recruitment evaluation. See Appendix 8 for the Completion of Specific CRF Guidelines for instructions on completing the Screen Failure Log.

The Screen Failure Log will be maintained to document all patients considered for enrollment but not randomized to provide basic information on this population. This log will allow a better understanding of the population considered, the population enrolled and the reasons for ineligibility. See Appendix 2 for Screen Failure Log and decision tree tool.

3.6 Prohibited Therapy

No other diabetes treatment medications (i.e., oral agents, IV or subcutaneous insulin) besides the assigned protocol treatment will be allowed during the 72-hour treatment period because such medications would confound the study. The use of non FDA cleared devices for IA therapy is not allowed. Patients taking PO diets must eat protocol-specified diets as defined in Section 5.

4. Enrollment Procedures

Enrollment will be overseen by an enrolling investigator as designated on the site Delegation of Authority Log.

4.1 Obtaining Informed Consent

Consent will be obtained by either the Principal Investigator or by a designated member of the study team prior to performing any procedures solely for the purpose of research. In every case, alternative available treatments will be explained and it will be made clear that the patient is under no obligation to participate in any research project being offered. In obtaining and documenting informed consent, each investigator will comply with the applicable regulatory requirements and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent must be the IRB-approved version corresponding to the version of the protocol approved when the screening was initiated. The name of the study team member obtaining consent should be clearly documented, and this person should sign the informed consent document and provide the date of their signature and time as required per local site procedures.

Informed consent is to be obtained from the patient or patient's LAR. Eligibility of a person to serve as a subject's LAR is determined in accordance with local law at the study site. The consent document should include the subject's name, LAR's name and relation to the subject (if a LAR provides consent), as well as the date the consent was signed. This information should be completed by the subject or the LAR. The study team should not fill in the date the consent was signed for the subject or LAR.

Additional informed consent procedures may be required for ancillary studies.

HIPAA consent must be similarly obtained and documented in keeping with local institutional and IRB regulation for form format (i.e. contained in body of ICF or a separate document.)

Sites must follow local IRB procedures when consenting non-English speaking patients. The informed consent process should be clearly documented. This documentation may occur in the patient's medical record or research record. Templates for documenting the informed consent process are located on the SHINE website (www.SHINETrial.org) in the Study Toolbox. The patient or LAR must receive a copy of the signed consent form.

Signed ICF copies are typically filed in the clinical chart and are required to be stored in the secure study file and in accordance with local site regulations.

4.2 Sample Informed Consent

A sample informed consent document is located in Appendix 3.

4.3 Enrollment

Once eligibility criteria have been met and the informed consent procedure is complete the patient can then be randomized by accessing the trial web site (https://webdcu.musc.edu/). A patient who has completed the informed consent procedure and has been randomized is considered enrolled and must be followed until the end of the study per intention to treat (ITT) principles.

Enrollment in appropriate ancillary studies may also need to be considered.

4.3.1 Randomization by WebDCU™

The SDMC developed web-based randomization module will be used by all authorized Hub/Spoke and SHINE Ancillary sites to randomize eligible patients. The WebDCU™ subject randomization module automatically generates unique subject IDs without storing any personal identifying information.

Randomization is available 24/7 at https://webdcu.musc.edu/ . To randomize a patient, study site personnel will log onto the WebDCU™ SHINE™ web-based system using a unique username and confidential password. The user then confirms eligibility (based on the predetermined inclusion and exclusion criteria) by data entering and submitting the Eligibility (Form 00), NIHSS (Form 04) and Randomization (Form 07) forms into WebDCU™, with all eligibility criteria met.

Required information for the Eligibility form includes date of birth, date/time of symptom onset, date/time of arrival at enrolling hospital, inclusion and exclusion criteria. The admission blood glucose is the first finger stick POC glucose measurement. The most recent finger stick POC glucose at the time of randomization will be used to confirm eligibility. It is not necessary for study purposes to re-check glucose prior to randomization. Only finger stick POC glucose measurements (not serum laboratory glucose measurements) are used for randomization and all insulin dosing calculations.

The full NIHSS and the date/time of assessment must be entered on the NIHSS form. The third form that is required to randomize a subject is the Randomization form. This form includes fields to indicate whether IV tPA was initiated or ordered(y/n) and name of enrolling investigator, which should be an investigator who is listed on the delegation of authority log. The date/time of randomization will automatically be generated by WebDCU™. If all eligibility criteria are not met, randomization will be blocked.

After the Eligibility and Randomization form is submitted, a subject ID and treatment assignment will automatically be created in the WebDCU™ system. This is reported directly to the enrolling investigator via the web based screen.

In addition, an automatic e-mail notification of enrollment is sent to the appropriate parties (e.g., the SHINE leadership team). If, under rare

circumstances the web system is not available, use the emergency randomization hotline to obtain a randomization treatment assignment and subject ID (866-450-2016).

4.3.2 **Emergency Randomization Procedures**

In the event that WebDCU™ cannot be accessed (either by direct computer access, or if during normal business hours, by contacting DCU personnel), emergency randomization may occur.

Should a site have randomization questions during business hours, please contact Kavita Patel at pateka@musc.edu (843-876-1167) or Catherine Dillon at rileycp@musc.edu (843-876-1942) to request a treatment assignment and subject ID. If these parties are unavailable, please call DCU's emergency randomization hotline: 866-450-2016.

If a site has emergency randomization questions after hours or is unable to reach the DCU, the site should call the emergency randomization hotline (866-450-2016) to request the treatment assignment and subject ID.

4.4 **Successful Enrollment**

All NETT hubs and affiliate hubs (independent sites) were surveyed using a formal data-driven instrument or evaluated by a data driven formula to establish their individual annual recruitment estimates. Annual recruitment estimates are reviewed, discussed and amended during the readiness call. As recruitment trends have been established across all sites, adjustments have been made to the annual enrollment targets based upon site stroke volume, diabetes penetrance by geographic location, study team coverage and competing stroke trials. Sites are expected to meet and/or exceed their previous quarter's enrollment. For sites enrolling less than their established estimates, a collaborative process of developing new strategies for recruitment in a close working partnership with the recruitment team will take place. Appendix 9 includes details of the Site Recruitment Performance and Milestone Plan and Recruitment Milestones.

5. Study Treatment Procedures

5.1 **Treatment Procedures**

The study treatment time begins at the time of randomization. Treatment should be initiated as quickly as possible following randomization.

5.1.1 **Intervention and control group protocols**

Intervention Group
Study treatment: continuous IV insulin + subcutaneous meal insulin or saline injections **Target blood glucose**: 80-130 mg/dL