study leadership, in coordination with the DSMB will perform ongoing monitoring of the randomization among different subgroups and may cap a particular subgroup to ensure proper representation of the SIHD population in the trial for generalizability of the trial results.

4.3. Inclusion/Exclusion Criteria
New Text:
Screening for inclusion/exclusion criteria will include assessment for ~~be conducted in two phases. First,~~ clinical and ischemia criteria at the local site, ability and willingness to provide ~~will be used to obtain~~ informed consent~~;~~ and ~~second, after informed consent is obtained but before randomization,~~ the need ~~criteria~~ for CCTA. ~~eligibility will be assessed. Stress imaging c~~Core labs will work with sites to ensure randomization of participants with at least moderate ischemia.

Rationale for Change:
Clarification of the language as the process of screening at sites may vary.

4.3.1. Criteria Prior to Informed Consent
Exclusion (pre informed consent)
New Text:
4. ~~Prior known coronary~~Coronary anatomy unsuitable for either PCI or CABG

Rationale for Change:
Clarification of the language.

New Text:
9. PCI ~~or CABG~~ within the previous 12 months

Rationale for Change:
A new exclusion of patients with prior CABG has been added (see exclusion #28), leading to this revision.

New Text:
10. Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time

Rationale for Change:

Patients with spontaneous intracranial hemorrhage are at increased risk of bleeding from dual antiplatelet therapy. However, this is not applicable to patients with other forms of remote intracranial hemorrhage such as trauma.

New Text:

11. History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause

Rationale for Change:

Patients with at least moderate ischemia and ventricular tachycardia (VT) are typically referred for cardiac catheterization and revascularization. The revised language clarifies that in patients where the VT was due to a transient reversible cause (such as electrolyte imbalance) and the cause has been corrected, these patients are still eligible for the trial.

New Text:

14. End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min (not an exclusion criterion for CKD ancillary trial, see CKD ancillary trial, section 18)

Rationale for Change:

Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

New Text:

15. Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial ~~within 5 years~~

Rationale for Change:

The language incorporates the rapid growth of percutaneous valvular therapies as an alternative to surgical valvular therapies. In addition, the “within 5 years” restriction was lifted as patients can enter into the trial at various time points including close to trial completion when there would be a much shorter follow-up time than the 5 years stated in the old exclusion criterion.

New Text:

17. Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery)

Rationale for Change:

To qualify this exclusion criterion so that patients may be considered for the trial after planned surgery.

New Text:

18. Life expectancy less than ~~5 years~~the duration of the trial due to non-cardiovascular comorbidity

Rationale for Change:

Patients can enter into the trial at various time points including close to trial completion when there would be a much shorter follow-up time than the 5 years stated in the old exclusion criteria.

New Text:

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 (Those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core lab)

Rationale for Change:
Language clarification for the exclusion criteria to apply to all participants; those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core lab.

New Text:
24. Canadian Cardiovascular Society Class III angina of recent onset, OR angina of **any class** with a rapidly progressive or accelerating pattern

Rationale for Change:
This new exclusion criterion fills a gap in already existing angina exclusion criteria and provides clarification. New onset CCS Class III angina was associated with a higher rate of crossover from OMT to PCI in COURAGE. This criterion has been added to reduce the likelihood of crossover of CON subjects and the need for urgent revascularization soon after randomization in either assigned strategy.

New Text:
25. Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina

Rationale for Change:
The intent was to exclude these patients based on the two other angina exclusion criteria; this is to further clarify these criteria based on CCS class. These subjects will be excluded since the presence of CCS class IV, inability to perform any activities without angina, typically requires revascularization for relief of symptoms, and is therefore more likely to lead to cross-over after randomization if randomized to CON.

New Text:
26. High risk of bleeding which would contraindicate the use of dual antiplatelet therapy

Rationale for Change:
Since subjects randomized to the invasive arm who undergo PCI would require dual antiplatelet therapy, subjects who would not be able to receive this required therapy will be excluded. This was previously covered by an exclusion related to ICH and bleeding risk and has been separated for clarity.

New Text:
27. Cardiac transplant recipient

Rationale for Change:
Subjects status post cardiac transplantation are likely to have a different etiology for ischemia on stress testing (concentric transplant vasculopathy) which is not responsive to optimal medical therapy for SIHD, and thus their enrollment is not appropriate.

