ISCHEMIA
STATISTICAL ANALYSIS PLAN

August 14, 2018

Version 1.0 - Final

STATISICAL ANALYSIS PLAN VERSION AND AMMENDMENT TRACKING

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1.0	August 14, 2018

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan is to outline the types of analyses and data presentations that will be used to answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed. It describes the study's planned final analysis for presentation in the primary and selected secondary manuscripts, planned interim endpoint comparisons by treatment performed for the Data & Safety and Monitoring Board (DSMB), and various additional planned interim analyses performed for operational monitoring and quality assurance.

2. STUDY DESIGN

ISCHEMIA is an international comparative effectiveness study. Participants are recruited following clinically indicated stress testing and randomized in a 1:1 fashion to an invasive or conservative strategy.

3. STUDY OBJECTIVES

The primary aim of ISCHEMIA is to determine for participants with stable ischemic heart disease (SIHD) and at least moderate ischemia by non-invasive assessment whether an initial invasive (INV) strategy of cardiac catheterization and feasible optimal revascularization in addition to optimal medical therapy

(OMT) will reduce adverse cardiovascular events when compared with an initial conservative (CON) strategy of OMT alone with catheterization and revascularization reserved for failure of OMT.

The primary endpoint is the composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. This 5-item composite endpoint was the primary endpoint in the NHLBI grant application in 2010 but then was listed as a secondary endpoint in the original protocol. The primary endpoint in the original protocol was the 2-item composite of CV death or MI. The primary endpoint was changed back to the 5-item composite in June 2017 after following a protocol-defined process to re-estimate power based on blinded review of accumulating study data and finding that power for the original 2-item primary composite endpoint was lower than originally expected (see Section 11.5 and the SAP Appendix for Contingency Plan for Insufficient Primary Endpoint Events for details; this was done with approval of the Director of the NHLBI).

The incidence of the 2-item composite of CV death or MI will be compared between the INV and CON strategies and will be the major secondary analysis of the ISCHEMIA trial.

Other secondary objectives include comparing the incidence of the following between the INV and CON strategies:

1. Inclusion of stroke with other components of the primary and the major secondary endpoints to assess "Net Clinical Benefit" as follows:

    a. Cardiovascular events including CV death, non-fatal MI, and hospitalization for unstable angina, hospitalization for heart failure, resuscitated cardiac arrest or stroke

    b. CV death, non-fatal MI or stroke

2. Individual components of the primary composite endpoint

3. Stroke

4. All-cause death

Another secondary objective is to determine whether an INV strategy is more effective than a 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.

Finally, health resource utilization, cost, and cost-effectiveness will also be compared between the two randomized strategies. Separate Statistical Analysis Plans for secondary manuscripts will be developed for the analysis of disease-specific quality of life data.

4. SAMPLE SIZE CONSIDERATIONS

In designing ISCHEMIA, it was originally estimated that a study with 8,000 participants followed for an average of 3.7 years would have 90% power to detect a 15% relative reduction in the 4-year rate of the primary endpoint in participants randomized to an invasive strategy as compared with a conservative strategy, assuming a 4-year rate of the primary endpoint of 20% in the conservative strategy group. A

modest relative reduction was used in power calculations in light of ISCHEMIA's strategy trial design which includes participants without prior known anatomy and the expectation that not all participants in the target population will be suitable for revascularization or benefit equally from an invasive strategy. The modest between-group difference was also intended to account for attenuation of the treatment effect by non-adherence to the randomized treatment strategy. The between-group difference would be larger if a high adherence rate was expected. Participants in the conservative group who undergo catheterization for unacceptable angina despite maximal OMT are not considered non-adherent (because the conservative strategy includes performance of catheterization after OMT failure) but such catheterizations may reduce power for the primary endpoint if they, or the revascularizations that the catheterizations lead to, prevent the occurrence of primary endpoint events. Such attenuation was incorporated in sample size calculations by specifying a between-group difference that is smaller than it would be hypothetically if catheterization and revascularization was never performed in the conservative strategy.

Based on the trial's observed monthly randomization numbers, an analysis performed in August 2015 revealed that approximately 4,400 participants were projected to be randomized by the end of the trial's original planned enrollment period (October 2012 – June 2017). In response, the study's leadership proposed extending enrollment for 6 months beyond the original projected last enrollment date (from June 2017 to December 2017) and extending the follow-up period for 6 months beyond the original projected last follow-up date (from June 2018 to December 2018). Study leadership requested a reduction in sample size on the grounds that the original target of 8,000 was unlikely to be met and that the study would still be adequately powered albeit for a larger effect size. In August 2016, study leadership received permission from NHLBI to continue the study with a reduced sample size target of 5,000 randomized participants.

To ensure an adequate number of endpoint events for the primary analysis, the initial ISCHEMIA protocol (version 1.0 dated January 18, 2012) included a contingency plan to allow changing the primary endpoint from the 2-item to the 5-item endpoint after trial initiation by following a process with safeguards incorporated to protect against bias and inflation of the type-I error rate (see Section 11.5 and SAP Appendix for Contingency Plan for Insufficient Primary Endpoint Events for details). At various points in the trial, the primary endpoint event rate and statistical power were re-estimated using updated assumptions derived from blinded pooled analyses (not by treatment group) of the accumulating trial data. In May 2017, an independent panel was convened by NHLBI for the purpose of reviewing relevant blinded aggregate study data and power calculations and advising the NHLBI director and study leadership about possible design modifications. After reviewing updated power and precision estimates, the panel recommended reverting to the grant-funded 5-component primary endpoint and extending follow-up to the maximum duration feasible in order to increase power. The panel's recommendation was approved by NHLBI and study leadership in June 2017.

In February 2018, power was re-estimated for the study's revised primary endpoint (5-item composite) using updated event rate assumptions and assuming that participants would be followed until June 2019. The final sample size of 5,179 participants was estimated to provide 80% power to detect an 18.5% relative reduction in the 4-year rate of the 5-item primary composite endpoint. This sample size would also allow estimation of the hazard ratio to within a multiplicative margin of error of 1.17 with 0.95 confidence.

