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

Protocol Clarification Memo #3

November 05, 2014
for
ISCHEMIA Trial Protocol version 2.0, dated January 6, 2014

Summary of Clarification: This memorandum clarifies the Clinical Coordinating Center (CCC) exception to the process of stress core lab verification of ischemia. The majority of participating sites will be granted an exception to waiting for stress core lab confirmation before they perform cardiac computed tomography angiography (CCTA) and randomize participants that they determine to have at least moderate ischemia. This change will not have any effect on participant safety, the risk-to benefit ratio of study participation, or study informed consent forms.

Clarification Details

Section 5.4, Core Lab Verification of Ischemia states:
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.

Based upon accumulating trial experience, the CCC will allow exceptions as noted in the protocol text above for the majority of enrolling sites. The intended meaning of the term "exception" was to waive, on a site-by-site basis, the need to wait for core lab confirmation. It was not intended to mean that only a few selected sites would be granted permission to proceed without core lab confirmation. Sites will continue to upload stress test results for core lab review, core labs will continue to interpret stress tests, and CCTA core lab confirmation of eligibility will still be required prior to randomization of participants who undergo CCTA, as specified in the protocol. Sites will have the option to wait for stress core lab confirmation before CCTA or randomization (for patients who will not undergo CCTA) if they so choose.

Rationale

The following considerations resulted in this decision: 1) Most sites have demonstrated sufficient concordance with interpretation of stress tests by core labs; 2) The trial findings can be more readily applied to clinical practice based on use of local determination of the level of ischemia; and 3) The current workflow poses obstacles and burden to study staff and participants and has negatively impacted randomization rates. This will simplify participant workflow.

The possibility of implementing this simplification was anticipated when the protocol was written with the plan to base exceptions primarily on site performance in stress test interpretation. Exceptions already have been granted for a small number of sites to date. Sites will be notified by the CCC if they are granted an exception to waiting for core lab review, and will be notified as needed with any changes to this status.

The statistical analysis plan for the trial will include specifications for analysis of the subset of participants for whom the core lab agrees with the determination of moderate or severe ischemia. It will also include a plan for analysis of other subgroups of interest. The detailed analysis plan will be available for IRB review when finalized.

Implementation

IRB/EC approval of this Clarification Memorandum is not required by the sponsor prior to implementation; however, sites must submit this to memorandum to their IRBs/ECs for their information, or if required by the IRBs/ECs, for their approval prior to implementation.

All administrative corrections including grammatical corrections and clarifications will be incorporated into the next revision of the protocol.