New Text:

28. Prior CABG, unless CABG was performed more than 12 months ago and coronary anatomy has been demonstrated to be suitable for PCI or CABG to accomplish complete revascularization of ischemic areas (CCC approval required)

Rationale for Change:
Many subjects with prior CABG who have been enrolled in the ISCHEMIA trial and randomized to the invasive arm have not undergone the intended revascularization due to unsuitable coronary anatomy, and the minority of patients who did undergo revascularization had largely incomplete revascularization for anatomic reasons. If this were to continue, this would dilute our ability to adequately test the primary study aim and hence the exclusion.

4.3.2. Criteria After Enrollment (Informed Consent) and Prior to Randomization
New Text:
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~~assessment of ischemia by the relevant ~~stress imaging~~ core lab and may undergo a blinded CCTA (if eGFR ≥60 ml/min or as per the MOO). Participants meeting the following exclusion criteria will not be randomized.

Rationale for Change:
To include the possibility of alternative ischemia test modalities to determine patient eligibility, and to permit flexibility in the protocol description for exceptions to CCTA where appropriate.

Exclusion (after informed consent and before randomization)
New Text:
3. Finding of "no obstructive coronary artery disease" (<50% stenosis) in all major epicardial vessels on CCTA (participants excluded from randomization for this reason will be considered for CIAO-ISCHEMIA ancillary study; see appendix B)

Rationale for Change:
To introduce the possibility of enrolling ISCHEMIA screen failures due to a finding of non-obstructive disease on CCTA in a proposed ancillary study CIAO-ISCHEMIA.

New Text:
5. Interval development of a clinical ~~exclusion criterion or~~event e.g., a primary or secondary endpoint event or interval development or discovery of an exclusion criterion

Rationale for Change:
To clarify why a participant may become ineligible prior to randomization.

5. Section 5. Study Procedures

5.1. Qualifying Ischemia Test

New Text:

~~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~~ test modality and the rationale for their selection are ~~listed~~described in ~~Table 1~~protocol appendix A.~~Stress~~ Ischemia tests documenting eligibility may be performed before or after medical therapy for SIHD has been initiated and adjusted. Similarly, participants already taking medical therapy for SIHD may have been on or off medications on the day of the ~~stress imaging study~~ischemia test documenting eligibility, consistent with customary clinical practice.[40, 41] A 24-hour, 7-day helpline will be available to sites for assistance with ascertainment of eligibility, enrollment, and adherence to protocol. Sites may send anonymized ischemia tests (images and/or ECG) for core lab verification before trial enrollment, as permissible by local IRBs/ECs and privacy boards.

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

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

Rationale for Change:

For symmetry, ischemia imaging criteria have been moved with the new ETT eligibility criteria to Appendix A in the protocol amendment. In the event that ETT criteria are revised as we gain experience with this test as a qualifying modality, we will minimize site regulatory work e.g., site IRB amendment approval can be followed by submission of the one page appendix A for IRB approval.

In addition, we added pre-enrollment core-lab verification of ischemia to reduce the number of screen failures based on insufficient ischemia, at the request of sites.

5.2. Informed Consent Process

New Text:

The study will be reviewed with the prospective study participant by the investigator or his/her designee. ~~The~~This discussion is a critical component of the consent process and the prospective study participant will be given adequate time for this discussion and to read the

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

Rationale for Change:
Added emphasis on the importance of the process of consent, not just the consent form, and study rationale, equipoise about the two treatment strategies, and variability in practice patterns as a means of full disclosure to participants.

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

Rationale for Change:
To clarify that the biorepository substudy is optional, and includes optional biomarker and genetic analysis.

5.4. Core Lab Ischemia Verification
New Text:
Ischemia ~~Stress imaging studies for all participants~~test data (e.g., images, ECG, reports) will be transferred electronically to the appropriate ~~stress imaging~~ core lab ~~following enrollment of the participant into the study~~for enrolled participants. The core labs will review and interpret the degree of ischemia. Sites will wait for verification of ischemia before CCTA (or, for patients who will not undergo CCTA, before randomization) unless the CCC permits an exception. ~~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.)~~

Rationale for Change:
Core lab verification of ischemia should occur before CCTA or randomization (if not undergoing CCTA), to avoid unnecessary CCTAs in patients who are not eligible for randomization and to avoid randomization of participants with insufficient ischemia. The CCC will grant exceptions under certain circumstances, such as to sites with excellent performance in ischemia interpretation.

