Stroke Hyperglycemia Insulin Network Effort Trial
NIH-NINDS Sponsored Trial
In collaboration with the Neurological Emergencies Treatment Trials network (NETT)

Pharmacy Plan Guidance

The pharmacy plan is a tool used during the site readiness process to develop and document the site-specific procedures for study drug ordering, labeling and dispensing for the SHINE trial. Please include a ½-1 page summary that details the following:

STUDY DRUG: List the study drugs that will be used at your site based on your hospital formulary

DRUG SUPPLY & STORAGE: Detail how study drugs will be supplied and where they will be stored

RANDOMIZATION: Describe the randomization process as it pertains to your site pharmacy **(**how is the randomization assignment provided to pharmacy and documentation of this maintained)

DRUG ORDERING & DISPENSING: Describe the process for ordering/dispensing study-required treatments; Detail the system used to place orders (electronic, hard copy orders, etc.)

STUDY DRUG NAMING & LABELS: Describe how the study drug will appear in the medical record and how the actual treatments (vials, infusion bags) are labeled

PHARMACY CONTACT INFORMATION: Include name & contact info for pharmacist who will be working with SHINE

In addition to the Pharmacy Plan summary, please attach study order sets (screenshots of electronic orders, actual hard copy orders or instructions for manual order entry into an electronic system), pharmacy instructions and labels as available and upload the compiled document in WebDCU.

Please reference the instructions that follow on developing study orders for SHINE as you begin to draft the study order set, or contact Dr. Askiel Bruno for more information or for sample plans and order sets.

Contact Askiel Bruno (ABRUNO@augusta.edu) with questions about study orders and pharmacy plan.

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Developing study orders for SHINE

We have compiled the information included below as a resource for developing the SHINE study order set. We would encourage you to adapt the template language organized by treatment group on the following pages to draft your study orders. Additionally, several enrolling sites have shared copies of their site pharmacy plan and orders, and these are posted on the SHINE study website (https://www.nett.umich.edu/nett/shine_toolbox) for your reference.

We are available to work with your study team and pharmacy to develop the study orders for your site and recommend starting to work on this early. Because of the complexity of the protocol and dosing regimens, prior to the readiness call, we will review copies of your site study order sets. If corrections or updates to the orders are required, this can delay overall site readiness, so again we encourage you to start early. When complete, study orders are compiled and uploaded in WebDCU with the ½ to 1 page pharmacy plan that addresses the process, labeling and pharmacy contact information.

Pharmacy/Medication orders and Physician to Nurse/Nursing communication orders

Please plan to incorporate both the orders for the study treatments as well as the necessary communication orders to manage the study protocol during the 72 hour treatment period. Orders should be implemented using the standard practice for research at your institution. Hard copy or paper orders, templates for manual order entry or an electronic order set are all acceptable formats for the orders.

Labels

- Consider what will print on the labels.
- The IV infusion should be blinded since it will be hanging in the patient's room.
- The labels for the SQ treatments do not have to be blinded as these can be drawn up outside of the view of the patient/family.
- SHINE study drug stickers
    - These are supplied by UVA to be applied by the pharmacy on the study infusion bag. (Orange – control group; Blue – intervention group)
    - Pharmacy preparation instructions should detail the application of the study drug sticker on the study infusion bag.
    - These study drug stickers must only be applied by the pharmacy.
    - The MOP specifies that the study team retains one study drug sticker per subject for monitoring purposes. This can be removed from the infusion bag and retained, or a color-copy can be made of the bag/sticker with the subject ID visible, and the bag can be discarded.
    - Please contact Heather M. Haughey (hmh8f@virginia.edu) for resupply, allowing 2 weeks for these to arrive.

Documentation in the medical record/charting

- Consider how the study treatments will be charted in the medical record
- The study monitors will review source documentation to confirm the name of the actual study treatment administered with time and dose.