5. RANDOMIZATION METHODOLOGY

Enrollment and randomization is accomplished by contact with the interactive web/voice randomization system (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 or log into the IXRS to receive a participant identification number. At this point the participant is registered as enrolled. In order to randomize the participant, the study coordinator or investigator must call or log into the IXRS a second time. Participants meeting all clinical and site inclusion criteria are then randomized to either the INV or CON strategy and registered as randomized. Ischemia severity is determined by sites and is reported according to independent core laboratory review. Randomization information, including the randomized treatment assignment, is transmitted to the participant's electronic case book within the electronic data capture (EDC) system.

The original randomization scheme for ISCHEMIA was a permuted block design with stratification by enrolling site to balance the distribution of treatment assignments within the sites. The block sizes for each site were chosen at random to reduce the likelihood of an investigator predicting the next treatment group assignment. Beginning in March 2014, ISCHEMIA's randomization system was modified to facilitate enrollment of participants into the ISCHEMIA-CKD ancillary trial. The randomization lists that were originally generated for ISCHEMIA were subsequently used for randomizing both ISCHEMIA and ISCHEMIA-CKD participants together. Assigned participant identification numbers are different depending on whether the participant was enrolled in ISCHEMIA-CKD or the ISCHEMIA main trial. Details about distinguishing between ISCHEMIA-CKD and ISCHEMIA main trial participants can be found in the SAP Appendix for Definitions and Reporting Conventions.

6. PARTICIPANT POPULATIONS

All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention-to-treat"; that is, participants will be analyzed according to the treatment group to which participants were randomized, regardless of subsequent non-adherence to protocol. Participant populations of interest are described below.

6.1. Intention-to-treat population

The intention-to-treat (ITT) population will include all participants who receive a randomized treatment assignment, including those who are later determined not to meet trial eligibility criteria, unless the randomization was an unintentional administrative error, as determined by the Clinical Coordinating Center (CCC) in conjunction with the Statistical and Data Coordinating Center (SDCC) and National Heart, Lung, and Blood Institute (NHLBI) program officers. Of note, the ITT population will include participants who are randomized prior to or in absence of core-lab determination of ischemia regardless of subsequent core lab findings. Similarly, participants randomized prior to or in absence of a study CCTA will be included regardless of any subsequent determination of left main disease or no obstructive disease.

6.2. Protocol Version 2.0 population

The Protocol Version 2.0 population will include all randomized participants except for those with a documented violation of trial eligibility criteria and those with prior CABG enrolled under Protocol

Version 1.0. In general, determination of eligibility will be based on the version of the protocol under which the participant was randomized. Participants with prior CABG enrolled under Version 1.0 are excluded in order to better reflect the final Version 2.0 target population which excludes prior CABG participants unless their coronary anatomy is known to be suitable for PCI or repeat CABG. Unlike the ITT population, the Protocol Version 2.0 population will exclude participants accidentally randomized despite having left main disease or no obstructive disease on study CCTA. For determining eligibility, the presence of at least moderate ischemia will be based on the local site interpretation rather than the core lab interpretation. Presence of left main disease or no obstructive CAD and ejection fraction will be based on diagnostic procedures performed prior to randomization and will not include information obtained from protocol-assigned catheterization procedures or core lab reviews of left ventricular angiography.

6.3. Core-lab determined ischemia population

The core-lab determined ischemia population is a subset of the ITT population. It consists of participants determined by the core lab to have moderate or severe ischemia on a pre-randomization imaging stress test or severe ischemia on a pre-randomization non-imaging exercise tolerance test (ETT). Hereafter in this document, "moderate or severe ischemia" refers collectively to moderate or severe ischemia by stress imaging or severe ischemia by non-imaging ETT.

6.4. Procedure-based populations

Safety analyses will be performed in subgroups of participants for whom the safety issue is relevant. Thus, complications of protocol-assigned CCTA, catheterization, PCI, and CABG procedures will be evaluated in the subset of participants undergoing these procedures. Only procedure-related complications are systematically collected. Complications of adjunctive therapies such as dual anti-platelet therapy are not systematically collected.

7. DATA HANDLING

7.1. Sources of Data Used in Analyses

The data used for analysis will come from 4 main sources: the Interactive Web/Voice Response System (IXRS), the e-CRF, the clinical events committee (CEC) database, and the Clinical Trial Management System (CTMS) database. Data from the IXRS will be used to determine trial assignment (ISCHEMIA or ISCHEMIA-CKD) and treatment group. The e-CRF will be the source for site-level geographic information, all baseline and follow-up data, and will also contain data entered by the central core labs (CCTA, ECG, angiography, imaging). The CEC will provide adjudicated endpoints for primary analyses and auxiliary data, such as highest marker values associated with MI events, for secondary analyses. The CTMS database will provide site-level dates of site activation and deactivation. Primary analyses of outcomes by treatment will pool data from across all sites and will not stratify by site.

7.2. Methods for Handling Missing Data

Every effort will be made to obtain complete data. In the unlikely event that there is missing data, rules on how to handle the missing data will be used. These rules for how to handle the missing data will be discussed in appropriate places in the analysis plan below. Further details on how missing data will be handled can be found in the SAP Appendix for Definitions and Reporting Conventions.

In general, all available data will be included in data listings and tabulations. Population denominators will be displayed in column headers. Individual denominators will be displayed for each summary such that the amount of missing values will be evident. Participants who withdraw from the study or are lost to follow-up will still be included in the denominators for any proportions where data are available prior to study withdrawal or when the participant is lost to follow up.

8. ENROLLMENT SUMMARY

An enrollment summary will be provided by geographic region and country. Country information will be obtained from the clinical database. Countries will be grouped as follows:

Regions	Countries
North America	Canada, USA
Europe	Austria, Belgium, France, Germany, Hungary, Italy, Lithuania, Macedonia, Netherlands, Poland, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, United Kingdom.
Latin America	Argentina, Brazil, Mexico, Peru
Asia	China, India, Japan, Korea, Malaysia, Russia, Singapore, Taiwan, Thailand
Pacifica	Australia, New Zealand
Africa	Egypt, South Africa
Middle East	Israel, Saudi Arabia, United Arab Emirates

The total number of enrolled and randomized participants and enrolling sites will be tabulated by region, country and overall for review by the DSMB and study leadership.