5.5. Coronary Computed Tomography Angiography (CCTA)
New Text:
In general ~~C~~coronary computed tomography angiography (CCTA) will be performed in ~~all~~ participants with eGFR ≥60ml/min to identify and exclude participants with ~~obstructive~~ significant 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~~<60 ml/min will in general not undergo a CCTA due to the risk of developing contrast-induced nephropathy~~.~~ and trial eligibility will be based on physician determination of the likelihood of significant left main stenosis. 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~~.~~, where applicable. However, if a significant left main stenosis is suspected, these participants will not be enrolled into the study. There will be additional exceptions to eGFR-based determination of use of CCTA (see section 4.1 and the MOO). If local calculation of eGFR is different from the IXRS-generated eGFR, the site investigator must follow local practices regarding patient eligibility for CCTA (i.e., site may use local eGFR calculation to decide whether the participant is CCTA eligible or not). Participants qualifying via non-imaging exercise tolerance testing (ETT) will undergo CCTA prior to randomization unless they have a specified exception, e.g., patients who have had CCTA or invasive angiography within 12 months (see MOO for other exceptions).

Rationale for Change:
As above, this text has been changed to reflect exceptions to eGFR-based determination of CCTA performance and incorporation of exercise tolerance testing without imaging as an ischemia assessment modality. In addition, this provides flexibility in case the local laboratory calculation of eGFR differs from the study calculation.

New Text:
Radiation reduction techniques will be used. We will ~~prescribe~~ suggest standardized patient-specific image acquisition protocols that permit high quality CCTA with low dose radiation.

Rationale for Change:
To clarify that the patient-specific image acquisition protocols provided to sites are recommendations.

New Text:
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.~~ stenosis or incidental findings. 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.~~except as in section 4.1. ~~Participants with incidental findings of clinical importance, such as aortic aneurysm or suspected neoplasm; see MOO for details), will not be randomized~~ and tThe interpretation of the CT, including coronary anatomy, will be made available to the treating physicians for participants excluded based on CCTA findings (see section 4.1 and MOO for details). 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. The interpretation of these trial-specified incidental findings by the core lab will be made available to the treating physicians who are expected to request local clinical review and reporting of the incidental findings and to remain blinded to coronary findings (see MOO). ~~In such cases, treating physicians will be given access to and will be encouraged to review the CT images locally.~~

Rationale for Change:

Clarification of incidental findings review process; refer to earlier section to reduce potential for error.

New Text:
Participants meeting the clinical, ischemia, and CCTA eligibility (or physician judgment for participants ~~with eGFR 30-59 ml/min~~who will not undergo CCTA) 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).

Rationale for Change:
As above, this text has been changed to reflect exceptions to eGFR-based determination of CCTA requirement.

6. Section 6. Management Strategies

6.4. Optimal Revascularization Therapy (ORT)

New Text:

- Revascularization should be performed with a goal of relieving all areas of significant ischemia, i.e., ischemia that would be detected by non-invasive imaging or FFR.

Rationale for Change:
Optimal revascularization for the trial is based on relief of all areas of ischemia identified either by non-invasive imaging or by FFR.

6.5. Maximizing Adherence to CON Strategy

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

Rationale for Change:
To clarify that adherence to the treatment strategies is relevant only after randomization.

New Text:
Sites ~~must~~are instructed to call the 24-hour helpline when elective cath is being considered, and they must complete a checklist.

Rationale for Change:
Calling the 24-hour helpline is not a requirement prior to elective cath, rather it is a recommendation to ensure elective cath is appropriate.

7. Section 7. Auxiliary Screening Log and Survey

7.1. Screening Log

New Text:
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~~).~~) and intended management strategy for patients who are eligible but not enrolled, if known.

Rationale for Change:
To better understand the intended management strategy of moderate or severe ischemia of patients who are not randomized in the trial, if known.

8. **Section 8. Study Assessments**

8.2. Standard Blood Tests
New Text:
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~~the following should be obtained: ~~(~~complete blood count, lipid profile, and HbA1c ~~required (~~for diabetics only~~). but recommended for all participants).~~ Liver transaminases should only be obtained if not available before starting statin therapy. An attempt will be made to coordinate participant follow-up visits so that they occur close in time to routine follow-up visits with their physicians when routine blood tests are performed. At 6 month follow-up visits, if lipid tests (and HbA1c at annual visits for diabetics) are not available within specified time windows they will be obtained by the study coordinator or participants will be referred to their treating physicians for the tests. Creatinine values obtained clinically for participants with eGFR <60 at the three month follow-up visit and annually will also be recorded.