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Naming conventions

- GlucoStabilizer is the name for the commercially available decision support tool. The company that has developed the decision support tool has asked that we do not refer to the programming that they have done for the control protocol and data entry as GlucoStabilizer.
- For the control group, you may refer to the control protocol, control treatment screen, study sliding scale, study laptop, etc. (e.g. Rate per study laptop)
- For the intervention group, you may refer to GlucoStabilizer, intervention protocol, study laptop, etc. (e.g. Timing of glucose checks: q1 to q2 hours per GlucoStabilizer)

Dosing calculations for the intervention group

The GlucoStabilizer calculations for the insulin infusion, meal insulin and D50 follow.

- **Regular insulin infusion**: There is not a hard maximum cutoff to the IV regular insulin dosage recommendation. The recommendation is calculated based on the formula "(BG - 60) * multiplier". However if the insulin dose is > 32, a warning message is displayed to check with the physician before proceeding.
- For the **rapid acting analog (meal) insulin** dosing, the insulin to carbohydrate ratio is 1:15. One unit of insulin will be recommended for every 15 grams of carbs consumed. Based on the study protocol diet and instructions for estimating consumption, carbohydrate intake per meal will be estimated to be either 30 or 60 grams. Two units of rapid acting analog insulin will be recommended for patients that partially consume the meal (entry of 30 into Cover Carbs option in GlucoStabilizer). Four units of SQ rapid acting analog insulin will be recommended for patients that consume all or nearly all of the meal (entry of 60 into Cover Carbs option in GlucoStabilizer). If none or nearly none of the meal is consumed, there should be no entry in GlucoStabilizer, and no rapid acting analog insulin given for that meal.
- For **dextrose 50% in Water (D50)**, when the BG < 80mg/dL, an individualized dose is calculated per GlucoStabilizer based on the following formula: (100 - BG) * 0.4
  The lowest value that is allowed for the BG is 1, so the highest theoretical value for D50 in the intervention group is (100 - 1) * 0.4 = 40mL. (As a reminder in the control group, IV D50 25 mL (1/2 amp D50) will be given every 15 minutes when the BG <80mg/dL.)

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CONTROL GROUP

1) **Glucose checks**
   - **POC glucose tests**
     i) Check glucose levels using finger stick testing every hour for the first 4 hours, then every 3 hours for the remaining treatment period (03:00, 06:00, 09:00, 12:00, 15:00, 18:00, 21:00, & 24:00).
     Use capillary blood only unless otherwise directed by study team. POC testing ONLY
     Adjust saline infusion with each glucose check.

     OR

   - **POC glucose checks**
     i) Blood Glucose Monitoring POCT
        (1) Frequency: Q1hours
        (2) Duration: 4 hours
        (3) Special instructions: Use capillary blood only unless otherwise directed by study team. POC testing ONLY. Complete on POC test to start the study infusion and then hourly for four hours (POC to start study infusion____mg/dL _ _:_ _; H1 _ mg/dL _ _:_ _; H2 _mg/dL _ _:_ _; H3 ___mg/dL _ _:_ _; and H4____mg/dL _ _:_ _; then transition to the schedule for Q3hour checks
     ii) Blood Glucose Monitoring POCT
        (1) Frequency: Q3hours
        (2) Duration: Up to 66 hours
        (3) Special Instructions: Time testing 0300; 0600; 0900; 1200; 1500; 1800; 2100; 24:00
        (4) Special instructions: Use capillary blood only unless otherwise directed by study team. POC testing ONLY

2) **IV saline -** SHINE Study Drug in Normal Saline _ _ _mL infusion (1:1); Insulin regular human or placebo in NS _ _ _mL infusion (1:1)
   - IV continuous
   - Adjusted with each glucose check
   - Rate determined per control treatment screen
     - 4mL/hr for glucose of 80-179
     - 5mL/hr for glucose of ≥180mg/dL
   - If glucose is < 80 mg/dL, administer NO saline or SQ insulin and initiate study hypoglycemia protocol

