as well as any additional information, suggestions, reminders, or advice that may be appropriate or necessary.

14.4 DSMB Reports

A NIH-NINDS appointed independent DSMB will monitor all aspects of safety in this trial. Interim reports containing summary tables describing patient enrollment, baseline characteristics of patients, safety information, losses to follow up, outcome information, data quality information and any other information requested related to data integrity, continued relevance of the research questions, or patient safety will be provided every 6 months or as requested to the DSMB. The DSMB will follow the guidelines as described in the National Institutes of Health (NIH) issued policy on data and safety monitoring. The DSMB may pause or halt the trial at any time based on data from this or other trials. The DSMB will meet twice yearly unless otherwise determined. The results of all DSMB meetings will be summarized to the study PI and forwarded to site study teams for IRB submission at the enrolling institutions.

14.5 Recruitment and Retention Reports

The SHINE trial procedures include standards for monitoring sites for recruitment/enrollment performance. At the request of the trial's Data Safety Monitoring Board, the SHINE recruitment team reviews enrollments and reports findings to the SHINE Executive Committee regularly. On a quarterly basis, all NETT hubs and SHINE Ancillary sites are provided with a site-specific recruitment report.

15. Site Recruitment, Training and Initiation

15.1 Site Start-Up and Initiation

Prior to the enrollment of the first subject, site initiation will occur. Site initiation will take place by telephone (Readiness Call) after the site is deemed "Regulatory Ready". Sites will not be allowed to enroll subjects until all regulatory documents are complete. All regulatory documents must remain current throughout the course of the trial. It is the responsibility of the hub and/or ancillary site to ensure regulatory compliance is maintained at the enrolling site/spoke. The NETT-CCC will routinely monitor the WebDCU™ SHINE database for regulatory compliance.

Regulatory documents specific to the SHINE trial include:

- Investigator's Agreement Form
- Documentation of Full Study IRB Application Submittal
- IRB approval of SHINE Protocol/Full Study IRB approval
- IRB Approved Informed Consent Form
- Institutional Federalwide Assurance (FWA)
- Human Subjects Protection Policy
- Electronic Delegation of Authority Log (eDOA)
- CLIA
- Current Medical/Professional license
- Current CV
- NIHSS Certification
- mRS Certification

- Human Subjects Training Certification or Waiver
- HIPAA Training Certification or Waiver
- SHINE Protocol Training Certification
- SHINE Data Training Certification
- SHINE Pharmacy Plan
- SHINE Recruitment Plan
- SHINE Nurse Inservice Sign-in Sheets

A description of each requirement and what needs to be uploaded into WebDCU™ SHINE (Regulatory Parameters Document) can be found on the WebDCU™ SHINE Regulatory database under Toolbox/Project Documents. Once these documents are uploaded into the WebDCU™ SHINE Regulatory database and accepted, a Readiness Call will be scheduled.

In preparation for the Readiness Call, each study team will be asked to complete a Readiness Checklist documenting regulatory readiness and study logistics; a checklist can be downloaded from the SHINE Website under Toolbox for sites to complete. The Readiness Checklist, Recruitment Plan and Pharmacy Plan will be reviewed during the readiness call..

Following the Readiness Call, a Readiness Report will be entered in WebDCU™ by the NETT-CCC. The NETT-CCC will activate the site to begin enrollment.

15.2 Training for Study Personnel

All training is located on the SHINE website (www.shinetrial.com). Study team members may be required to complete the following certifications:

- Modified Rankin Scale (mRS): Required for all study team members who will be completing this assessment.
- NIH Stroke Scale (NIHSS): Required for all study team members who will be completing this assessment.
- Database Training: Required for all study team members who will be entering data in WebDCU™.
- Randomization Database Training: Required for all study team members who will be randomizing subjects.
- Health Insurance Portability and Accountability Act (HIPAA): Required for all study team members. This may be taken at your own institution.
- Human Subjects Protection (HSP): Required for all study team members. This may be taken at your own institution.

Instructions to create an account to access and complete the SHINE trial trainings follow:

The training modules are located on the SHINE Education and Training page on the SHINE website. In order to access this page you will need to create a UM Friend Account. If you've already created one then follow the instructions below. If you have not created one please go to http://www.itcs.umich.edu/itcsdocs/s4316/#how to create an account.

Instructions to access SHINE Training and Resources:

1. Go to http://nett.umich.edu

2. Click on NETT LOGIN at the top of the homepage, and enter your UM Friend Account.

3. Click on the SHINE tile on the homepage, then the Education and Training link.

Once you've accessed the SHINE Education and Training page, click on the Regulatory Parameters Document at the top of the page. This will be your guide to what is required for each role in the study.

