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

Protocol Addendum

September 22, 2016

This document is the required IRB/EC notification about ISCHEMIA protocol modifications.

Summary:

This document is an addendum to the ISCHEMIA protocol describing changes to:

1. Minimum and average duration of follow-up for randomized participants, and
2. Number of randomized participants planned for ISCHEMIA and ISCHEMIA-CKD trials
3. The timeframe for serum creatinine measurement at enrollment for participants on dialysis

The ISCHEMIA Data Safety and Monitoring Board and NHLBI approved these changes. These changes will not have any effect on participant safety or the risk-to-benefit ratio of study participation.

Site IRBs/ECs should determine whether the sample size and minimum follow-up duration in the informed consent, if referenced, need to be changed. Any changes to the ISCHEMIA informed consent forms will require IRB/EC submission, review and approval. Sites are required to send copies of the IRB/EC approval letter and informed consent to the ISCHEMIA Clinical Coordinating Center when received.

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1. ***Minimum and average duration of follow-up for randomized participants***

   Based on the ISCHEMIA and ISCHEMIA-CKD trials' current observed randomization trajectory, enrollment and last follow-up dates will be extended beyond the original projected dates. Therefore, to achieve objectives within timelines allotted by the Sponsor, the minimum follow-up duration for randomized participants will be approximately 12-18 months (reduced from 18-24 months), with the average follow-up estimated to be approximately 3 years (reduced from 4 years).

2. ***Number of randomized participants projected for ISCHEMIA and ISCHEMIA-CKD trials, modified to achieve the trials' objectives within timelines allotted by the Sponsor, NHLBI.***

   2.1. ***For ISCHEMIA, approximately 5,000 to 6,000 participants are projected to be randomized; a reduction from the original planned 8,000 randomized participants.***

   The original planned sample size of approximately 8,000 participants afforded robust power (over 90%) to detect a 15% reduction in the rate of the primary endpoint of cardiovascular (CV) death or myocardial infarction (MI). It was more than three times the size of all prior strategy trials of cardiac catheterization/prompt revascularization vs. medical therapy only in both stable ischemic heart disease and non-ST elevation acute coronary syndrome (ACS, different population from ISCHEMIA).

With a sample size of 5,000 participants followed for an average of 3 years (minimum of approximately 12 months), the trial will have ≥ 83% power to detect an 18% reduction (from 20% to 16.4%) in the 4-year rate of the primary composite endpoint in participants randomized to an invasive strategy (INV) as compared with a conservative strategy (CON), assuming a 4-year rate of the primary endpoint of 20% in the CON group. The true hazard ratio can be estimated to within a multiplicative margin of error of 1.15 with 0.95 confidence.

Based on the trial's current observed randomization trajectory, the sample size was reduced to achieve the enrollment objectives within timelines allotted by the Sponsor, while maintaining a high level of statistical precision and adequate power to achieve original objectives. The projections are estimates based on randomization rates. If these rates increase, the number of randomized participants may exceed 6000. As expected the number of ***enrolled*** patients exceeds the number randomized due to failure to confirm eligibility in all enrolled participants.

2.2. **ISCHEMIA-CKD ancillary trial, approximately 500 to 700 participants are projected to be randomized, a reduction from the original planned 1,000 participants.**

The original planned sample size of approximately 1,000 participants was designed to provide 80-95% power to compare the primary endpoint across the two randomized groups assuming the 4-year cumulative rate of the primary composite endpoint is 50%-70% in participants randomized to the CON strategy and is less by a factor of 15% to 19% (relative reduction) in participants randomized to the INV strategy.

Since the initial design, several sources of evidence reinforced the primary event rate assumed for the trial. Although none of the studies report the exact information needed for this trial, we have assumed a conservative death or MI event rate of 60% to 75%. Given the high risk of the CKD trial cohort, it is reasonable to power for a larger relative risk reduction than our previous assumption.

With a final sample size of 500 participants, followed for an average of 3 years (minimum of approximately 18 months), the trial will have power of >81% for detecting a 23%-27% reduction in the 4-year rate of the primary endpoint, assuming a cumulative 4-year event rate of 60% to 75% in the CON group.

Based on the trial's current observed randomization trajectory, the sample size was reduced to achieve the enrollment objectives within timelines allotted by the Sponsor, while maintaining a high level of statistical precision and adequate power to achieve original objectives. The projections are estimates based on randomization rates. If these rates increase, the number of randomized participants may exceed 700. As expected the number of ***enrolled*** patients exceeds the number randomized due to failure to confirm eligibility in all enrolled participants.

3. ***The timeframe for serum creatinine measurement at enrollment for participants on dialysis***

The protocol requires serum creatinine measurement within 90 days prior to enrollment. This is to ensure that the renal function of enrolled participants is current. However, this is not applicable to participants who are already on dialysis, as serum creatinine is not needed in these participants for trial purposes.