permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of study treatment.

Other Serious (Important Medical Events): Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization.

The submission of an SAE will generate an automatic email notification to the SHINE Site Manager (SM). The SM will review the SAE for completeness of information in WebDCU™. If the information is insufficient, the SM will indicate on the Web-form 'information is insufficient' and enter a comment indicating what additional information is required. The process triggers an automatic email notification to the site PI and coordinator requesting the additional information. Once the SM feels that SAE has been properly entered and is ready for clinical review, they will indicate this in WebDCU™ which will prompt review by the Internal Quality and Safety Reviewer (IQSR). If the information is insufficient, the IQSR will indicate on the Web-form 'information is insufficient' and enter a comment indicating what additional information is required. The process triggers an automatic email notification to the site PI and coordinator requesting the additional information. When the IQSR completes his or her clinical review, they will indicate this, prompting an automatic e-mail notification to be forwarded to the Independent Safety Monitor. The Independent Safety Monitor will review SAEs to determine relatedness and whether expected or unexpected. This review must be completed and entered within 48 hours of notification.

9. Protocol Adherence

9.1 Protocol Deviations

Protocol deviations must be assessed throughout each subject's participation in the study.

Protocol deviations must be reported in WebDCU™ when applicable. Protocol deviations must also be reported to the IRB per local site requirements. Once a deviation has been acknowledged by the IRB, it must be uploaded to WebDCU™.

Serious or repeated protocol deviations will require the development of a Corrective Action/Preventative Action (CAPA) plan (see Section 9.2).

9.2 Corrective Action/Preventative Action Plans

Development of a CAPA plan may be initiated by the site study team, local IRB, or the NETT-CCC. Potential triggers include protocol deviations, data quality problems, or systematic problems identified by study teams or monitors.

CAPA plans must be reviewed by the site study team, NETT-CCC site manager and monitor. The NETT-CCC site manager, NETT-CCC project monitors, or the SHINE project director may approve CAPA plans.

Once a CAPA plan has been approved and enacted, data must be collected as agreed upon in the plan until the study team demonstrates that the issue has been resolved. The criteria for determining this point will vary depending upon the frequency and severity of the issue. After it has been demonstrated that the deficiency has been corrected, the CAPA plan will be closed by the NETT-CCC site manager, NETT-CCC site monitors, or the SHINE project director.

9.3 Protocol Adherence Monitoring Procedures

The overall goal of site monitoring and aggregate protocol adherence monitoring in the SHINE trial is to identify patterns suggestive of overall study protocol issues or individual site issues that may require support and/or retraining on study treatment procedures.

Details of the SHINE Protocol Adherence Monitoring Procedures can be found in Appendix 12.

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.
(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 <70mg/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.