Rationale for Change:
Clarification added to reduce site burden and only collect tests that are clinically relevant. Creatinine values obtained clinically will also be reported for participants with eGFR <60 to monitor kidney function.

8.4. Blood Biomarkers and Genomics Biorepository
New Text:
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.~~analysis.

Rationale for Change:
Clarification that genetic analysis will be performed rather than genetic testing.

New Text:
At the time of randomization, up to a maximum of 49 mL of whole blood will be collected, which will be processed and stored as serum, plasma, RNA and, where allowable, DNA. At the 3 month follow-up visit, up to 49 mL of blood may be drawn. (If needed, specimen collection for genetic analysis may be collected at any point during the trial.)

Rationale for Change:
Clarification to indicate that specimen collection for genetic analysis may be collected at any point in the trial to provide more flexibility for the sites and participants.

8.8. Economics Assessment
New Text:

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.

Rationale for Change:
Economics data collection may not be required throughout the trial because the desired power may be achieved before the trial ends.

9. Section 9. Schedule of Assessments

Overview of Visits
New Text:
All participants will undergo eligibility screening, informed consent~~, CCTA (for all participants with eGFR ≥60 ml/min)~~ and randomization procedures.~~–~~ Participants will undergo CCTA according to criteria in section 5.5 and the MOO.

Rationale for Change:
To allow for flexibility around CCTA requirements as described above.

New Text:
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 no ~~n~~obstructive 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. All ~~P~~participants, including those ~~who are~~ excluded based on CCTA or ischemia~~stress~~ test findings will be asked to provide consent for future contact for research purposes.

Rationale for Change:
To clarify that participants excluded between enrollment and randomization (without restriction to specific categories) will be asked to provide consent for future contact for research purposes.

Quality of Life (QOL) and Economics Overview
New Text:
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. For the ISCHEMIA-CKD ancillary trial, only the Brief/Symptom/QOL questionnaire is required, the Full QOL questionnaire will not be collected.

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol where only a brief QOL questionnaire is required.

New Text:
The medical billing data will be obtained, extracted, data processed and analyzed by the EQOLCC (not applicable to the ISCHEMIA CKD ancillary trial).

Collection of economic and QOL data may be capped within any subgroup or overall if needed based on achieved power and operational needs.

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol. Additionally to clarify that economic and QOL data collected may be capped based on accruing power.

Table 2: Schedule of Study Assessments and Procedures
New Text:
Table 2 and footnotes updated

Rationale for Change:
To reduce site burden and only collect tests that are clinically relevant. Revised lipid guidelines do not recommend assessments at this particular time point.

Footnotes updated also to incorporate ISCHEMIA-CKD ancillary trial in the study protocol and to permit flexibility in the protocol description for exceptions to CCTA where appropriate.

See rationale for change below regarding clarification of biomarker collection pre- and post-invasive procedure.

Screening Visit:
New Text:

- Consented participants ~~with an eGFR ≥30ml/min~~ will receive a study ID number via IVRS/IXRS. These participants are considered "enrolled" (not randomized).

Rationale for Change:
Deletion of 'with an eGFR >=30 ml/min' for the incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

CCTA Visit:
New Text:

- For participants with eGFR ≥60ml/min and selected participants with lower eGFR, blinded CCTA will be performed (exceptions apply, see sections 4.1 and 5.5 and MOO)

Rationale for Change:
To include flexibility in the protocol description for exceptions to CCTA where appropriate.

New Text:

- Participants with eGFR ~~30-59~~ <60 ml/min do not require CCTA before randomization (exceptions apply, see sections 4.1 and 5.5 and MOO)

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

New Text:

- Participants excluded due to no obstructive CAD on CCTA will be considered for ~~an~~ CIAO-ISCHEMIA ancillary study at participating sites (see appendix B)

Rationale for Change:
To introduce the possibility of enrolling ISCHEMIA screen failures due to a finding of no ~~n-~~ obstructive disease on CCTA in a proposed ancillary study CIAO-ISCHEMIA

Randomization Visit
New Text:

- Full QOL assessment will be collected (prior to actual randomization)(not applicable to the ISCHEMIA-CKD ancillary trial)

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol where only a brief SAQ questionnaire is collected.