9. BASELINE SUMMARIES

9.1. Definition and timing of baseline variables

For most summaries, the baseline value is the value given closest to the date and time of randomization. Weight, heart rate, and blood pressure are measured per protocol at the time of randomization or up to 30 days prior. Baseline laboratory assessments (lipids, HbA1c, liver enzymes, complete blood counts, chemistry panel) are based on the most recent lab results available within 6 months prior to the randomization or up to 2 weeks post randomization if pre-randomization laboratory results are unavailable. Age will be computed as the difference in years between the participant's date of birth and

randomization date. Body Mass Index (BMI) will be computed as weight (kg) / ((height (cm)/100)^2). Obesity will be defined as values of BMI 30 kg/m^2 or higher.

9.2. Demographics and clinical history

Baseline demographic and clinical characteristics will be tabulated by region and treatment group for the ITT population. The occurrence of incidental findings of clinical significance on study-related CCTA will be summarized overall and by type (ascending aortic dissection, descending aortic dissection, aortic aneurysm, large pleural effusion, pulmonary embolism, pulmonary mass, non-calcified pulmonary nodules ≥ 4mm, pulmonary infiltrate, pneumothorax, and moderate or large pericardial effusion).

9.3. Protocol-assigned catheterization in the INV group

Core-lab angiographic findings from the first post-randomization diagnostic catheterization procedure in participants assigned to INV will be summarized by the frequency distribution of the number of native vessels with at least 50% stenosis and the percentage of participants with at least 50% stenosis in specific locations (left anterior descending [LAD] disease, proximal LAD disease, circumflex disease, right coronary artery disease, left main disease). Summaries of native vessel stenosis will be presented for all participants and for the subset with no prior CABG. For participants with prior CABG, summaries will include the number vein or arterial grafts with ≥70% stenosis and the number of arterial grafts with at least ≥70% stenosis. Other scores summarizing the extent and/or severity of disease may be reported in supplemental analyses and reports.

10. ANALYSIS OF CLINICAL ENDPOINTS

10.1. CEC adjudication

CEC-adjudicated endpoints include CV death, myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke. Definitions of these endpoints are included in the CEC Charter.

Two versions of MI will be adjudicated in ISCHEMIA: a Primary Definition and Secondary Definition. Each definition includes a hierarchy of markers and threshold values as well as a set of rules for diagnosing MI when one or more key elements of the medical record are missing. The Primary Definition is based upon the Universal Definition of MI (UMI) [1] for Types 1, 2, and 3 MIs, but relies upon site-reported MI decision limits for troponin (which may or may not be the same as the manufacturer 99% upper reference limit (URL)). In contrast, for MI after PCI or CABG (Type 4a, 5), CK-MB is the preferred biomarker and takes precedence over troponin, and unlike the UMI, troponin is compared against the site-reported MI Decision Limit. The Secondary Definition is based closely on the UMI definition, but includes contingencies to allow diagnosing MI when various elements of the medical record are missing. Troponin is compared against the 99% URL from the assay manufacturer's package insert if known and against the laboratory-specific MI Decision Limit if the manufacturer 99th percentile is unknown. Additional supporting criteria (e.g. angiographic and ECG) are identical to the UMI definition for Type 4a MI. Analysis plans below refer to the Primary Definition unless otherwise specified.

Confirmed MI events will also be classified by the CEC as “complicated” or “not complicated” using criteria outlined in the CEC charter. The intent of the “complicated” designation is to identify a subset of MIs with features highly associated with poor prognosis. A complicated MI includes MIs occurring with serious complications such as hemodynamic instability, cardiogenic shock, a drop in ejection fraction greater than 10%, life-threatening ventricular arrhythmias, or acute heart failure.

For all confirmed MI events, the CEC will record highest marker values for Troponin I, Troponin T, CK, and CKMB when these markers are available. The laboratory-specific upper limit of normal (ULN) will be recorded for all types of markers and the manufacturer-specified upper reference limit (i.e. the 99th percentile; URL) will be recorded for Troponins only.

Confirmed MIs will be classified by the CEC using MI types provided by the UMI as follows:

- Type 1: Spontaneous MI
- Type 2: Secondary MI
- Type 3: Sudden Death MI
- Type 4a: MI related to PCI
- Type 4b: MI related to stent thrombosis
- Type 4c: MI related to stent restenosis
- Type 5: MI related to CABG

There will be some secondary analyses that will group together several MI types. There will be two resulting groups of MI types that will be analyzed. One group will correspond to procedural MIs and include Type 4a and 5 MIs. The other group will correspond to non-procedural MIs and include Type 1, 2, 4b and 4c MIs.

10.2. General

Statistical comparisons will be performed using two-sided significance tests and two-sided confidence intervals. Statistical comparisons of the two randomized groups with respect to primary and secondary clinical endpoints will be based on time-to-event analyses. In the time-to-event analyses, all available follow up information will be used. Recurrent events will be ignored in the primary analysis but will be analyzed in planned secondary manuscripts. Follow up will begin at the time of randomization and will be considered to be censored at the time of each participant’s last study visit for those participants not having an event of interest. The occurrence and timing of clinical endpoint events in the primary analysis will be based solely on CEC adjudicated endpoint data. Unless otherwise stated, references to the non-fatal myocardial infarction (MI) event will refer to the Primary MI Definition (see Section 10.1 for details).

10.3. Primary and secondary clinical endpoints

The primary endpoint of this study is the composite of CV death, non-fatal myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest as evaluated in the ITT population. The study's original protocol defined the primary endpoint as the composite of CV death or MI. The primary endpoint was reverted from the 2-item composite to the original grant peer-reviewed and current 5-item composite in June 2017 after following a protocol-defined process and receiving input from an NHLBI-convened independent Advisory Panel (see Section

11.5 and the SAP Appendix for Contingency Plan for Insufficient Primary Endpoint Events for details, with approval of the Director of the NHLBI).