3) **Regular Insulin SQ (Humulin R or Novolin R)**
   - Route: SQ Insulin regular subcutaneous
   - Frequency: Q6 hours, up to four times a day -- ONLY at 06:00, 12:00, 18:00, & 24:00
   - Dose per Level 1, 2 or 3 on study sliding scale
   - Duration: Up to 72 hours
   - Special instructions: Level will be determined by study team every 24 hours period on study protocol based on the last two POCT BG results

4) **Dextrose 50%**
   - Route: IV
   - Frequency: Every 15 MIN PRN (Blood glucose < 80mg/dL)
   - Dose: 25mL
   - Special instructions: Recheck blood glucose every 15 minutes and repeat treatment until blood glucose > 80. When blood glucose > 80, restart study saline infusion and insulin SQ per protocol.

5) **Basal insulin SQ (Glargine (Lantus))**
   - **Route:** SQ

Contact Askiel Bruno (ABRUNO@augusta.edu) with questions about study orders and pharmacy plan.

- Dose: To be determined by study team per special instructions
- Frequency: Once
- Special Instructions: For Level 3, one-time SQ basal insulin injection at a dose of 40% of previous 24 hours entire insulin requirement (≥.5 round up; <.5, round down). This dose of basal insulin should be given as close as possible to the 48 hour point regardless of time of day.

6) Hypoglycemia prevention and management

- Hypoglycemia protocol for BG < 80 mg/dL
  - i) Stop the saline infusion and hold all subcutaneous insulin injections
  - ii) A dose of IV D50 25 ml (1/2 amp) will be given (slow IV push over 1-2 minutes) q 15 min until blood glucose is ≥80 mg/dL.
  - iii) Repeat finger stick glucose checks and treatment q 15 min until glucose is ≥80 mg/dL.

b) Additional steps for blood glucose <70mg/dL
  - i) Draw a STAT laboratory serum glucose measurement but do not delay treatment with D50.
  - ii) Screen the patient for hypoglycemia symptoms using Hypoglycemia Symptomatic Questionnaire.
    - (1) Repeat q15 min when glucose is <70mg/dL.
    - (2) Once the glucose is ≥ 70mg/dL, no further assessment with the Hypoglycemia Symptomatic Questionnaire is required.
  - iii) Screen the patient for neurological worsening.
  - iv) Once the glucose is ≥80 mg/dL, the timing of glucose checks and saline infusion rate will again be determined by the control treatment screen.

6) Diet/Nutrition Orders – Control group

a) 60 gram carbohydrate diet for PO patients for breakfast lunch and dinner & protocol approved snacks
  - i) Timing of meals
    - (1) Breakfast after 06:00 check
    - (2) Lunch after 12:00 check
    - (3) Dinner after 18:00 check

b) Patients should not consume additional food not included on the meal tray from the hospital kitchen.

c) Family, friends and visitors should be instructed not to consume food from the patient's trays unless approved by the nurses, after patients finish eating.

7) Procedures for pauses/interruptions in study protocol

a) Notify the study team
OR

b) When the study protocol needs to be paused, stop the IV saline infusion.

c) Upon return to the unit, if glucose checks or subcutaneous insulin injections **were not missed**, maintain schedule for sliding scale checks and dosing. Resume saline infusion at the next scheduled glucose check.

d) Upon return to the unit, if glucose checks or subcutaneous insulin injections **were missed**, the following procedures should be followed:
  - i) Immediately check the finger stick point of care glucose upon return to the unit.
  - ii) Resume the saline infusion according to the sliding scale using the glucose measurement.
  - iii) If one of the time points for scheduled subcutaneous injections was missed, use the result of the glucose check and sliding scale to determine if a subcutaneous insulin dose is indicated.
  - iv) If indicated per sliding scale, give subcutaneous insulin injection immediately (rather than waiting for next scheduled dose).
  - v) Return to schedule for glucose checks and subcutaneous insulin injections.
    - (1) Do not check glucose levels <1 hour apart unless it is a check associated with a scheduled insulin dose. If the next check is <1 hour from the check that happened upon return to the unit, skip to the next scheduled check.