Cath and Revascularization for participants randomized to INV strategy
For participants undergoing PCI
New Text:

- Blood draw for both CK-MB and troponin before PCI, and at 8-16 ± 2 hours post-PCI or at hospital discharge, whichever comes earlier, whenever possible ~~(troponin to be measured if CK-MB not available)~~

Rationale for Change:
There is no consensus as to whether CK-MB or troponin is the best biomarker for the adjudication of procedural MI. The trial will adjudicate MI using various definitions and elements from various definitions (eg, Universal MI definition, ISCHEMIA trial MI definition, which has elements from the published SCAI MI definition); some of theseuse CK-MB and others troponin. The language clarifies the need to obtain both. In addition, the same biomarker thresholds post procedure may not be applicable for participants who have elevated biomarker level pre-procedure and hence the need to collect biomarkers before PCI.

For participants undergoing CABG
New Text:

- Blood draw for both CK-MB and troponin before CABG, and at 18 ± 6 hours post-CABG, whenever possible ~~(troponin to be measured if CK-MB not available)~~

Rationale for Change:
Since both assays for CK-MB and troponin are useful in adjudicating various MI definitions, we hope to capture all clinically relevant information to adjudicate potential events.

1.5 month (6 week) visit (Visit 1)
Deleted Text:

- ~~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.~~

Rationale for Change:
To reduce site burden and only collect tests that are clinically relevant. Revised lipid guidelines do not recommend assessments at this particular time point.

3 month visit (Visit 2)
New Text:

- Biorepository blood draw ~~will~~may be performed if additional funding is obtained

Rationale for Change:

Biorepository sample collection may only be performed at this time point if additional funding is obtained.

3 month visit (Visit 2), 12/24/36 month visits (Visits 4,6,8 respectively)
New Text:

- Full QOL assessment will be collected (not applicable to the ISCHEMIA-CKD ancillary trial)

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

New Text:

- 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. Creatinine values obtained clinically for participants with eGFR <60 will be recorded.

Rationale for Change:
Additional clarification added to reduce site burden and only collect tests that are clinically relevant, including creatinine values for participants with low eGFR.

6/18/30 month visits (Visits 3,5,7 respectively), Continuing Follow-up Visits (every 6 months following the 36 month visit until close out)
New Text:

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

Rationale for Change:
To reduce site burden and only collect tests that are clinically relevant.

Close out visit
New Text:

- Full QOL assessment will be collected (until 36 months) (not applicable to the ISCHEMIA-CKD ancillary trial)

Rationale for Change:
Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

10. **Section 10. Adjudication of Clinical Events**
New Text:
Endpoints to be adjudicated include death (including cause), myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke~~, and transient ischemic attack~~.

Rationale for Change:
TIA will not be one of the adjudicated events.

11. **Section 12. Data Handling and Record Keeping**

12.3. Data Confidentiality and Security

New Text:

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

Rationale for Change:

Reflects capability of image processing software. Sites which require that date of study be stripped from images before transfer are to remove the date of study manually before uploading.

12.5. Records Retention

New Text:

Study records will be maintained by the site investigators for a period of ~~six (6~~three (3) years following the expiration of the grant or length of time as required by local regulations, whichever is longer.

Rationale for Change:

Requirement for study record retention amended.

12. Section 13. Safety Monitoring Plan

13.2 Risks and Benefits

New Text:

As noted above participants with eGFR ~~30-59~~<60 ml/min will not undergo CCTA to minimize risk from this procedure in the trial, except as noted in sections 4.1, 5.5 and the MOO.~~Patients with eGFR<30 ml/min will be excluded.~~

Rationale for Change:

Incorporation of ISCHEMIA-CKD ancillary trial in study protocol.

New Text:

It is recognized that CCTA, as a 3-dimensional imaging modality, does not correlate perfectly with and may be more accurate for localization of a stenosis to a particular arterial segment than 2-dimensional invasive angiography. Therefore CCTA may rarely be interpreted as showing no significant left main stenosis when invasive angiography shows left main stenosis >50%.