Protocol-defined secondary endpoints are:

(a) Composite of cardiovascular death or non-fatal MI
(b) Angina control as measured by the Seattle Angina Questionnaire
(c) Disease-specific quality of life as measured by the Seattle Angina Questionnaire
(d) Composite of cardiovascular death, non-fatal MI or stroke
(e) All-cause death
(f) Cardiovascular death
(g) Myocardial infarction
(h) Resuscitated cardiac arrest
(i) Hospitalization for unstable angina
(j) Hospitalization for heart failure
(k) Stroke
(l) Composite of cardiovascular death, non-fatal MI, stroke, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest

Additional pre-specified secondary endpoints are:

(m) MI as determined by the CEC Charter's secondary MI definition
(n) Composite of cardiovascular death or complicated MI as defined in the CEC charter
(o) Complicated MI as defined in the CEC charter

Other endpoints for supportive analyses to aid interpretation of the trial's primary and secondary analyses include:

(p) Composite of all-cause death or nonfatal MI
(q) Composite of all-cause death, nonfatal MI, or stroke
(r) Composite of all-cause death, nonfatal MI, or hospitalization for resuscitated cardiac arrest, unstable angina or heart failure
(s) Composite of all-cause death, nonfatal MI, stroke, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest

For the analysis of MI and for composite endpoints that include MI as a component endpoint, analysis will be based primarily on the CEC Charter's primary MI definition and secondarily on the CEC Charter's secondary MI definition. Additional definitions of MI using criteria to categorize large infarctions are expected to be developed and reported in secondary manuscripts but are not included in the current statistical analysis plan.

10.4. Analysis of the primary endpoint

Time from randomization to the first occurrence of the primary endpoint will be compared between treatment groups using the statistical framework of Cox regression [2]. As described below in this section, estimation of event rates with 95% confidence intervals not assuming proportional hazards will be performed as an important secondary analysis. To preserve power and generalizability in the face of outcome heterogeneity due to variation across participants in important baseline variables [3-5], the Cox

model for each endpoint will be adjusted for a set of prognostically important baseline covariates, to include age, sex, estimated glomerular filtration rate (eGFR), ejection fraction, and diabetes, as detailed in Section 10.4.1 below. Ties in event times will be handled using Efron's approximation.

Multiple endpoint events in the same participant, such as a recurrent non-fatal event, will not be considered in the primary results analysis, but will be analyzed in planned secondary analyses.

The hazard ratio from the covariate-adjusted Cox model will be reported along with its two-sided 95% Wald-type confidence interval, and the associated p-value will be the primary measure of statistical significance. The half width of this confidence interval is expected to be 1.17 under the null hypothesis of identical covariate-specific time-to-event distributions. The critical value required for declaring endpoint differences to be statistically significant at the 0.05 level will depend on the exact timing of interim analyses, as described in Section 11.4 below.

In addition to Cox regression, cumulative endpoint event rates will be estimated as a function of follow-up time in each treatment group using Kalbfleisch & Prentice's nonparametric estimator of the cumulative incidence function (CIF) [6]. The Kalbfleisch & Prentice CIF estimator is equivalent to the Kaplan-Meier[7] estimator when applied to endpoints that are not subject to competing risks. It was selected for this study in order to account for the competing risk of non-cardiac deaths in the analysis of the primary endpoint and the occurrence of any type of death in the analysis of individual non-fatal endpoints. Cumulative endpoint event rates and differences in cumulative endpoint event rates for INV versus CON at yearly time points will be estimated and presented with 95% confidence intervals. These non-parametric analyses are important for descriptive purposes, to assess overall clinical impact, and will be a focus of interpretation if the event rate curves cross [8, 9]. These non-parametric analyses may also be used to construct summary measures of treatment effect which are interpretable when the proportional hazards assumption is violated. [9, 10]

In addition to comparing overall outcomes for the two randomized groups, we will perform additional analyses to assess whether the treatment effect varies according to pre-specified participant baseline characteristics, as described in Section 10.6 below.

Finally, as a sensitivity analysis, the analyses described in this section will be repeated in the Protocol Version 2.0 population and the core-lab ischemia population, as defined in Section 6.2 and 6.3 above.

10.4.1. Cox model for primary endpoint analysis.

As noted above, analysis of the primary endpoint will be adjusted for covariates and will be performed using the framework of Cox regression. Pre-specified covariates will consist of the following:

- Age
- Sex
- Estimated glomerular filtration rate (eGFR)
- Ejection fraction
- Diabetes

Covariates were selected on the basis of their established prognostic importance in other SIHD cohorts, highly complete data capture, and a sufficient range of values for risk to vary among participants meeting trial eligibility criteria. The following definitions and data handling conventions will be adopted:

- Age will be computed as the difference in years between the participant's date of birth and randomization date as collected in the IXRS. The date of birth is only entered in the e-CRF in the event that the date of birth information entered in the IXRS system at the time of enrollment is incorrect. If the IXRS system information is correct, then the date of birth as entered into the IXRS system at the time of enrollment will be used. Otherwise, the e-CRF entered date of birth will be used.
- Sex will be based on data collected in the DEMOGRAPHICS section of the e-CRF. In the unexpected event of missing data, the participant's sex will instead be obtained from information entered in the IXRS system at the time of enrollment.
- Estimated glomerular filtration rate (eGFR) will be calculated according to the 1999 Modification of Diet in Renal Disease (MDRD) formula using data captured in the DEMOGRAPHICS and MEDICAL HISTORY sections of the e-CRF. The formula is:
  $\text{eGFR} = 186.3 \times \text{SerumCr}^{-1.154} \times \text{age}^{-0.2013} \times 1.212(\text{if participant is black}) \times 0.742 \text{ (if female)}$
  where SerumCr denotes serum creatinine in mg/dL, and age denotes the participant's age in years. eGFR values will be obtained from information entered in the IXRS system at the time of enrollment or from data entered in baseline CRF's if the IXRS-entered value is unavailable.
- Ejection fraction will be based on the site-reported value if available and on the core-lab entered value if the site-reported value is unavailable. Because missing data was anticipated in the design phase, the e-CRF was structured to capture ejection fraction as a categorical variable in participants for whom the categorical value is known but the continuous value is unknown. Categorical ejection fraction data will be incorporated in a multiple imputation procedure in order to impute continuous ejection fraction values in participants with only categorical values entered.
- Diabetes will be modeled as a simple indicator (yes/no) and will be based on data collected in the DEMOGRAPHICS section of the e-CRF.

10.4.2. Modeling of continuous variables

To allow for non-linear covariate effects, the continuous variables of age, ejection fraction and eGFR will be modeled as restricted cubic splines with knots at the approximate 10th, 50th, and 90th percentiles of each variable's empirical distribution.

