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ISCHEMIA: Establishing the Primary Endpoint

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"Intelligence is the ability to adapt to change"

- Stephen William Hawking (1942 - 2018)

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) (NCT01471522) is a National Heart, Lung, and Blood Institute (NHLBI)-funded randomized comparative effectiveness trial testing the incremental value of an invasive strategy of cardiac catheterization and revascularization (if suitable) when added to optimal medical therapy in patients with at least moderate ischemia on stress testing and symptoms controllable with anti-anginal medication, as compared with an initial strategy of optimal medical therapy with cardiac catheterization reserved for failure of medical therapy. The trial successfully completed enrollment in January 2018 and is currently in the follow-up phase. Herein we provide the rationale for choosing the trial's primary and key secondary endpoints and the processes leading to their ultimate selection.

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Primary Endpoint Planning in ISCHEMIA

The ISCHEMIA grant application, funded by NHLBI in 2011, designated a 5-component primary endpoint consisting of cardiovascular death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.[1] The trial was designed to optimize precision around point estimates for important clinical outcomes, to inform shared decision-making between patients and clinicians guided by robust data on the risks and benefits of alternative therapies for a common condition. After the award, we sought and received approval from the study's data safety monitoring board (DSMB), which was charged with protocol review, and the NHLBI to change the primary endpoint to cardiovascular death or MI, with a contingency plan clearly articulated in the protocol before its final approval to switch back to the 5-component endpoint to retain power if an insufficient number of primary endpoint events accrued at a designated time point during the trial (before accrual of 75% of endpoint events). This contingency plan was developed to avoid a common pitfall of other trials, namely lower than projected power because of lower than projected event rates. An event-driven trial was considered as an alternative but was not possible because the duration of follow-up and thus costs would be uncertain. The plan to adopt the 5-component primary endpoint if aggregate, blinded accruing data demonstrated a lower than expected event rate (or total number of events) was finalized in 2011, approved by the DSMB and included in the original protocol version dated January 2012, before any patients were enrolled in the trial.

The projected 4-year primary endpoint event rate of 20% in the conservative strategy was based on multiple data sources, including the COURAGE nuclear sub-study[2] and several stress imaging registries. Although we believed that the projected rate was conservative, we recognized that precision around these estimates in the literature were wide, that the ISCHEMIA endpoint definitions were more stringent than in the studies from which estimates were derived, and that participants enrolled in clinical trials tend to have lower event rates, in part because of advances in medical therapy. In this regard it is not uncommon for large clinical trials to have lower than anticipated event rates, and any changes to the primary endpoint during the trial should be pre-specified, similar to what was done in ISCHEMIA.[3]

When and how was the contingency plan activated?

The contingency plan in the trial protocol, which has not changed since 2012, specified that that an NHLBI-appointed Advisory Panel, independent from the DSMB (as they would have access to unblinded data) would be convened by NHLBI (if needed) for the purpose of reviewing unconditional power estimates and making a recommendation to the NHLBI regarding the need for protocol modifications to preserve trial power. Members of this panel would not have access to unblinded data by treatment group or other data that might bias their recommendation.

Projections in 2015, using updated assumptions for the randomization rate, suggested that the initially planned 8,000 randomized participant sample size would not be reached, and concurrent accruing data suggested that the observed rate of inappropriate cardiac

catheterization in the conservative strategy arm was substantially lower than projected. A formal request to reduce the randomization target to 5,000 was accepted by NHLBI in 2016. The first analysis to project the final aggregate number of primary endpoint events was conducted in 2016, blinded to treatment group. Based on the pooled aggregate event rate at that time, in concert with revised recruitment projections, study leadership determined there was a need to discuss activation of the contingency plan with the Steering Committee and investigators. In 2016, the projected need to increase the power by extending follow-up and reverting to the 5-component endpoint as the primary endpoint was discussed at Steering Committee and Investigator meetings and communicated to participating sites.

