10. Management of Hypoglycemia

10.1 Hypoglycemia Protocols

10.1.1 Initiating hypoglycemia protocol (Glucose concentration < 80 mg/dL)

All insulin therapy will be stopped in the event that glucose drops below 80 mg/dL and the following protocol will be initiated:

(1) Stop all IV infusions and hold all subcutaneous injections.
(2) D50 will be stored to allow immediate availability at the bedside.
(3) Glucose administration
  (a) Control Group – A dose of IV D50 25 ml (1/2 amp) will be given (slow IV push over 1-2 minutes) every 15 minutes until blood glucose is ≥ 80 mg/dL. Repeat POC glucose checks and treatment every 15 minutes if needed until glucose is ≥ 80 mg/dL.
  (b) Intervention Group – An individualized dose of IV D50 will be given (slow IV push over 1-2 minutes). The specific dose will be determined by GlucoStabilizer® based on the glucose concentration. Recheck blood glucose every 15 minutes as directed by GlucoStabilizer®. Repeat treatment every 15 minutes as directed by GlucoStabilizer® until glucose is ≥ 80 mg/dL.
  (c) Glucose level entry into the SHINE Trial Portal needs to occur q15 minutes +/- 5 minute window to remain protocol compliant.
(4) Once glucose is ≥ 80 mg/dL:
  (a) Restart IV insulin or saline per protocol
  (b) Restart SQ insulin or saline per protocol

10.1.2 Extra steps for hypoglycemia < 70 mg/dL

Continue to use the hypoglycemia protocol above (e.g. hold insulin, give D50, repeat glucose checks every 15 minutes).

- Draw a STAT laboratory <u>serum</u> glucose measurement but do not delay treatment with D50 by waiting for this blood draw result. Only the results from POC checks should be used for study protocol dosing. The result of the serum glucose measurement will be captured in the Hypoglycemic Event CRF (Form 17).
- Screen the patient for hypoglycemia symptoms using Hypoglycemia Symptomatic Questionnaire (downloadable from NETT SHINE website).
  - The worksheet and instructions will be available on paper and on the desktop of the laptops.
  - The Hypoglycemia Symptomatic Questionnaire must be repeated every 15 minutes when glucose is < 70 mg/dL.
  - **Once the glucose is ≥ 70 mg/dL, one final assessment with the Hypoglycemia Symptomatic Questionnaire is required.**
  - Once the glucose is ≥ 80 mg/dL, the timing of glucose checks and insulin infusion rate will again be determined by the study computer.
- Screen the patient for neurological worsening.
  - An assessment of neurological change is required per site standard care (“neuro check”) every 15 minutes when glucose is < 70mg/dL.

- The SHINE study definition of neurological worsening is any clinical change that is associated with a ≥ 4 point increase from most recent NIHSS score that lasts ≥ 24 hours.
- Any patient with neurological worsening will be assessed for hypoglycemia and for relatedness of the hypoglycemia to neurological worsening if present.
- If the patient has not returned to neurological baseline within 24 hours, a NIHSS assessment is required at 24 hours(+/- 4 hours) from onset of hypoglycemic event (< 70 mg/dL). If the patient has returned to neurological baseline at any point in less than 24 hours, the NIHSS is not required at 24 hours.
- If neurological worsening persists for ≥ 24 hours and is associated with a glucose concentration < 55 mg/dL, an SAE form is required.

- If the glucose falls below 40 mg/dL at any time, an SAE form is required. The SAE must be entered into WebDCU within 24 h of discovery. In addition, this SAE must be filed with your local IRB per their guidelines.

10.1.3 **Severe Hypoglycemia (Glucose concentration < 40 mg/dL)**

All glucose measurements < 40 mg/dL will be captured as severe hypoglycemia. Each event will be characterized as symptomatic or asymptomatic based on symptoms and signs. All spontaneous symptomatic complaints will trigger a stat glucose measure per standard care. Nonverbal patients will be assessed for only the physiologic signs of symptomatic hypoglycemia.

10.1.4 **Determining Symptomatic Hypoglycemia**

The Hypoglycemia Symptomatic Questionnaire will be used to assess symptomatic hypoglycemia in patients with glucose levels below 70 mg/dL.

Symptomatic hypoglycemia, which consistently differentiates hypoglycemia from euglycemia, will be assessed using questions of: shaky, heart pounding, nervous, sweaty, hungry, tingly, warm, weak, confused and drowsy. Of these symptoms, shakiness, heart pounding and nervousness may be reduced in patients on medication that result in adrenergic blockade though the other symptoms persist despite such medications.

In addition, spontaneous complaints of these symptoms will trigger an immediate glucose level assessment. Standard care orders should specify PRN glucose level check for patient complaints of these symptoms or others suggestive of hypoglycemia. Aphasic patients, unresponsive patients or patients who cannot otherwise participate in the hypoglycemic questionnaire will be evaluated for signs of a physiologic response to hypoglycemia only and not symptoms on the questionnaire (See Appendix 6).

10.1.5 **Additional steps for ≥ 3 episodes of hypoglycemia (Glucose concentration < 70 mg/dL) in 24 hour period**

- Intervention Group
  - For any study patient in the intervention 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).

- Control Group
  - 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).
  - 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