16. Patient Recruitment and Retention

16.1 Recruitment

Recruitment is the dialogue which takes place between an investigator and a potential participant prior to the initiation of the consent process. It begins with the identification, targeting and enlistment of participants for the research study. It involves providing information to the potential participants and generating their interest in the proposed study. To successfully enroll patients into the trial, the study team must be able to explain in an enthusiastic, informative and convincing manner that the trial is something in which they would want to participate. Subject recruitment includes frequent collaboration with the hospital stroke team, radiologist(s), ED team and house staff as a primary referral mechanism. It is, however, important to have multiple recruitment strategies to reach all potential patients at all times. The site PI, coordinator, and study team will agree to a screening plan before initiating patient enrollment. Each site will provide a recruitment plan including estimates of volumes for patients to be screened and enrolled. Other strategies aimed at improving recruitment include identifying site-specific barriers by telephone or in person and the implementation of a recognition system for excellent recruitment, retention and data quality.

16.2 Retention

16.2.1 Retention and Study Participation

Before leaving the hospital, the coordinator will obtain multiple forms of contact information in order to avoid loss to follow-up.

The participant/LAR will be called at 6 weeks (+/- 14 days) to evaluate the participant's progress thus far. The coordinator will make every effort to begin making this contact early in the window of opportunity.

The 90-day post follow-up visit will include the mRS, NIHSS, BI, SSQOL, assessment of SAEs and unblinding questionnaires. The target for this visit will be (+/-) 14 days. Late data will be collected and analyzed for the 90 day visit with a window of (+30 days/-14 days) for the primary outcome. In the event that the study team cannot make contact with the participant/LAR, the mRS may be assessed using information provided by caregivers or other individuals with current knowledge of the patient's condition. Late data may be collected and analyzed for the 90 day visit with a window of (+90 days/-14 days) for secondary analyses. In the event that a subject is not lost to follow up but has missed the target for the primary analysis, it is recommended that the 90 day outcomes are captured whenever possible. SAEs will be captured from the time of randomization until the end of the study. End of study may be past 90days from randomization if the final study visit is conducted late however SAEs will not be captured past 120days from randomization or end of study, whichever occurs first.

16.2.2 Lost to Follow Up

A subject can be classified as lost to follow-up at the clinical site only when the study team has tried numerous ways to contact the subject and has been unsuccessful.

All attempts must be documented and include the following, but are not limited to:

- Repeated phone calls are made to the subject and documented on a log
- Contact is attempted with all individuals listed on the Patient Information page within the medical record

- A certified letter is sent to the subject's address, with a return envelope included, asking the subject if they wish to continue participation in the trial
- Contact is made with the subject's primary care physician and a message is left for the subject to contact the Coordinator
- The local appointment scheduler is consulted to determine when the subject is returning for a clinic visit and where they could be reached, even if the appointment is in a different specialty
- The use of the people locating service was considered (and used), as appropriate. The outcome of the search using the people locating service will be documented, if applicable.
- If all methods of contact have been attempted and are unsuccessful, the Coordinator should indicate that the subject is lost to follow up on the End of Study CRF.
- The site study team member(s) (PI/coordinator will be asked to present the case on a scheduled NETT Operations Committee call in order to adjudicate the case.

16.3 **Use of People Locating Service (OmniTrace)**

The SHINE trial has partnered with a licensed people search company, OmniTrace, to assist in locating contact information for subjects that are at risk of being lost to follow up. The service will serve to obtain current contact information (address, phone number) for participants who have become unable to be located. Only sites that have the Omnitrace language approved within their consent forms are able to use this service.

The SHINE trial recruitment team will work with enrolling sites to determine whether use of the locating service is warranted for subjects who cannot be located for completion of scheduled follow up. When a subject is not able to be located and the SHINE recruitment team determines use of the service is indicated, this information will be communicated to the site. The enrolling site will complete the Patient Information Form located in the SHINE Toolbox and provide directly to OmniTrace. OmniTrace will complete a search for updated contact information and will provide directly to the enrolling site.

OmniTrace maintains strict patient privacy guidelines and data security policies. The University of Virginia has a business agreement with OmniTrace and will pay OmniTrace directly for all completed searches. OmniTrace does not access patient medical records and does not electronically store patient data.

The Patient Information Form, OmniTrace FAQs, and an introductory memo are found in Appendix 12.

16.4 **Discontinuation of Study Participation**

The treatment period for the study is 72 hours or until discharged, whichever comes first. If discharge is clinically indicated, the treating team can stop study treatment before 72 hours. Subjects who are discharged prior to 72 hours are considered to have completed the study treatment and will be followed for the duration of the study. This is **not** considered discontinuation from participation and is distinct from discontinuation that is initiated by the subject/LAR or the treating or study team for safety reasons.

There are two categories of discontinuation of study participation: A subject can have the treatment protocol discontinued but remain in the study until completion of the 90-day follow up. Alternatively, the subject or LAR may withdraw informed consent and terminate all further participation in the study. Procedures on how to process and document these discontinuations follows.

A distinction will be made between subjects who fail to complete all visits on schedule or who miss some follow up assessments and the withdrawal of consent. Missed or rescheduled visits will be documented, but the subject will continue to be followed in the future according to protocol requirements.

16.4.1 Discontinuation of Study Participation

16.4.1.1 *Initiated by Subject or LAR*

As participation in the SHINE trial is voluntary, a subject or LAR can request that treatment be discontinued at any time. Study team members should attempt to understand the subject or LAR's reasons for desiring discontinuation. Further discussion with the subject/LAR about their concerns and the subject's treatment and treatment alternatives may enhance retention. Study team members should also discern whether the subject/LAR would like the treatment ceased or if they would like to withdraw informed consent. If a subject or LAR decides to discontinue study treatment but is willing to remain in the study, the reason for discontinuation should be documented in the research file and reported on the Study Treatment CRF (Form 15).