Certificates of completion should be saved electronically. The study personnel at the site responsible for regulatory document management will upload these certifications to the WebDCU™ SHINE. It is the responsibility of the site PI to train or update the personnel site study team members with regard to the SHINE protocol and trial procedures.

Study team members that will randomize subject and/or enter CRF data will require access to the SHINE database. To receive access to the SHINE database, study personnel must view the SHINE Data Training which is found on the SHINE trial website under 'SHINE Education and Training'. After viewing, the electronic Data Training Certificate must be completed and uploaded to the WebDCU™ SHINE database. Once uploaded, the CCC will approve the certification. Once approved, a Data Manager at SDMC will grant SHINE database permissions. When access has been granted, an email notification will be sent to each user, with a username and password.

15.3 Training for Site Clinical Personnel (Non-Study Team Members)

Site study investigators, coordinators and lead clinical nurses will attend SHINE Investigator Meetings as appropriate. Each site study team will then use a train-the-trainer approach to train site clinical nurses. Training content will include SHINE protocol and study procedures with a focus on GlucoStabilizer® and study laptops. In response to staff nurse turnover, there will need to be a continuous education plan at each site. There will not be any sponsor-required individual certifications required for the nurses caring for subjects. An informal review on the use of the study laptops should also take place between nursing shifts by trained personnel on an as needed basis.

Protocol Changes: Any protocol changes in the study impacting the GlucoStabilizer® or control treatment screen will mandate re-training. Such training will be planned as face-to-face training, but may also include on-line or other options as deemed appropriate by the PI based on the nature of the protocol change.

15.4 Training Investigator Meeting

Clinical site Principal Investigators and Study Coordinators will receive training in the protocol, trial procedures (e.g., assessments), CRF completion, WebDCU™ procedures, etc. at the SHINE Investigator Meeting, and at subsequent SHINE Investigator Meetings. At the meetings, SHINE investigators and personnel from the DCU will present training material on the current protocol, the Manual of Procedures, and use of the WebDCU™ data entry system (generally with a Power Point or comparable presentation or other forms and instructions, as necessary). A goal of these training sessions is to ensure that all clinical site personnel who are able to attend receive the same information; and with

regard to data collection, to try to standardize the methods of data collection to help ensure comparability of data across sites.

Specific elements of the Investigator Meeting include the following:

Protocol-Specific Training: Prior to the initiation of SHINE at any participating site, Principal Investigators, co-Investigators, Study Coordinators, and other study personnel will participate and complete the Protocol-Specific Training. The training includes protocol details, GlucoStabilizer® procedures, WebDCU™ procedures, and other forms and instructions as necessary. To promote adherence with the study protocol, aggressive training, reminders, and encouragement will be provided to each participating site. The CCC can mandate re-training or additional training as needed for specific sites based on site performance.

Study Laptop Training: Hands-on GlucoStabilizer® and control treatment screen training will be conducted during the Investigator Meeting. Each site will be provided a laptop to use at the meeting during the training. The laptop will be returned to the site for training other study team members and for use in the trial.

Data Training/WebDCU™: Primary Study Coordinators will be trained (train-the-trainer) in study procedures, subject enrollment, and data entry procedures at the SHINE Investigator Meeting. The goal of the training is to standardize the methods of data collection to help ensure comparability of data across sites. Once the Primary Study Coordinator has received his/her training, it is the responsibility of that person to train other site personnel as needed.

The SDMC will conduct data training via webcasts on an as needed basis for study personnel wishing to receive additional training. Additionally, the WebDCU™ User Manual (See Appendix 4), which contains step-by-step entry instructions, is also available online, and NETT-SDMC personnel are available during working hours to answer questions regarding data collection and entry.

15.5 Site Re-Training (Due to Lack of Subject Enrollments in 6 Months)

Trial-specific refresher training will be mandated for Hub Complexes and SHINE Ancillary sites that do not enroll a subject in the specified trial for six (6) consecutive months. Retraining will include:

1. Nursing Inservices for nursing staff or provide with a just-in-time nursing training plan.
2. Protocol training in the form of reviewing the protocol training video OR review the recruitment, protocol adherence quizzes and FAQs for investigators and study coordinators
3. Review of Data/Randomization Training Series by team member as appropriate to their role.
4. For sites participating in ISPOT study, review ISPOT blood collection and processing procedures and expiration dates for blue tops in their collection kits.
5. Ensure study laptop is updated and there are no internet connectivity issues.

Once the above are completed, upload the all training certifications and Hub PI attestation into the SHINE Regulatory Database. For more details regarding procedures, refer to the NETT SOP for Hub Performance Assessment or contact SHINE site manager.