The proportionality assumption of the Cox model will be assessed by examining log-log survival plots and by adding a time-dependent covariate to the Cox model representing the interaction between treatment and time. If this interaction is large and statistically significant, then there is evidence of non-proportionality. In that case, a cautious interpretation of the Cox model hazard ratio will be encouraged, and non-parametric event rate estimates will be emphasized.

10.4.3. Missing data

Prior to selecting model covariates, participant baseline characteristics captured in the e-CRF were individually discussed by study investigators from the standpoint of prognostic significance and data

quality. With the exception of diabetes, covariates appearing in the model are required to be assessed by study coordinators for the purpose of determining trial eligibility and are therefore expected to be 100% complete on all participants. For example, participants cannot be randomized by the IXRS until after entering the participant's age and creatinine in the IXRS system. Missing, out-of-range, or illogical values will be identified by the SDCC and will result in queries to ensure complete high-quality data.

For each covariate to be used in the primary analysis, the number of missing records projected by study leadership is 10 or fewer. To make full use of the available covariate data, missing baseline covariate data will be imputed using multiple imputation statistical techniques. These techniques will account for additional variation in the analyses due to the fact that some of the data are missing. The imputation will use chained equations and predictive mean matching. Further details on what multiple imputation techniques will be used to impute missing baseline covariate data are found in the SAP Appendix for Multiple Imputation of Primary Baseline Covariates. Any rules of how to handle missing data prior to imputation are found in the SAP Appendix for Definitions and Reporting Conventions.

10.4.4. Additional supportive analyses for the primary endpoint

To supplement the conventional significance testing and confidence interval approaches that will constitute the major analyses for the primary endpoint, we will provide additional perspective on the assessment of the treatment effect by re-estimating the primary covariate-adjusted Cox model in a Bayesian statistical framework [11, 12]. Using the Bayesian posterior distribution, we will calculate the posterior probability that the unknown covariate-adjusted hazard ratio exceeds thresholds of 1.0, 1.05, 1.10, 1.15, and 1.20 and reciprocals of those numbers. Because Bayesian inferences may be sensitive to the choice of prior distribution, sensitivity analyses will be performed and reported for a range of possible prior distributions. Additional details of the proposed Bayesian model and prior distributions are provided in the SAP Appendix for Bayesian Analysis of Primary Endpoint.

10.5. Consideration for the analysis of the core-lab ischemia population

In October 2014, operating procedures for ISCHEMIA were modified to remove the requirement for pre-randomization core-lab determination of ischemia severity for most sites. The intent of this change was to simplify the work flow, increase the number of eligible participants, and improve site morale. It was determined that the imaging coordinating center would continue to interpret baseline stress tests for 100% of randomized participants, but the core-lab review may occur after randomization and would not determine a participant's eligibility. Under the new process, approximately 80% to 90% of randomized participants were projected to meet trial criteria by core lab interpretation.

- Primary analysis will be based on the ITT population which includes 100% of randomized participants.
- Analysis of the core-lab determined ischemia population will be a major secondary analysis.

Analysis of each of these cohorts is of interest for different reasons.

- Analysis of the ITT population is of particular relevance because real-world treatment decisions are based on local rather than core-lab interpretations of a patient's degree of ischemia. Except for possible administrative randomization errors, all participants in the ITT population will have moderate or severe ischemia by local site interpretation.

- The core-lab determined ischemia population is of particular interest because the efficacy of an invasive strategy as compared with a conservative strategy has never been tested in a large cohort of SIHD participants with core-lab determined moderate or severe ischemia. Theoretically, if the hypothesized benefit of an invasive strategy is concentrated in participants with moderate or severe ischemia, then the ITT treatment effect may be attenuated by unintentional inclusion of participants with mild or no ischemia.

Endpoint comparisons for the primary analysis will be repeated in the population of participants where the core-lab agreed that criteria for moderate or severe ischemia were met. As discussed in Section 10.6.3, results of the core-lab determined ischemia population will be stated in strict context by prioritizing the results of the ITT cohort and by noting the increased potential for a type-I error.

10.6. Analyses of heterogeneity of treatment effect (HTE)

Analyses of HTE will focus on estimating hazard ratios for INV versus CON as a function of participant baseline characteristics, as listed below. The list of primary baseline characteristics to use for the HTE analyses was intentionally limited to only a few variables in order to reduce the potential for spurious findings and to focus attention on variables that were most likely to interact with treatment based on prior literature and clinical experience.

10.6.1. Covariates for HTE analyses

<u>Pre-specified baseline covariates (primary interest)</u>

- Core-lab determination of moderate or severe ischemia on stress test
- Diabetes
- New onset or worsening angina within 3 months
- Participants who have a high level of medical therapy optimization at baseline, defined as participants with all of the following characteristics at baseline:
    - Systolic blood pressure < 140 mmHg (a secondary analysis will be completed incorporating a systolic blood pressure goal of < 130 mmHg)
    - LDL <70 mg/dL and on any statin
    - Not smoking
    - Taking aspirin

Another pre-specified baseline covariate of primary interest is the severity and extent of CAD as determined by core lab review of pre-randomization CCTA for those who have had that procedure completed.

<u>Other pre-specified baseline covariates of interest</u>

- Ejection fraction
- Estimated GFR

Ejection fraction and estimated GFR were not included in the list of pre-specified baseline covariates of primary interest due to the fact that it was anticipated that these covariates would have insufficient variation to be able to detect an appreciable difference in the treatment hazard ratios across the range of the covariates.

The following other baseline covariates are expected to be analyzed for descriptive purposes and completeness: age, sex, imaging modality (nuclear, echo, CMR, non-imaging ETT), prior MI, prior PCI, prior CABG, prior catheterization (≤12 months, >12 months, none), severity of angina as assessed by the SAQ and Canadian Cardiovascular Society (CCS) Class.

Another pre-specified baseline covariate of interest is the presence of anterior ischemia for those participants with adequate stress imaging from the baseline screening process. **As discussed in Section 10.5, analysis of participants with core-lab determination of moderate or severe ischemia is of particular scientific interest and will constitute a major pre-planned secondary analysis.**

10.6.2. Assessment of covariate-by-treatment interactions

For each baseline covariate listed above, the Cox model described in Section 10.4.1 will be augmented to include the covariate (if it is not already in the model) and the interaction between the covariate and treatment group. A treatment-by-covariate interaction test will be used to assess whether variation in the estimated treatment effect across levels of the covariate is consistent with chance. Continuous covariates will be modeled as restricted cubic splines with three knots, requiring two parameters per variable with one of the parameters being for the non-linear effect. For categorical covariates, category-specific hazard ratios will be estimated and reported with 95% confidence intervals. For continuous covariates, covariate-specific hazard ratios will be estimated across the range of the continuous covariate and plotted as a continuous function and/or tabulated for representative numerical values of the covariate along with pointwise 95% confidence intervals.