If a subject/LAR wishes to discontinue treatment unless they are unblinded to which treatment the subject is receiving, they may be unblinded. However, these requests must first be presented to the SHINE Study Hotline and may be minimized by thorough discussion by the study team of the rationale for blinding and the subject/LAR's specific concerns about the differences in treatment groups.

16.4.1.2 *Initiated by Treating Investigator or Treating Physician*

A treating investigator or treating physician may discontinue the study treatment if it is determined that continued participation is not in the subject's best interests. Prior to discontinuing for this reason, the treating investigator or treating physician is encouraged to contact the SHINE Study Hotline to discuss discontinuation with a SHINE study Principal Investigator. If a subject is discontinued for clinical or safety reasons, this should be clearly documented in the research file and reported on the Study Treatment CRF (Form 15).

16.4.1.3 *Discontinuation of Treatment for Other Reasons*

If treatment is discontinued for other reasons (e.g., death, discharge, subject is transferred to a floor where IV insulin cannot be given, etc.), it should be reported on the Study Treatment CRF (Form 15). Early discontinuation may also need to be reported as a protocol deviation and reported to the IRB.

16.4.2 Procedures for Withdrawal of Informed Consent

A subject or LAR may withdraw informed consent at any time, and will not be contacted for any further study data collection. However, any data already collected on the subject up to the point of withdrawal will continue to be used in the study. In

instances where a subject wishes to withdraw consent, the date and reason for consent withdrawal should be documented in the research file and documented on the End of Study CRF (Form 14). Additionally, if a subject withdraws consent during the treatment period, this should be documented on the Study Treatment CRF (Form 15). Subject data will be included in the analysis up to the date of the consent withdrawal. Notify the SHINE Study Hotline when a subject has withdrawn consent to participate in all trial activities by calling 800-915-7320 (ext 1).

If a subject/LAR wishes to withdraw consent unless they are unblinded to which treatment the subject is receiving, they may be unblinded. However, these requests may be minimized by thorough discussion by the study team of the rationale for blinding and the subject/LAR's specific concerns about the differences in treatment groups. Every measure should be taken to ensure that blinded study team members remain blind, even in the event the patient becomes unblinded.

16.4.2.1 ***Required Documents***

Subjects wishing to withdraw informed consent should provide written documentation of his or her withdrawal to the extent possible.

16.4.2.2 ***Procedures***

If a subject/LAR wishes to withdraw consent, the following procedure should be followed:

- Check for the development of adverse events.
- Complete the End-of-Study CRF (Form 14) and include an explanation of why the subject/LAR is withdrawing. If the subject is receiving study treatment, complete the Study Treatment CRF (Form 15), indicating that the subject has withdrawn consent.
- Subject or LAR will be asked to document in writing his or her desire to withdraw.

16.5 Milestones and Subject Payments to Clinical Sites

SHINE sites will receive milestone-based payments prior to enrollment of their first patient. A summary of these payments is provided below.

16.5.1 **Milestone**

MILESTONE 1

- Enter Hub, spoke(s) or ancillary site into WebDCU™, assigning the site to the SHINE trial
- If the site IRB requires review of the Informed Consent at this point, submit site-specific informed consent to the NETT CCC for review/approval (if not, see Milestone 2)
- Upload copy of above submission into WebDCU™ (document should be titled, "SHINE IRB Submittal")

MILESTONE 2

- Reconcile regulatory documents in WebDCU™
- Confirm that all contracts (site, investigational pharmacy, etc.) and required training are in place
- Complete site readiness call
- Upload IRB approval
- Obtain approval to begin subject enrollment

MILESTONE 3

- Continuation of enrollment at the Hub

16.5.2 Per Subject Payments

SHINE sites will receive two per-subject payments based on the schedule outlined below. In order to qualify for payment for an individual subject, all associated CRFs must be complete and query free to show as ready for payment. The site is then eligible to request payment by submitting an institutional acceptable invoice document to the subcontractor for payment. Figures provided represent "total payments", and thus include any Indirect Cost recovery.

Payment 1

Payment 1 is provided when the following criteria are met:

- Eligible subject is enrolled and completes initial study visit
- All data for eligible visit is entered into WebDCU™
- All queries are resolved for the visit
- Subject visit reads "Ready" in WebDCU™

Payment 2

Payment 2 is provided when the following criteria are met:

- Subject is not lost to follow up
- Eligible subject completes all required components of 3-month outcomes visit
- All required data for second visit is entered into WebDCU™
- All queries are resolved for the visit
- Subject visit reads "Ready" in WebDCU™

Contact Information for Milestones and Payments

For NETT Hubs and Spoke Sites:
All email correspondence regarding milestone payments should be sent to the SHINE study team at SHINE-milestone@umich.edu.

For SHINE Ancillary Sites:
All email correspondence regarding milestone payments should be sent to the SHINE Grants and Contracts Administrator: Emily Gray at shine_invoices@Virginia.EDU.

17. Close-Out and Termination Stages

17.1 Site Closeout

Site Closeout procedures will be distributed and coordinated by the NETT-CCC Site Manager to ensure regulatory compliance. Contact site manager with questions.

17.2 Retention of Study Records

Study records will be retained for a minimum of 5 years from the approval date of the sponsor's final study report in accordance with contract or grant stipulations or until you are otherwise notified by NIH. These include, but are not limited to:

1. Patient CRF binders and informed consent forms
2. Patient medical charts containing progress notes, laboratory reports, etc.