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International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)

Protocol Guidance

December 03, 2018

The purpose of this guidance is to activate the **long-term follow-up** of participants currently randomized into the ISCHEMIA and ISCHEMIA-CKD trials. These trials will assess whether an initial invasive strategy (INV)—cardiac catheterization and revascularization for suitable participants plus optimal medical therapy (OMT)—reduces **long-term all-cause mortality** compared to a conservative strategy (CON) of OMT with cardiac catheterization reserved for failure of medical therapy, for stable ischemic heart disease (SIHD) participants with at least moderate ischemia on cardiac stress testing.

Per the Protocol version 1.0 Section 10/Protocol version 2.0 Section 9, Overview of Visits:

“Dependent on additional funding, telephone or email follow-up every 6 months or ascertainment of database information on vital status may continue after all clinic visits have been completed, unless prohibited by local regulations.”

The projected average follow-up of ISCHEMIA participants in the initial follow-up period contributing to the primary data set is approximately 3.5 years. Based on aggregate event rates, it is estimated that **an additional 5.5 years of participant follow-up after the last participant last study visit (LPLV) is likely to be needed for adequate power to detect a difference in all-cause mortality for INV vs. CON groups.** The long-term follow-up will assess whether there is a potential mortality benefit from an initial invasive strategy, whether or not there is a difference in the composite primary endpoint between randomized treatment groups. Therefore, participants' vital status will be collected for a minimum of 5.5 years after LPLV (initial follow-up period) and up to the number of years stated in the participants' consent form.

Participant accrual and all study procedures have been completed so this planned follow-up extension (already included in the IRB-approved protocol) poses no additional risk to the participants.

As indicated in the protocol, the follow-up will ascertain participants' **vital status** by either of the following methods, depending on local regulations, available databases, study staffing, and as described in participants' consent forms:

- 1) Communication with the participant every 6 months via telephone or email,
- 2) National/regional health or death database searches, or searches within other publicly accessible databases with vital status information

The follow-up contacts may be conducted by the staff of:

- (1) the site where the participant is currently followed,
- (2) the Clinical Coordinating Center (CCC) at New York University School of Medicine, or
- (3) a local/regional Research Organization or ISCHEMIA site that serves as a Coordinating Center.

At the discretion of CCC and with the agreement of all parties involved, the responsibility for follow-up contacts may be transferred to staff at another site if language barriers or other reasons prevent central follow-up by the NYU or local/regional CCC. All regulatory and privacy requirements will be met in such cases.

Participant last contact date, date of death, and cause of death (if available), and source of information will be collected and entered into a web-based electronic data capture (EDC) system.

The ISCHEMIA consent specifies that for up to 20 additional years after study visits are completed, or until funding for the study runs out, participants may continue to be contacted every 6 months and/or national health databases may be searched to determine participant vital status, depending on local regulations. If this language was not included in the consent used at your site, seek IRB/EC guidance on the easiest method to obtain permission from subjects for their continued participation such as through verbal permission at the time of their next follow-up. If no alternatives are available, participants will be asked to sign an IRB/EC approved ISCHEMIA Long-Term Follow-up consent or provide consent by phone or other electronic means, as allowed by the IRB/EC, and HIPAA authorization, if applicable.

Additionally, the ISCHEMIA consent also includes language allowing the transfer of PHI to a coordinating center for the purpose of this extended follow-up. If this language was not included in the consent, participants may be asked to sign an IRB/EC approved supplemental consent or provide consent by phone or other electronic means, as allowed by the IRB/EC, allowing the transfer of PHI.