• Control Group
  o For any study patient in the control group who experiences 3 or more episodes of hypoglycemia (glucose concentration of < 70 mg/dL) in a 24 hour period, the SHINE Safety Hotline must be notified (800-915-7320 ext 2).
  o Also, at the 24 and 48 hour intervals, regardless of the previous two glucose measurements, do NOT advance to a higher level on the subcutaneous sliding scale.

10.1.6 Additional steps for severe hyperglycemia (Glucose concentration ≥ 500 mg/dL)

If a POC meter shows that the blood glucose is too high to provide an exact measurement (generally greater than 500-600 mg/dL depending on the meter) or the glucose reads ≥ 500 mg/dL

1. Draw a STAT laboratory serum glucose measurement
2. Call the SHINE Independent Safety Monitor (800-915-7320 ext 2).

11. Safety Monitoring
11.1 Safety Reporting
The Independent Safety Monitor and DSMB will receive periodic safety reports of all adverse events and serious adverse events. The DSMB will have the ability to review all serious AEs in real time. Statistical monitoring for safety will be limited to severe hypoglycemia (< 40 mg/dL) during the treatment period, death rate within 90 days post randomization and neurological worsening lasting > 24 hours and associated with blood glucose < 55 mg/dL. All adverse events and serious adverse events will be summarized by MedDRA code in terms of frequency of the event, number of subjects having the event, severity, and relatedness to the study treatment.

11.2 Safety Review Process
The project Site Manager (SM), Internal Quality and Safety Reviewer (IQSR), Independent Safety Monitor (ISM) and/or the designated backup personnel participate in the Safety Review process.

When an SAE occurs, the clinical research staff at the respective site enters the SAE into WebDCU™ via the AE case report form (CRF). The study site team will determine and enter: the seriousness, severity, the relatedness to the study protocol, action taken as a result of the SAE, the outcome and date of resolution (if applicable or known) and a narrative of the event. The submission of the CRF triggers an automatic e-mail that will be sent via the WebDCU™ system to the SM. This e-mail will alert the SM that an SAE has occurred, and the date and time will be included in this e-mail. The SM will access the event information within 48 hours via the password protected WebDCU™, reviewing the SAE for completeness of information. Once the SM determines that SAE has been properly entered and is ready for clinical review, this will be indicated in WebDCU™ which will prompt an automated email to be sent to the IQSR as a notification of the pending review. The IQSR will review the SAE within 48 hours for clinical accuracy and completeness in WebDCU™. When the IQSR completes the review process, an automatic e-mail notification will be triggered to the ISM. The ISM will access the event information, subsequently making a designation of causality, severity and
expectedness. This review must be completed and entered within 48 hours of notified. After 48 hours, WebDCU™ will close the review process. Should the ISM, IQSR or SM require changes and/or additional information about the SAE, a data clarification request will be entered alerting the site of the query. If additional information is required by a site in order to make a designation of causality and severity, the 2 day data entry deadline will be extended in order to gain the necessary information.

All AEs, regardless of seriousness, will be coded centrally via MedDRA. All AEs, regardless of seriousness, will be aggregated and provided via quarterly safety reports via the unblinded statistician to the ISM for review. These reports will present all SAEs and AEs by treatment arm as well as by treatment relation and severity. Relative risks with 95% confidence intervals will be reported for treatment related SAEs.

If any safety concerns arise, the ISM will report these concerns to the DSMB chair via the DSMB liaison.

11.3 Blinding
This is a single blinded trial with double blinded outcome assessments. Patients will remain blinded throughout the trial as they all will receive an IV infusion and SQ injections. The treating team (physicians/nurses) will be unblinded to treatment to assure appropriate patient safety. The outcome assessments will be performed by blinded investigators who did not participate in the acute care. The subjects will not be told of their actual treatment until the trial completion. The protocol adherence team monitors unblinding questionnaire responses in aggregate and by site.

The DSMB is partially unblinded for the closed reports. However, if it so wishes, it may be completely unblinded at any time during the trial. If the DSMB wishes to be unblinded on a particular subject only, the NINDS Liaison to the DSMB should email the request to the unblinded SDMC biostatistician.

At the time of the scheduled follow-up assessments, the blinded assessor and subject each complete the blinding assessment CRF.

11.4 Emergency Unblinding
No emergency unblinding is anticipated. Any emergency unblinding requests must be directed to the SHINE Study Hotline (800-915-7320).

12.1 Study Design
SHINE is a Phase III, randomized, single-blinded, controlled trial of approximately 1400 patients at approximately 60 US sites. The study is composed of two treatment groups:

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

**Control Group:** IV saline + subcutaneous sliding scale insulin (Target blood glucose: < 180 mg/dL)

Study drugs are NOT supplied by the sponsor. Study-specific accountability is not required. Sites must establish and adhere to pharmacy procedures for the preparation and storage of study medications required for the SHINE treatment protocols.