(2) Do not give SQ regular insulin injections <3 hours apart. If a subcutaneous injection is given upon return to the unit (as described above) AND the next scheduled injection is <3 hours do not give insulin at the next scheduled injection time.

8) Steps for ≥3 episodes of hypoglycemia (Glucose < 70mg/dL) in 24 hour period

a) Notify the study team (Study team contacts safety monitor)
b) 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.

9) Severe hyperglycemia (Glucose ≥500mg/dL)

a) Draw a STAT laboratory serum glucose measurement
b) Notify the study team (Study team contacts safety monitor)

10) Discharge prep instructions

a) Notify study team as study treatment must be discontinued 6 hours in advance of discharge

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Subcutaneous Insulin Sliding Scale and IV Saline (Placebo)
Table for SHINE Control Group

Check finger stick glucose Q 1 hr for the first 4 hours, then Q 3hrs (3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00), but give sq insulin if indicated only 4/day (6:00, 12:00, 18:00, and 24:00)				
IV Saline	**SQ Human Regular Insulin (Humulin R or Novolin R) Sliding Scale**			
Start at rate indicated below and adjust if indicated each time glucose is checked.	Start at Level 1. If at the end of the first 24 hours, the previous two glucose levels remain ≥ 180mg/dL, advance to Level 2. If after 24 hours on Level 2, the previous two glucose levels remain ≥ 180mg/dL, proceed to Level 3. In Level 3, give a one-time subcutaneous basal insulin injection (Glargine) at a dose equal to 40% of previous day's entire insulin dose and continue Level 2 insulin dose.			
mL/hr	**Glucose (mg/dL)**	**Level 1 Insulin dose (units)**	**Level 2 Insulin dose (units)**	**Level 3 One time sq basal insulin (Glargine) and continue Level 2 Insulin dose (units)**
5	>450	8	16	16
5	400-450	7	14	14
5	351-399	6	12	12
5	300-350	5	10	10
5	251-299	4	8	8
5	200-250	3	6	6
5	180-199	2	4	4
4	80-179	0	0	0
0	<80	See hypoglycemia protocol (Click Here)		

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INTERVENTION GROUP

1) **Glucose checks-Intervention group**
   - **POC glucose tests**
     Check glucose levels using finger stick testing as instructed by GlucoStabilizer
     Use capillary blood only unless otherwise directed by study team. POC testing ONLY

     OR

   - **POC glucose checks**
     i) Blood Glucose Monitoring POCT
        (1) Frequency: Q1hours per GlucoStabilizer
        (2) Duration: 4 hours
        (3) Special instructions: Use capillary blood only unless otherwise directed by study team. POC testing ONLY

     vi) Blood Glucose Monitoring POCT
        (1) Frequency: Q1-2 hours per GlucoStabilizer
        (2) Duration: Up to 68 hours
        (3) Special instructions: Use capillary blood only unless otherwise directed by study team. POC testing ONLY

2) **IV insulin (human insulin regular- Humulin R or Novolin R) -** SHINE Study Drug in Normal Saline _ _ _mL infusion (1:1); Insulin regular human or placebo in NS _ _ _mL infusion (1:1)
   - Route: IV continuous
   - Frequency: Adjusted with each glucose check
   - Rate: Rate determined per GlucoStabilizer
   - Special instructions: If glucose is < 80 mg/dL, administer NO IV insulin or SQ insulin or saline and initiate study hypoglycemia protocol

3) **Meal insulin (Rapid acting analog insulin SQ - Lispro (Humalog), Aspart (Novolog) or Glulisine (Apidra)**
   - Route: SQ
   - Frequency: Up to three times daily with meals
   - Duration: Up to 72 hours
   - Dose: To be determined by carbohydrate count using GlucoStabilizer tool
   - Special instructions: Approximately 20 minutes after patient begins eating, estimate meal consumption.
     - If none or nearly none, DO NOT enter carbohydrate amount in GlucoStabilizer and do not give meal insulin SQ
     - If partial meal consumption, enter 30gm carbohydrate in GlucoStabilizer and give SQ rapid acting insulin according to recommendation by GlucoStabilizer tool.
     - If all or nearly all, enter 60gm carbohydrate in GlucoStabilizer give SQ rapid acting insulin according to recommendation by GlucoStabilizer tool.