10.6.3. Multiplicity considerations for HTE analyses

Statistical reporting of HTE analyses will emphasize estimation over hypothesis testing and will make liberal use of confidence intervals and other measures of statistical uncertainty. To provide context for interpreting treatment group comparisons within subgroups, subgroup-specific estimates will be accompanied by formal interaction tests. Differences in statistical significance of treatment effect estimates across subgroups will not be interpreted as evidence of heterogeneity. Because interaction tests are expected to have low statistical power for detecting a difference, these tests will be reported mainly for the purpose of encouraging readers to take an appropriately cautious interpretation of observed differences across the subgroups.

As noted above, the subset analysis of participants with core-lab determination of sufficient ischemia is regarded as a major pre-planned secondary analysis. To ensure an appropriately cautious interpretation of results for this cohort, the following reporting guidelines have been agreed upon by study leadership:

- If the 95% confidence interval for the hazard ratio excludes 1.0 (or, equivalently, the p-value is less than 0.05), the results section of the primary manuscript (as well as methods and discussion) should report that this confidence interval or p-value was not adjusted for multiple comparisons. The result should not be described as being "statistically significant" and the methods section should not state a p-value that was considered to be "statistically significant".

If the primary analysis fails to detect a difference in outcomes between the two randomized groups, the main conclusion of the study's primary manuscript will reflect the lack of significance for the primary analysis. In this setting, if the 95% CI for the hazard ratio comparing the primary endpoint for INV versus

CON excludes 1.0 in the subset of participants with core-lab determined moderate or severe ischemia, this result may be referenced in the conclusion of the study's primary manuscript, but the wording will be strictly consistent with the hypothesis that the observed result may be attributable to sampling variation. An example of wording that was regarded as appropriate by study leadership was: "In a pre-planned secondary analysis of participants with core-lab determined moderate or severe ischemia, participants assigned to the invasive [or conservative] strategy had a lower rate of cardiovascular death or myocardial infarction."

10.7. Analysis of angina control and QOL

Plans for these endpoints are addressed in a separate SAP developed by the Economics and Quality of Life (EQOL) Coordinating Center.

10.8. Analysis of protocol-defined secondary clinical endpoints

For these secondary clinical endpoints, including the major secondary endpoint of CV death or MI, 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. Analysis of each secondary endpoint will be based on a covariate-adjusted Cox model with adjustment for variables specified in Section 10.4 above. For each secondary endpoint, non-parametric cumulative incidence estimates will be calculated by treatment group and reported with 95% confidence intervals. P-values for each secondary clinical endpoint will be individually calculated and reported without adjustment for multiple comparisons (see Section 10.12).

Just as what will be done for the analysis of primary clinical endpoints, multiple endpoint events in the same participant, such as a recurrent non-fatal event, will not be considered in the primary results analysis, but will be analyzed in planned secondary analyses.

10.9. Clinical endpoint data presentation

As described above, cumulative incidence estimates of endpoint probabilities will be displayed graphically and tabulated at yearly intervals following randomization along with two-sided 95% pointwise confidence intervals. In addition to these cumulative incidence estimates, the number of clinical endpoints by treatment group will also be presented. For MI, the number of CEC-confirmed endpoints will be reported overall, by UMI type (1, 2, 3, 4a, 4b, 4c, 5), and by presence/absence of the designation of "complicated MI", as defined in the CEC Charter, and "large MI". For these descriptive summaries, only the first MI event per participant will be counted. Not all of these analyses of MI data will be included in the primary manuscript.

10.10. Supportive analyses to quantify the size of MI's

To shed light on the size of MI's occurring in each treatment group, the distribution of CEC-determined highest marker elevation ratios (highest value divided by ULN as well as by the 99^{th} percentile) will be summarized for all CEC-confirmed MI events with non-missing CKMB or troponin values. Summaries will be stratified by treatment group, MI type, and whether or not there was a Q-wave infarction. Marker elevation will be summarized by marker type, assay type, and/or degree of assay sensitivity. The resulting summaries will be regarded as informal descriptive statistics and will not be considered a primary or secondary protocol analysis.

10.11. Supportive analyses to adjust for treatment non-adherence

Although the proposed primary analysis will be a standard ITT analysis, additional secondary analyses may be performed using inverse-probability-of-treatment weighting estimators to assess the causal effect of treatment assignment had all participants adhered to their assigned treatment strategy.[13-16] This type of inference will be of particular interest if the study fails to detect a difference between INV and CON, as the observed treatment effect may have been attenuated by frequent non-adherence to protocol. An assessment of the causal effect of treatment assignment will also be addressed through the analyses of the primary and secondary endpoints in the Protocol Version 2.0 population. Detailed plans for these supportive analyses may be developed after completion of the primary analysis if this topic is prioritized by the publications committee. Simple methods of adjusting for non-adherence to the randomized treatment strategy, such as censoring at the time of crossover, will not be used in this study as they are susceptible to bias [17, 18] and do not estimate a well-defined parameter of interest. [16]

10.12. Multiple comparisons

With the various primary and secondary endpoints, and multiple subgroup analyses, we recognize that there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one of the comparisons could be statistically "significant" by chance. Although the overall level of significance for the assessment of the primary composite endpoint will not be adjusted to account for the analysis of other important endpoints and subgroups, we will be appropriately conservative in the interpretation of these secondary analyses, taking into account the magnitude of observed differences, the robustness of statistical significance, and looking for consistency across endpoints and subgroups. It is important to emphasize that several of the secondary endpoints involve components of the primary endpoint, and therefore a major purpose in comparing the randomized groups with respect to these endpoints is to aid in the interpretation of any differences between groups observed in the primary endpoint. The actual p-value for each comparison will be reported to aid in the overall interpretation.

11. INTERIM ANALYSES

The primary objective of interim analyses is to ensure the safety of the participants enrolled in the trial and to 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 including potential geographic differences. Details of the study's major planned interim analyses are documented below.

11.1. Violations of inclusion/exclusion criteria

The number of participants with violations of the inclusion/exclusion criteria will be presented. Eligibility criteria not met will be identified directly from the RANDIE (randomization inclusion/exclusion criteria) panel of the e-CRF or will be identified indirectly based on site- and core-lab entered data from the enrollment and randomization visits.

11.2. Completion of follow-up visits

Visit pages will be monitored for late entry in the clinical trial data base by the SDCC data management process. Additional summaries of visit completion by treatment will include the ratio of completed visits to expected visits and the percentage of visits performed within the expected visit time window. These visit completion summaries will also be completed for the final analysis.

11.3. Adherence to assigned treatment strategy

11.3.1. Use of catheterization and revascularization in INV

The INV strategy mandates use of early catheterization within a target of 30 days after randomization and revascularization soon thereafter, if appropriate, based upon coronary anatomy and other clinical considerations. To assess adherence to these requirements, the distributions of time from randomization to catheterization and time from randomization to revascularization will be estimated using the cumulative incidence function method for competing risks data.[6] For this analysis, participant follow-up will be censored at the date of last study visit. Death prior to catheterization or revascularization will be regarded as a competing risk. The cumulative proportion of participants receiving catheterization and revascularization will be estimated at specific time intervals (e.g. 30 days post randomization) both overall and within subgroups (e.g. prior CABG). For participants not undergoing catheterization by the time of the six-week and 3 month visits, the site-reported reason for no catheterization will be tabulated based on CRF-defined categories (participant preference, physician preference, intercurrent illness, participant died, other, unknown). For participants with site-reported planned medical therapy following catheterization, the reason for planned medical therapy will be tabulated according to CRF-defined categories (no obstructive CAD, anatomy not suitable for any mode of revascularization, participant preference, other).

11.3.2. Non-use of discretionary catheterization and revascularization in CON

The CON strategy mandates non-use of catheterization or revascularization procedures except in the case of suspected acute events (acute coronary syndrome, resuscitated cardiac arrest, or acute ischemic heart failure) or unacceptable angina refractory to maximally tolerated medical therapy. Catheterization or revascularization performed for other reasons, such as physician or participant preference, is considered non-adherence. A pattern of frequent early discretionary catheterization or revascularization in CON participants, especially those without prior endpoint events, may attenuate the treatment effect and cloud the interpretation of the study's primary ITT analysis.

Two types of analyses will be performed for estimating the cumulative incidence of catheterization and revascularization in the CON group. The first type of analysis will ignore the occurrence and timing of clinical endpoint events. The second type of analysis will only consider catheterization and revascularization procedures performed before the participant's first primary clinical endpoint event. The latter analysis is of particular interest because procedures performed after the occurrence of a clinical endpoint event will not impact power or interpretation for analyses of that type of endpoint. Quantities to be estimated will include all or a subset of the following:

- Cumulative incidence of catheterization for any reason
    - All
    - Occurring before participant's first primary endpoint event
- Cumulative incidence of catheterization for a suspected acute event

    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of catheterization for site-reported OMT failure/refractory angina
    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of catheterization for any other reason (non-adherence)
    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of revascularization for any reason
    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of revascularization for a suspected acute event
    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of revascularization for site-reported OMT failure/refractory angina
    - All
    - Occurring before participant’s first primary endpoint event
- Cumulative incidence of revascularization for any other reason (non-adherence)
    - All
    - Occurring before participant’s first primary endpoint event

Incidence rates for each quantity listed above will be estimated using the cumulative incidence function method for competing risks data.[6] Participant follow-up will be censored at the last contact date or terminated after the participant’s death date, whichever occurs first. For estimating rates of catheterization and revascularization prior to endpoint events, occurrence of an endpoint event will be regarded as a competing risk. Reasons for catheterization will be based on the site-reported indication for the catheterization procedure as captured on the SITECATH1 form of the e-CRF. If one of the site-reported indications for the catheterization procedure includes MI, resuscitated cardiac arrest, or worsening or new onset heart failure, then the catheterization will be classified as “catheterization for a suspected acute event”. Otherwise, if one of the site-reported indications is “Failure of OMT/Refractory angina” then the catheterization will be classified as “catheterization for OMT failure/refractory angina”. Otherwise, if neither of the above conditions is met, the catheterization will be considered to be non-adherent to the CON strategy. Primary endpoints include MI, hospitalization for heart failure, hospitalization for unstable angina, and resuscitated cardiac arrest and will be based on best available data (i.e. adjudicated endpoints, if available, otherwise unadjudicated data will be used) while event adjudication is in progress. Endpoints occurring on the same day as catheterization or revascularization will be considered to occur before the catheterization or revascularization unless the endpoint was a PCI-related or CABG-related MI.

The main goal of the analyses described above is to monitor the frequency of transitions from the state of "no post-randomization catheterization" to "at least 1 post-randomization catheterization" in CON participants. Transitions occurring before the participant's first primary endpoint event are of particular concern because these have the potential to dilute power for the primary endpoint. Transitions occurring after a confirmed primary endpoint event will not dilute power because the endpoint is already counted.

Transitions occurring because of a suspected acute event or OMT failure may dilute power (because they occurred prior to a confirmed endpoint event) but are not violations of the CON strategy (because the strategy includes catheterizations performed in the case of a suspected acute event or OMT failure). Although these may dilute power, they do not necessarily reflect negatively on the study's conduct (because they are part of the treatment being studied).

An additional set of analyses will focus on estimating the underlying hazard rates of elective catheterization and elective revascularization in the CON group. The main goal is to shed light on the extent to which statistical power may be attenuated by catheterization or revascularization performed on a non-emergency basis in the CON group. Analysis will focus on estimating the underlying "intensity rates" of elective catheterization and revascularization (as opposed to the cumulative incidence function accounting for competing risks) because power calculations using multi-state models and accounting for treatment crossover typically require specification of such intensity rate parameters. Because the analysis focuses specifically on "elective catheterization" and "elective revascularization," and to avoid counting catheterizations and revascularizations that may be true endpoint events, follow-up for these analyses will be censored 7 days prior to the participant's first best-available composite endpoint event (death, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, resuscitated cardiac arrest). The intensity rates of elective catheterization and elective revascularization will be estimated parametrically under an exponential and/or Weibull model and non-parametrically using a Nelson-Aalen type estimator. Because interpretable summary measures derived from the Nelson-Aalen estimator require the strong and arguably implausible assumption that elective catheterization and revascularization are independent of censoring and death, they will be regarded as informal and exploratory, and will be presented in the context of their inherent limitations.