Rationale for Change:

Since CCTA is not perfectly correlated with angiography, we include this disclaimer in the protocol. As suggested by the new text, it is possible for a stenosis truly located in the ostial left anterior descending coronary artery to appear on angiography to be located in the distal left main coronary artery. Furthermore, it is recognized that no imaging technology is perfect. Study leadership, in coordination with the DSMB, will monitor for participants who are randomized and subsequently found to have a ≥50% angiographic stenosis of the left main artery on invasive angiography.

13.5. Events to be Monitored

1. Complications of cardiovascular tests and therapeutic procedures CT coronary angiography

New Text:

4. Contrast induced nephropathy/dialysis

Rationale for Change:

To clarify that need for dialysis in patients not on dialysis will also be monitored.

New Text:

In addition the incidence of finding significant LM stenosis (≥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 according to the list specified in the MOO. ~~and~~ T~~t~~he participant may be excluded from the study based on certain incidental findings (e.g., large aortic aneurysm or neoplasm).

Rationale for Change:
Clarification on the report of incidental findings by the CCTA core lab which may preclude randomization**.**

Cardiac catheterization and PCI:
New Text:
4. Contrast-induced nephropathy/dialysis

Rationale for Change:
To clarify that need for dialysis in patients not on dialysis will also be monitored.

13. Section 14. Ethical Considerations

14.2. Informed Consent Process
New Text:
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).~~study CCTA.

Rationale for Change:
Also to clarify screening procedures preparatory for research, including sending anonymized ischemia testing data to core labs for verification that ischemia meets trial entry criteria before consenting patients for the study, where applicable.

14. Section 16. Data Access and Sharing
New Text:
The Publication Committee will authorize access to study data and biospecimens (in conjunction with the Biorepository Committee).

Rationale for Change:
To clarify that the Biorepository Committee will work in conjunction with the Publication Committee related to biospecimens.

15. Section 18. ISCHEMIA-CKD Ancillary Trial
New Text:
See section 18.

Rationale for Change:
Broadening the inclusion criteria of ISCHEMIA to permit enrollment of patients with eGFR <30 or on dialysis as part of the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches- Chronic Kidney Disease) ancillary trial.

16. Appendix A: Ischemia Test Eligibility Criteria
New Text:

~~Stress~~ Ischemia Test Eligibility Criteria

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

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

~~Imaging~~ Test Modality	Diagnostic criterion[3]
Nuclear perfusion via SPECT or PET[3]	≥10% myocardium ischemic
Echo[3]	≥3/16 segments with stress-induced severe hypokinesis or akinesis
CMR[3]	P~~p~~erfusion: ≥12% myocardium ischemic and/or W~~w~~all motion: • ≥3/16 segments with stress-induced severe hypokinesis or akinesis
Exercise Test without Imaging (Criteria 1-4 must all be met)	1. Clinical history of typical angina or typical angina during the exercise test 2. Absence of resting ST segment depression ≥1.0 mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.) 3. As compared to the baseline tracing, additional exercise-induced horizontal or downsloping ST segment depression ≥1.5 mm in 2 leads *or* ≥2.0 mm in any lead; ST segment elevation ≥1mm in a non-infarct territory. Both the J-point and the ST segment at 80 msec. need to meet criteria. When the HR is >130/min, the ST segment at 60 msec. may be used if the segment at 80 msec. cannot be determined. 4. Either of the following: a. Peak workload not to exceed completion of stage 2 of a standard Bruce protocol or <7 METS if a non-Bruce protocol is used *or* b. ST segment criteria are met at <75% of the maximum predicted HR

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

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

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

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

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

Rationale for Change:
As described above, ischemia imaging criteria have been moved with the new ETT eligibility criteria to Appendix A. In the event that ETT criteria are revised as we gain experience with this test as a qualifying modality, we will minimize site regulatory work e.g., site IRB amendment approval can be followed by submission of the one page appendix A for IRB approval.

17. Appendix B: CIAO-ISCHEMIA Ancillary Study

New Text:
See Appendix B in a separate protocol amendment document developed for ~75 sites

Rationale for Change: Optional ancillary study will be included as an appendix and will be limited to ~75 sites. Participants who are enrolled using stress echocardiography but are excluded from randomization due to no obstructive CAD on CCTA will be considered for inclusion at participating sites. By protocol they would then undergo assessment of symptoms at baseline and 1 year and repeat stress echocardiography at 1 year. This resubmitted ancillary study proposal is currently under review at the NIH; the initial proposal received a favorable score. This ancillary study is included here in order to avoid site burden of repeat protocol amendment in the near future.