3. Regulatory Binders
4. Study Reference Manual
5. All other personal/site files and documents related to the trial

18. Study Policies and Research Conduct

18.1 Protection of Human Subjects

Participating sites must maintain a human subjects protection program compliant with 45 CFR 46 and 21CFR 50 and 56 and with state, local or institutional requirements related to the protection of human subjects, an approved Assurance for human subjects research and an IRB registration number. Enrolling local institutions must also ensure the safe and appropriate performance of the research at its institution. This includes, but is not limited to, monitoring protocol compliance, managing any major protocol violations, managing any serious adverse events occurring at the institution, ensuring qualifications of research staff and providing a mechanism by which complaints about the research can be made by local study participants or others. Prior to enrolling subjects in SHINE, each site must submit documentation that the study has been approved by the local IRB, including locally approved informed consent forms.
Written, valid informed consent must be obtained from each SHINE participant as part of the subject enrollment process only after the investigator is satisfied that the participant understands the potential risks and benefits of participation in the study.

See also:
https://nett.umich.edu/sites/default/files/docs/sop_certification_for_protection_of_human_subjects_final01.pdf

18.2 The HIPAA Privacy Rule

Under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule, SHINE investigators are required by the Department of Health and Human Services (HHS) or the Food and Drug Administration (FDA) Protection of Human Subjects Regulations (45 CFR part 46 or 21 CFR parts 50 and 56, respectively) to take measures to protect personal health information (PHI) from inappropriate use or disclosure. PHI includes identifiable health information about subjects of clinical research gathered by a researcher who is a covered health care provider.

Compliance with HIPAA regulations is considered a local context issue and remains the purview of the local institution and local IRB. The HIPAA Privacy Rule is concerned with the risk to the subject's privacy associated with the use and disclosure of the subject's PHI, and permits researchers, as health care providers and therefore covered entities, to use or disclose PHI for research under certain circumstances and conditions, including if the subject of the PHI has granted specific written permission through an Authorization that satisfies section 164.508 and if the PHI has been de-identified in accordance with the standards set by the Privacy Rule at section 164.514(a)-(c) in which case, the health information is no longer PHI.

The individual SHINE IRBs will act as Privacy Boards (required by HIPAA) to review the use and disclosure of PHI and to determine whether subjects should sign a Subject Authorization for Release of PHI for Research in addition to the consent to participate in research, or if a Waiver of Authorization may be granted analogous to a Waiver of Consent under the Common Rule.

For a more detailed discussion of permitted uses or disclosures of PHI for clinical research under the Privacy Rule, refer to Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule; Research Repositories, Databases, and the HIPAA Privacy Rule; Institutional Review Boards and the HIPAA Privacy Rule; and Privacy Boards and the HIPAA Privacy

18.3 Protocol Amendments

Full protocol amendments are prepared to incorporate significant changes, those involving more than minimal impact on participant safety and risk-to-benefit ratio of participation in SHINE, and will result in the generation of a new protocol version with a new version number. When amendments are prepared, any prior protocol modifications specified in a contract or agreement are also incorporated into the amendment.

In accordance with 45 Code of Federal Regulations (CFR) 46.103(b) (4) (iii) and 21 CFR 56.108(a) (4), changes to the SHINE protocol or its related consent document must be approved by the IRB prior to implementation except where necessary to eliminate apparent immediate hazards to participants.

Once finalized by the NIH/DSMB, the amendment is distributed to all team members and participating study sites by the NETT-CCC Site Manager/staff. Sites must seek local IRB approval of the protocol and other associated documents for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted until after protocol approval is obtained. Participants enrolled in a study after approval of a protocol amendment must be consented to the study using the revised informed consent form associated with the amended version of the protocol.

For participants enrolled prior to approval and registration of an amendment, guidance on whether re-consenting is required (using the revised informed consent form associated with the amendment) will be provided by the CCC, typically in the summary of changes that accompanies the amended protocol.

Regardless of protocol team's recommendations, site IRBs may require re-consenting of previously enrolled participants; in such cases, IRB requirements must be followed.

18.4 Ancillary Studies

Proposals, budgets and personnel for ancillary studies will be reviewed by the Executive Committee. The committee will assure that all such studies are hypothesis driven, methodologically robust and contain complete and accurate data. Approval will follow the ancillary study approval process which defines the standard procedures for proposing, reviewing, and approving ancillary studies and/or sub-studies conducted within the trial.

Approval is conditional on the following:

1. Collaboration with the SHINE investigators and other SHINE ancillary study teams as necessary to support all the research being done under the auspices of the SHINE trial.
2. The use SHINE data and resources is permitted only for the agreed upon reasons. Additional use of SHINE data or resources requires additional review and approval by the SHINE executive team.
3. The ancillary study team must abide by all SHINE policies and procedures including the data sharing policies, publication policies.

4. No results that relate to the SHINE trial outcomes can be initiated until all outcomes are complete and validated in the study data set and approved for release to the ancillary teams by the SHINE executive committee and the SDMC.
5. Review and approval to publish or present SHINE data is required from the SHINE executive team. All publications must include at least 1 SHINE PI as well as the clause "for the SHINE investigators" in addition to an appendix of SHINE principal investigators (PIs) and coordinators. If the clause "for the SHINE investigators" is not allowed by the journal then the executive team should be considered for authorship and all SHINE PIs and coordinators must be listed in an appendix.
6. For ancillary studies that are funded, a representative from the ancillary study team is expected to participate on SHINE executive team meetings at least once monthly.
7. For ancillary studies that are funded, a representative from the ancillary study team must attend investigator meetings and all requested face to face meetings with the SHINE executive team.
8. The SHINE executive team and SHINE DSMB will monitor the execution of the ancillary study and reserve the right to alter the study should it impede the ability of the parent SHINE trial to succeed.
9. The conditions of this agreement should be included in applications for NIH or other funding.

Data will be controlled by the Executive Committee, which will review requests for access and specific analyses. Monitoring during the trial will be dictated by safety and scientific concerns rather than regulatory requirements. Publication of the results of these studies will be governed by the policies and procedures developed by the Executive Committee. Sites will not be required to participate in any ancillary study that requires additional data collection, but they will be encouraged to participate in accepted studies.

18.5 Publications and Presentations Policies and Procedures

The goal of the SHINE Trial Publications Policy is to provide guidelines for preparing, reviewing, submitting and maximizing productivity of high quality peer-reviewed publications. In addition to overseeing the performance of the trial, the Executive Committee is responsible for encouraging paper production, ensuring timely publication of data, maintaining a high standard for the quality of papers produced for SHINE, and determining appropriate authorship. When the Committee is discussing manuscripts associated with ancillary studies, the PI of the ancillary study and His/her designee will also join the Executive Committee for that discussion. Manuscript proposals will be submitted to the Executive Committee via a website based form at https://nett.umich.edu/clinical-trials/shine/data-analysis-publication-application-form. These proposals will include the type (primary, secondary, tertiary and quaternary), list of authors and their qualifications for authorship, a statement that no others deserving authorship have been omitted, the scientific rationale for the paper, the data needed and a description of the proposed analyses and any deadlines for submission of abstracts or presentation dates if applicable.

18.6 Data Sharing Policy and Procedures

Within one year of the primary publication or within two years of the last study visit of the last subject, a cleaned dataset and any supporting documentation required for the analysis of the data will be submitted to NINDS Office of Clinical Research.