4) **Saline SQ**
   - Dose: 0.05mL (equivalent to 5 Units)
   - Route: SQ
   - Frequency: BIS (0900,2100)
   - Duration: Up to 72 hours
   - Special Instructions: Administer for patient who are NPO or on continuous tube feeds to maintain the blind. Administer after the glucose checks closest to 09:00am and 21:00pm.

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5) Dextrose 50% - Intervention group

- Route: IV
- Frequency: Every 15 MIN PRN (Blood glucose < 80mg/dL)
- Dose: Dose determined by GlucoStabilizer tool
- Duration: Up to 72 hours
- Special instructions: Recheck blood glucose every 15 minutes and repeat treatment as directed by GlucoStabilizer until blood glucose > 80. When blood glucose > 80, restart study insulin infusion and insulin SQ or the saline SQ per protocol.

6) Hypoglycemia prevention and management- Intervention group

- Hypoglycemia protocol for BG < 80 mg/dL
  - v) Stop the insulin infusion and hold all subcutaneous insulin and saline injections
  - vi) An individualized dose of IV D50 will be recommended by GlucoStabilizer and should be administered slow IV push (over 1-2 minutes).
  - vii) Repeat finger stick glucose checks and treatment q 15 min per GlucoStabilizer until BG is ≥80 mg/dL.
- c) Additional steps for blood glucose <70mg/dL
  - i) Draw a STAT laboratory serum glucose measurement but do not delay treatment with D50.
  - ii) Screen the patient for hypoglycemia symptoms using Hypoglycemia Symptomatic Questionnaire.
    - (1) Repeat q15 min when glucose is <70mg/dL.
    - (2) Once the glucose is ≥ 70mg/dL, no further assessment with the Hypoglycemia Symptomatic Questionnaire is required.
  - iii) Screen the patient for neurological worsening.
  - iv) Once the glucose is ≥80 mg/dL, the timing of glucose checks and insulin infusion rate will again be determined by the GlucoStabilizer.

11) Diet/Nutrition Orders – Intervention group

a) 60 gram carbohydrate diet for PO patients for breakfast lunch and dinner & protocol approved snacks Estimate the proportion of the meal consumed approximately 20 minutes after the start of the meal
   i) Full or near full consumption → 60 grams carbohydrates
   ii) No or nearly no consumption → 0 grams carbohydrates
   iii) Partial consumption →30 grams carbohydrates
b) Patients should not consume additional food not included on the meal tray from the hospital kitchen.
c) Family, friends and visitors should be instructed not to consume food from the patient's trays unless approved by the nurses, after patients finish eating.

12) Procedures for pauses/interruptions in study protocol- Intervention group

a) Notify the study team
   OR
e) When the study protocol needs to be paused, stop the IV insulin infusion.
   i) Upon return to the unit, if the IV insulin infusion has been off for <3 hours, follow the protocol to **resume the drip**.
   ii) Upon return to the unit, if the IV insulin infusion has been off for ≥ 3 hours, follow the protocol to **start new drip**).

13) Steps for ≥3 episodes of hypoglycemia (Glucose < 70mg/dL) in 24 hour period

a) Notify the study team (Study team contacts safety monitor)

14) Severe hyperglycemia (Glucose ≥ 500mg/dL)

a) Draw a STAT laboratory serum glucose measurement
b) Notify the study team (Study team contacts safety monitor)

15) Discharge prep instructions

a) Notify study team as study treatment must be discontinued 6 hours in advance of discharge

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