The Independent Advisory Panel was convened by NHLBI in May 2017. Panel members were chosen based on their expertise in clinical trials and having had no role in the design or conduct of the ISCHEMIA Trial. The Independent Advisory Panel was presented with power and precision estimates for the 2-component and 5-component endpoints calculated using a range of assumptions about the extension of enrollment and follow-up[4] and incorporating event rate estimates derived from blinded review of the aggregate accruing study data.[5] The Independent Advisory Panel explicitly discussed the concern that the 5-component composite may be regarded as a "softer endpoint." After weighing these various options, the Independent Advisory Panel recommended to NHLBI and study leadership that the primary endpoint be reverted to the original 5-component composite endpoint, and that the 2-component composite endpoint be retained as a key secondary endpoint, in addition to extending follow-up. In June 2017, study leadership and NHLBI accepted the Panel's recommendation, which was communicated to the Steering Committee and Investigators at August and November 2017 in-person meetings and by e-mail to all participating sites.

Is the current primary endpoint clinically important?

The choice of a primary endpoint for a large clinical trial should be based on a variety of considerations including expected event rates, importance to patients, sensitivity to intervention, and susceptibility to bias in ascertainment and reporting. All-cause mortality is undoubtedly the most relevant, unbiased single endpoint. Unfortunately, the sample size required to detect a difference in all-cause mortality in the stable ischemic heart disease population receiving optimal medical therapy enrolled in ISCHEMIA would have been prohibitively high. Even though ISCHEMIA randomized 5179 participants, more than the sum of participants randomized in the COURAGE and BARI 2D trials, it was not adequately powered for a primary endpoint of all-cause mortality, which would have required a sample size of 11,656 patients (80% power for a 20% risk reduction. Power can be increased by extending the duration of follow-up, and we hope to be funded to execute the plan proposed in the protocol to extend duration of follow-up for several years after completion of the currently funded phase of the trial to assess all-cause mortality.

During the design of the trial, the study team had extensive discussions about which events were most relevant to add to cardiovascular death or MI for a composite endpoint. Unstable angina was selected because it is clinically relevant, has quality of life and economic impact, and because revascularization has the potential to reduce unstable angina by reducing the frequency and extent of ischemia. However, a clinical diagnosis of unstable angina is subject

to ascertainment and reporting bias by unblinded investigators and patients. Hence unstable angina was defined strictly (Table) and adjudicated centrally (see ascertainment bias mitigation measures below). Resuscitated cardiac arrest, defined as successful resuscitation for documented cardiac arrest, may be caused by severe ischemia; therefore, risk for this endpoint may be reduced by revascularization. Hospitalization for heart failure was chosen as a component of the primary endpoint because of its strong relationship with stable ischemic heart disease, its impact on subsequent mortality in other cardiovascular trials, and because of the pathophysiologic link between repeated ischemic or injury events and ischemic cardiomyopathy. Consequently, revascularization for extensive ischemia could theoretically prevent the development of heart failure.

While we recognize that some of these endpoints are not as “hard” as cardiovascular death or MI, unstable angina and heart failure hospitalization are valid and clinically important outcomes in a trial designed like ISCHEMIA for the following reasons:

1. Patients were randomized before cardiac catheterization. This is a critical design feature that distinguishes ISCHEMIA from COURAGE, BARI 2D, and FAME 2, in which participants were randomized with full knowledge of their coronary anatomy. During the design phase of the trial it was felt that knowledge of coronary anatomy could have led to exclusion of high risk subsets in these earlier trials. Moreover, knowledge of coronary anatomy can increase the risk of ascertainment bias among providers and patients, potentially increasing reported events and crossovers in participants randomized to a conservative strategy; although being masked to anatomy reduces the risk, it does not eliminate it.

2. Bias in the ascertainment of events is mitigated by carefully constructed data collection that focuses sites on endpoint events, screening of ECG and angiographic core laboratory data for possible events, including core lab reviewed routine two-year ECGs, site investigator and coordinator education about the importance of event reporting, use of triggers to complete an event form and provide source documents based on algorithms programmed to capture missed events (e.g., cardiac biomarker elevation; hospitalization for other reasons including chest pain, dyspnea, or pneumonia; and change in NYHA and or CCS class on consecutive study visits), request for information on potential events found during review of source documents. In addition, methods are employed to ensure reporting of hospitalizations, including periodic review of medical records by site coordinators, review of national, regional, or health insurance databases (where available), cross checking of US medical bills against reported hospitalizations and, at selected sites, monitoring visits with medical record review. The open label Occluded Artery Trial[6] also included hospitalization for heart failure in the primary endpoint and demonstrated no evidence of ascertainment bias, with no between group differences. During the conduct of ISCHEMIA, site variation in anticipated vs. observed event reporting has been reviewed. Sites with low reported event rates had additional monitoring (including on-site monitoring). No concerns have been identified thus far based on these efforts but this will continue to be carefully monitored.