11.4. Interim endpoint comparisons by treatment group

Interim analyses may occur when the adjudication of one or more events is in progress. Interim comparisons by treatment group will be performed primarily with only CEC adjudicated endpoint data and then repeated with best available data. Best available data will use the result of CEC adjudication if an event has been adjudicated. If an event has not been adjudicated, the site reported information for that event will be used.

Interim analyses by treatment group will be performed for three endpoints: all-cause mortality, the 2-item secondary composite endpoint consisting of cardiovascular death or MI, and the 5-item primary composite endpoint consisting of cardiovascular death, MI, or hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest.

Cox proportional hazard models with adjustment for baseline covariates (age, sex, ejection fraction, diabetes, eGFR) will be used for these interim analyses. Estimated 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 [19] will be used as a guide for interpreting these interim analyses. As specified in the protocol, monitoring boundaries for each endpoint will be based on a two-sided symmetric O'Brien-Fleming-type spending function with an overall two-sided significance level of $\alpha = 0.05$. The O'Brien-Fleming approach requires large critical values early in the study but relaxes (i.e., decreases) the critical value as the trial progresses. These

proposed monitoring boundaries are intended as a guide for interpreting the interim analyses and not as a rule for early termination.

On a DSMB teleconference on April 4, 2013, the DSMB formally resolved not to consider recommending early termination for efficacy until at least 50% of the expected number of events have accrued. Thus, they recommended that no alpha penalty should be incurred by early monitoring for safety. The DSMB further recommended that monitoring boundaries for subsequent examinations of unblinded data be computed using the Lan-DeMets alpha-spending approach with an O'Brien-Fleming-type alpha spending function.

In light of the April 4, 2013 DSMB recommendation, interim monitoring will be based on an alpha-spending function of the form

$$\alpha^*(\hat{t}_k) = \begin{cases} 0 & \text{if } \hat{t}_k < 1/2 \\ \alpha(\hat{t}_k) & \text{if } \hat{t}_k \geq 1/2 \end{cases}$$

where $\hat{t}_k$ denotes the estimated proportion of statistical information at the time of the k-th interim analysis and $\alpha(t) = \min\{2[1 - \Phi(Z_{\alpha/2}/\sqrt{t})], \alpha\}$ is the O'Brien-Fleming-type spending function with type-I error rate α, as defined in Lan and DeMets (1983). Critical values will be obtained based on integration of the multivariate normal distribution as implemented in R software with the gsDesign package Version 2.8-8 or later. Calculations of monitoring boundaries require an estimate of the variance of the treatment group coefficient (log hazard ratio) at each interim analysis. This variance will be obtained from the inverse of the observed information matrix evaluated at the unrestricted maximum partial-likelihood estimate (not the constrained estimate under H0). Monitoring boundaries will control the type-I error rate for each monitored endpoint separately (not overall) at an overall two-sided significance level of $\alpha = 0.05$.

11.5. Contingency plan for insufficient primary endpoint events

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. As described in the ISCHEMIA protocol, an independent Advisory Panel, separate from the DSMB, will be convened for the purpose of reviewing aggregate event rate data and making a recommendation to the NHLBI Director. Members of the Advisory Panel will not have access to unblinded data by treatment group or other data that would bias their recommendation.[20, 21] Prior to convening the Advisory Panel, the final number of projected primary endpoint events will be estimated and unconditional power (i.e. based on aggregate event rate; not by treatment group) will be re-calculated.[22] The protocol states that a design modification (e.g. extend follow-up, change the primary endpoint, or follow an independent panel recommendation) will be considered if power is less than the originally targeted 90%.

The first analysis for monitoring and projecting the final aggregate number of CEC-confirmed primary endpoint events will begin approximately 3 years after the first participant is enrolled. Subsequent analyses will be timed to coincide with scheduled DSMB reports. DSMB members will be informed of these interim analysis results but will not participate in deliberations about changing the primary endpoint or extending follow-up. The analysis plan for this activity is as follows:

At each interim analysis, the final number of CEC-confirmed primary endpoint events will be projected under a range of possible study assumptions. Scenarios for projecting endpoint events will be based on combinations of the following factors:

1. Accrual rate. Accrual rate scenarios will be constructed by combining the current observed accrual rate up to the time of analysis with a range of possible future assumptions, to be determined by the SDCC in consultation with the CCC and NHLBI project office.
2. Primary endpoint event rate. Event rate scenarios will be based on statistical estimates derived from the current available endpoint data at the time of interim analysis. The time-to-event curve will be estimated non-parametrically over the range of available follow-up and parametrically (based on extrapolation) beyond the range of follow-up. For these analyses, the target of estimation will be the distribution of time to first occurrence of a CEC-confirmed primary endpoint event. The method of Cook and Kosorok [23] will be used to adjust for incomplete CEC adjudication at the time of analysis.
3. Date of termination of accrual.
4. Date of termination of follow-up.

Factors #3 and #4 will be varied for the purpose of exploring the potential impact of shortening or extending accrual and/or follow-up. The projected final number of CEC-confirmed primary endpoint events will be calculated using a Markov model strategy similar to Cook [22].

Results will be shared with members of study leadership (e.g., study Chair and Co-Chair, SDCC and CCC faculty, NHLBI project officers) who will deliberate internally about the need for extending follow-up or changing the primary endpoint as pre-specified in the study protocol. Only individuals who are blinded to outcomes by treatment group will participate in these deliberations. If study leadership feels that it may be beneficial to extend follow-up or change the primary endpoint, an independent panel will be convened by NHLBI for the purpose of advising the NHLBI director.

Changing the primary endpoint after trial initiation may be counterproductive if it diminishes the trial's perceived integrity or credibility. To minimize controversy, a decision about changing the primary endpoint will be targeted to occur before 75% of the projected total primary endpoint events have accrued. If feasible, extending follow-up will be preferred over switching from a relatively harder to softer primary composite endpoint.

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