3. Patients with high levels of angina at baseline, a main driver for treatment crossovers from a conservative strategy, were excluded from randomization, thereby limiting the potential effects of participants' residual biases about revascularization on the unstable angina endpoint.

4. Although not directly mitigating reporting bias, the ISCHEMIA definitions of these endpoints include objective criteria that are more stringent than the recent FDA panel recommendation.[7] For example, the Table compares the criteria for unstable angina hospitalization from FAME 2[8] with those of ISCHEMIA. The ISCHEMIA criteria not only require symptoms and hospitalization, but also objective ECG criteria that must be read and confirmed by the ECG core lab, and/or specific angiographic findings confirmed by the angiographic core lab. Events that do not have ECGs available for core lab review or do not show specified changes are not confirmed as unstable angina. Similarly, the definition of hospitalization for heart failure requires all of the following: hospitalization for symptoms and physical signs of heart failure and need for additional or intensified therapy for heart failure.

5. The endpoints are adjudicated centrally by a Clinical Events Committee blinded to assigned treatment strategy.

Reporting bias due to anxiety related to not receiving a "desired treatment" is a real phenomenon but is complex due to the nature of patients' symptoms and the wide range of patient preferences. Furthermore, the desired treatment may differ between patients and providers. For example, in the Occluded Artery Trial (OAT) trial, the most common reason for patient refusal to participate was preference for conservative management whereas physician refusals were mainly due to their bias towards invasive strategy.[9]

The endpoint cardiovascular death or MI is a key secondary endpoint for ISCHEMIA and remains of major importance to all stakeholders. Of note, based on aggregate accrued data, the trial is projected to have 80% power to detect a 20% reduction in the 2-component endpoint. However, only all-cause mortality is truly incontrovertible. Numerous definitions of MI are in widespread use (especially for procedure-related events), and ascertainment bias may affect the assessment of MI events. Such bias is minimized in ISCHEMIA by protocol-driven biomarker and ECG assessments, and rigorous use of pre-specified MI definitions by the CEC, with components of the MI definition requiring confirmation by the ECG and/or angiographic core labs.

As we stated in our letter to the Editor,[10] "The ISCHEMIA Trial has been conducted in accordance with the most rigorous clinical trial standards. The process described above to change the primary endpoint was deliberate and carefully considered, involving the trial Leadership Committee, Steering Committee, NLHBI program staff, statisticians, and independent experts; it took nearly a year of planning. As leaders of this NHLBI-funded trial, we take seriously the humbling responsibility granted to us to conduct this trial, and we are confident that the wealth of trial data, the rigor with which it is collected, and our careful adherence to standards in the conduct of clinical trials will substantially advance our

knowledge about the management of patients with stable ischemic heart disease and at least moderate ischemia.”

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Table

Definition of hospitalization for unstable angina in FAME 2 and in ISCHEMIA

FAME 2	ISCHEMIA
Unplanned hospitalization leading to a urgent revascularization procedure Patient is hospitalized unexpectedly because of persisting or increasing complaints of chest pain (with or without ST-T changes) AND a revascularization is performed within the same hospitalization	**Hospitalization for Unstable Angina** Prolonged ischemic symptoms at rest (usually ≥10 minutes in duration), or accelerating pattern of chest pain that occurs with a lower activity threshold (CCS class III or IV) considered to be myocardial ischemia upon final diagnosis resulting in an unscheduled visit to a healthcare facility resulting in an overnight stay generally within 24 hours of the most recent symptoms, cardiac biomarkers not meeting MI criteria, and at least one of the following: • New or worsening ST or T wave changes on resting ECG* (core laboratory assessed) • Angiographic evidence of a ruptured/ulcerated plaque, or thrombus in an epicardial coronary artery believed to be responsible for the ischemic symptoms/signs (core laboratory assessed). *ECG Criteria: ST segment shifts and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads, or new ST segment elevation ≥0.1mV in 2 contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers.