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

Control Group
Study treatment: IV saline + subcutaneous sliding scale insulin injections
Target blood glucose: <180 mg/dL

The SHINE trial is a single-blinded study. Study patients **will not** know whether they are in the intervention or control group but will know that they will get both an IV solution and subcutaneous shots to manage high blood sugar. Both the treating and study teams **will** know the randomization. Care should be taken to maintain the blind. The study team is available to answer questions that study patients and their families or the treating teams have about the randomization and blinding.

5.1.2 Intervention Group

Study treatment: IV insulin + subcutaneous meal insulin (or saline injections for patients who are not eating)
Target blood glucose: 80-130 mg/dL

Once randomized to the intervention group (IV insulin + subcutaneous meal insulin or saline injections with a target blood glucose of 80-130 mg/dL), the GlucoStabilizer® (decision support tool) program will be activated on the study laptop. The determination of IV and subcutaneous meal insulin dosing and instructions will be indicated by the decision support tool. The required timing of blood glucose checks will be displayed by the decision support tool. Patients will continue on study treatment for 72 hours. Discontinuation prior to 72 hour is allowed when discharge is clinically indicated and requires that all study protocol treatments stop at least 6 hours in advance of scheduled discharge.

(1) IV insulin preparation

(a) **Drug preparation**

(i) Upon randomization, the SHINE site study team will contact the pharmacy to communicate the randomization allocation. Study treatment must begin as soon as possible following randomization.
(ii) Orders for study intervention group protocol should be entered by study investigator per site procedures.
(iii) The pharmacy will provide the study IV insulin per site procedures.
(iv) The concentration of the IV insulin infusion will be 1:1 (e.g. 100 Units of human regular insulin in 100 ml of normal saline (0.9% NaCl)) unless a site-specific exception is approved. See Section 12-Pharmacy Manual.

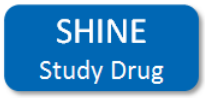
(b) **Study patient preparation**

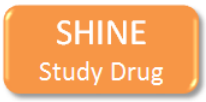
(i) The study team/clinical nurse will gather supplies for the IV insulin infusion protocol (IV catheter, IV tubing, infusion pump, syringes, etc.).
(ii) The SHINE study will encourage that 1 vial of Dextrose 50% in Water (D50) be stored to allow immediate availability at the bedside. If hypoglycemia occurs, patients in the intervention group will receive an individualized dose of D50 as indicated by the GlucoStabilizer® tool. For this reason, syringes with graduated marks for volume (mL) must be used.
(iii) An IV for study medication only will be placed. All other IV medications should be administered separately from the IV for study insulin infusion.

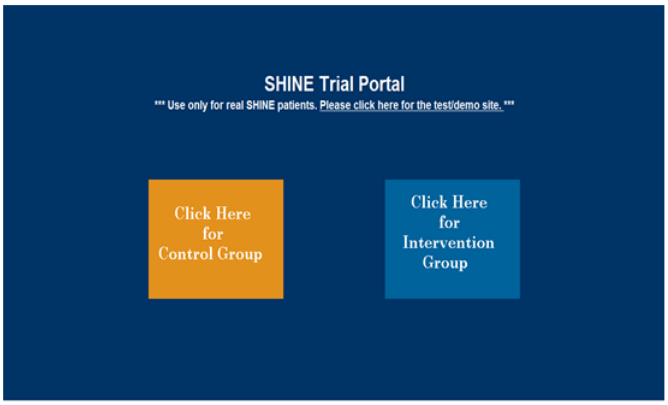
(iv) Upon receipt of the IV insulin bag from the pharmacy, the study team/clinical nurse will hang it with an infusion pump. The IV infusion pump should be programmed to maintain the blind (i.e., the display on the infusion pump should read SHINE Study Drug rather than insulin).

(v) The IV insulin bag will be labeled with a **BLUE** sticker that says SHINE study drug. The label **MUST** only be applied by the pharmacist who is preparing the IV infusion.

(vi) The background for the GlucoStabilizer® screens will be **BLUE** for the intervention group. Verify that these match to assure that the correct study drug has been provided.







(vii) The initial IV infusion rate and subsequent rate adjustments will be based on POC finger stick glucose measurements and calculated by the GlucoStabilizer® decision support tool.

(viii) Implementation of the recommended dose is by the patient's clinical or research nurse.

(2) **Blood glucose monitoring**

(a) The SHINE protocol recommends the use of capillary blood for the POC glucose tests. Finger stick POC glucose is required for randomization and should be the primary source for most patients, but other sources of blood may be used based on site standard practice.

(b) The Accu-Chek System is the SHINE study preferred system. Other blood glucose monitoring systems can be used per site procedures.

(c) The decision support tool requires POC glucose checks at least every 1-2 hours. The testing frequency is determined by the GlucoStabilizer® tool.

(d) If the blood glucose drops < 80 mg/dL, the GlucoStabilizer® tool will initiate the hypoglycemia prevention and management protocol. GlucoStabilizer® will recommend stopping all insulin, administering an individualized corrective dose of D50 and more frequent blood glucose monitoring (every 15 minutes).

(e) Glucose must be checked within +/-15 minutes of the scheduled time for a regular check and within +/-5 minutes of the scheduled time when the glucose is < 80 mg/dL..

(f) Only the results of the point of POC are glucose levels should be recorded in GlucoStabilizer®. Lab glucose levels should **NOT** be entered!

(3) **GlucoStabilizer® and IV insulin initiation**

(a) **Overview**

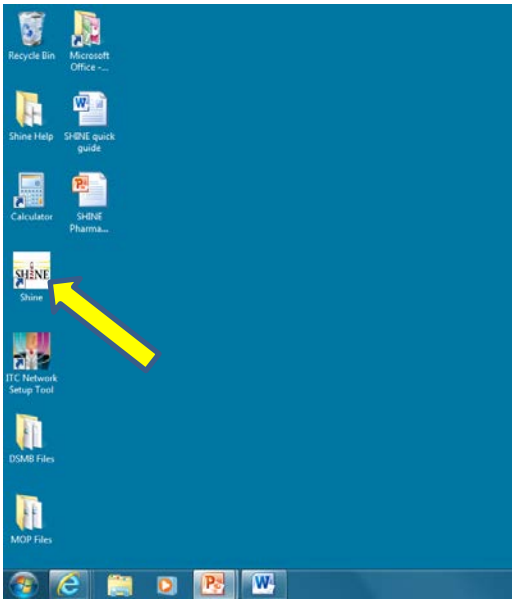
SHINE study laptops will be supplied to all participating sites and must be used to access the GlucoStabilizer® decision support tool. The icon for the SHINE Trial Portal will be located on the desktop of the laptop. Study laptops are to remain powered on and open throughout the treatment period. The screens for the intervention group will allow the clinical nurses/study team to see the time countdown to the next glucose check and to enter the current glucose levels and see the consequent GlucoStabilizer® IV insulin rate recommendations. The time between glucose checks will be determined by the GlucoStabilizer® tool.

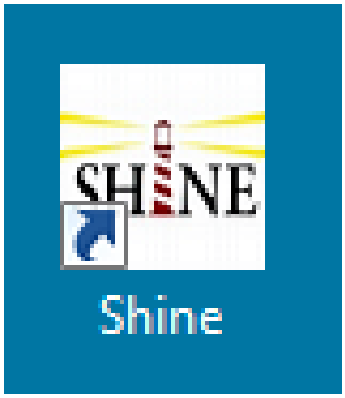
(b) **Administrative set up instructions**

1. Retrieve the study laptop and ensure internet connectivity per site procedures.
2. The initial setup for each subject will be done by the site study team.
3. The login for the computer is **SHINE** user profile, and the password is **shine**.
4. The GlucoStabilizer® login will be User ID: **shine**, Password: **shine** for all personnel and all sites. Contact the site study team with questions about the login.
5. The SHINE study ID is unique identification number for each randomized patient. This will be provided by the study team after the patient has been randomized in WebDCU™.

(c) **Initiating GlucoStabilizer® (Starting a New Drip)**

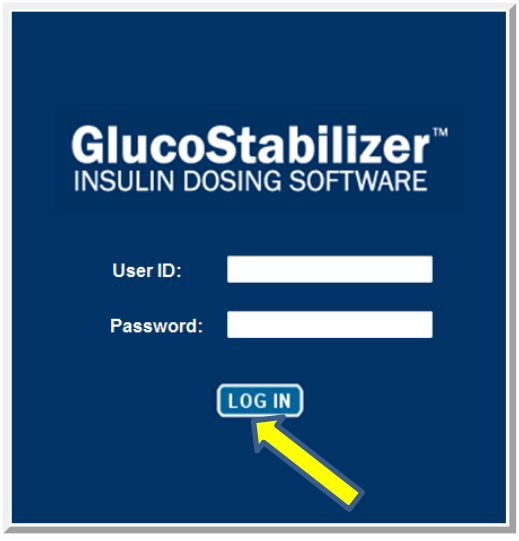
(i)Select SHINE icon on the desktop of the study laptop and the SHINE Trial Portal will open.



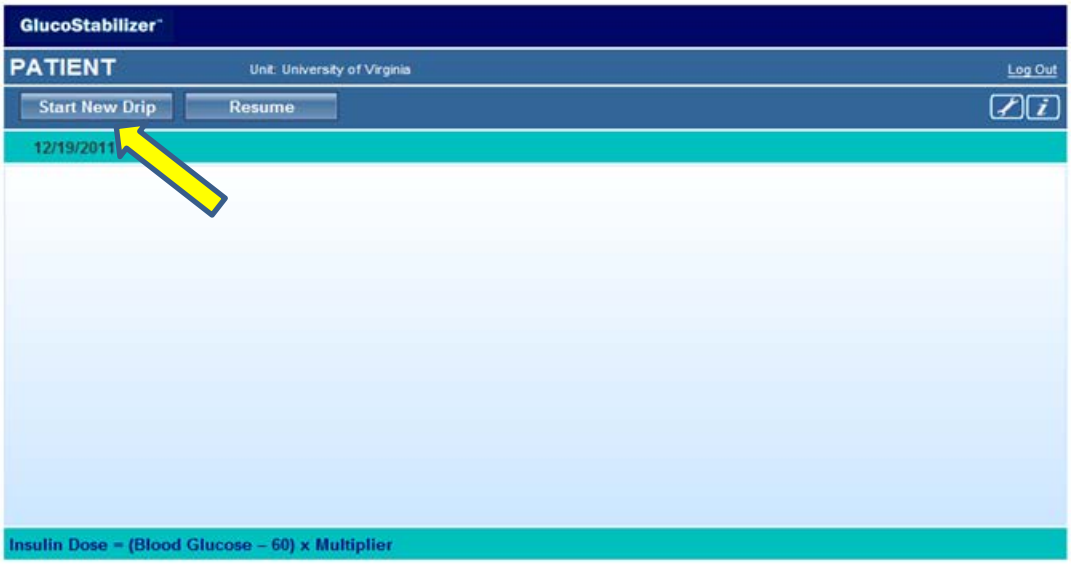


(ii)Check the hard copy of the randomization to confirm that the patient is in the intervention group. Click on the blue box **Click Here for Intervention Group**.

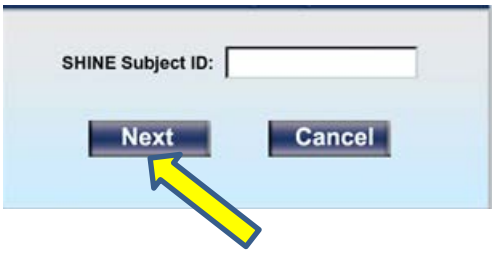
(iii) Enter User ID and Password (shine/shine). Click on **Log In** button.



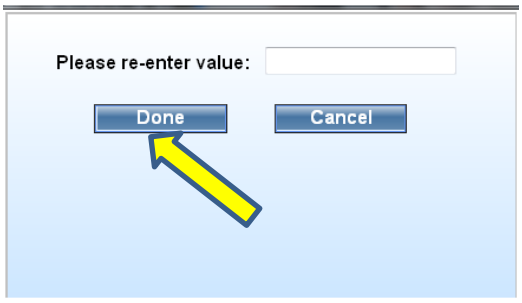
(iv) If this is the first time that GlucoStabilizer® is used for this study patient, select **Start New Drip** button.



(v) Enter the **SHINE Subject ID**. Select **Next**.



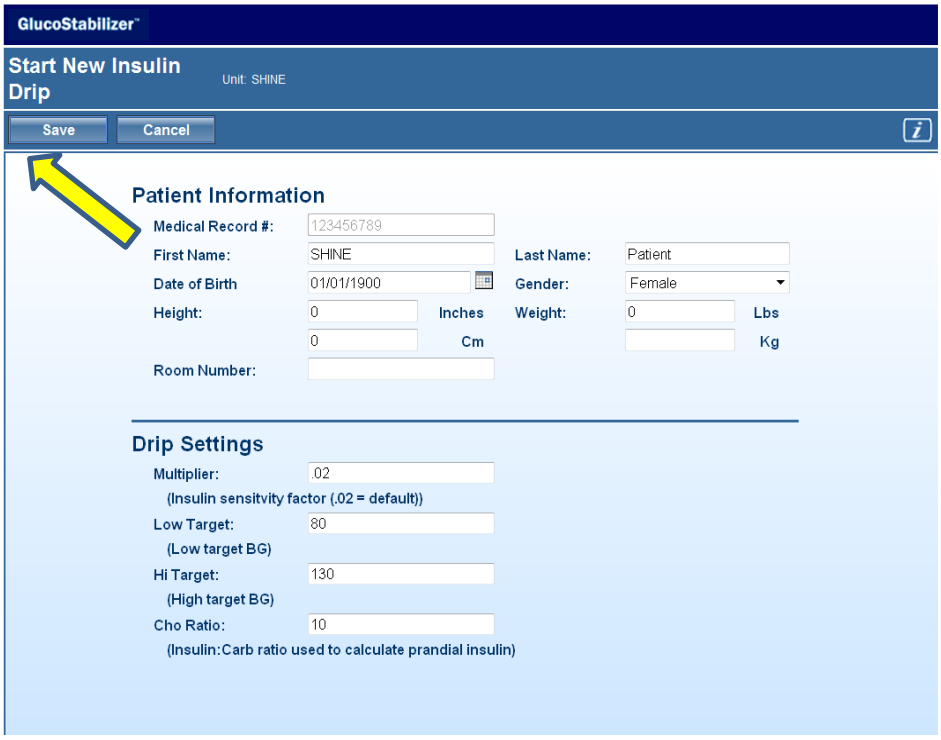
(vi) Re-enter the SHINE Subject ID. Select **Done**.



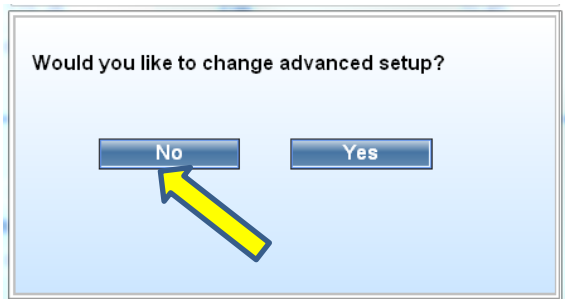
(vii) The next screen will display Patient Information and Drip Settings. Because this is a study patient, **NO IDENTIFIABLE PATIENT INFORMATION SHOULD BE ENTERED**.

(viii) DO NOT CHANGE ANY OF THE PREPOPULATED ITEMS ON THIS SCREEN. THESE ARE First Name: SHINE, Last name: Patient, DOB: 01/01/1900; Sex: Female). Drip settings will also be populated (Multiplier .02,

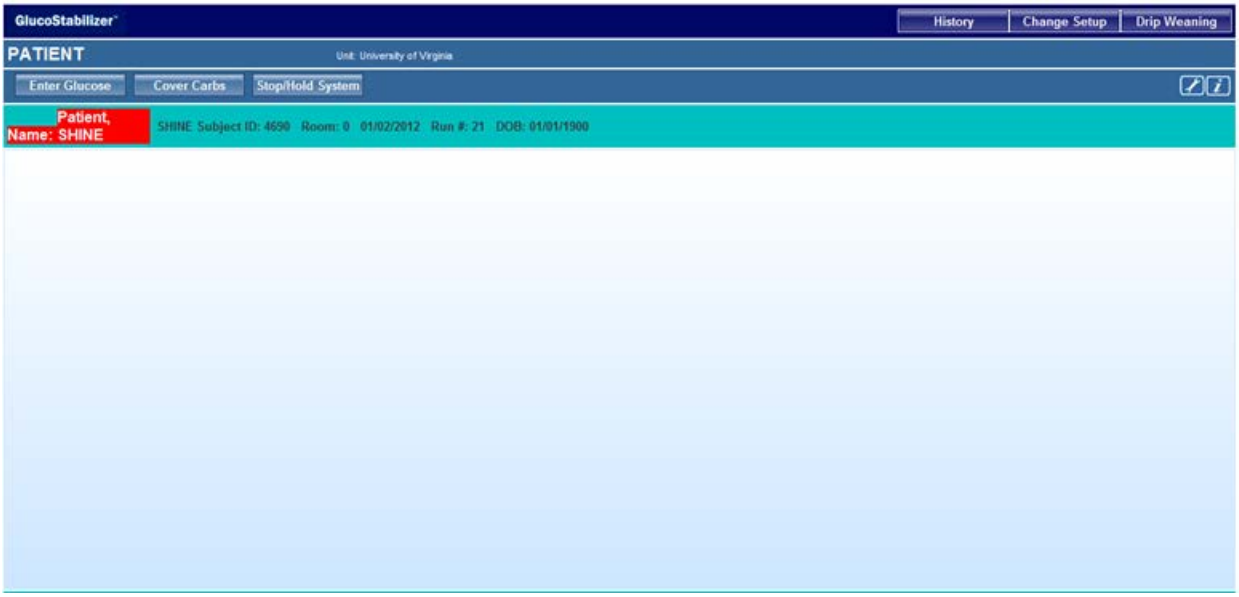
Low Target 80, Hi Target 130, Cho Ratio 15). **DO NOT ADJUST**. Select **Save**.



(ix) A pop-up will ask, "**Would you like to change to advanced setup**?" **SELECT NO**.



(x) The GlucoStabilizer® main page will be displayed



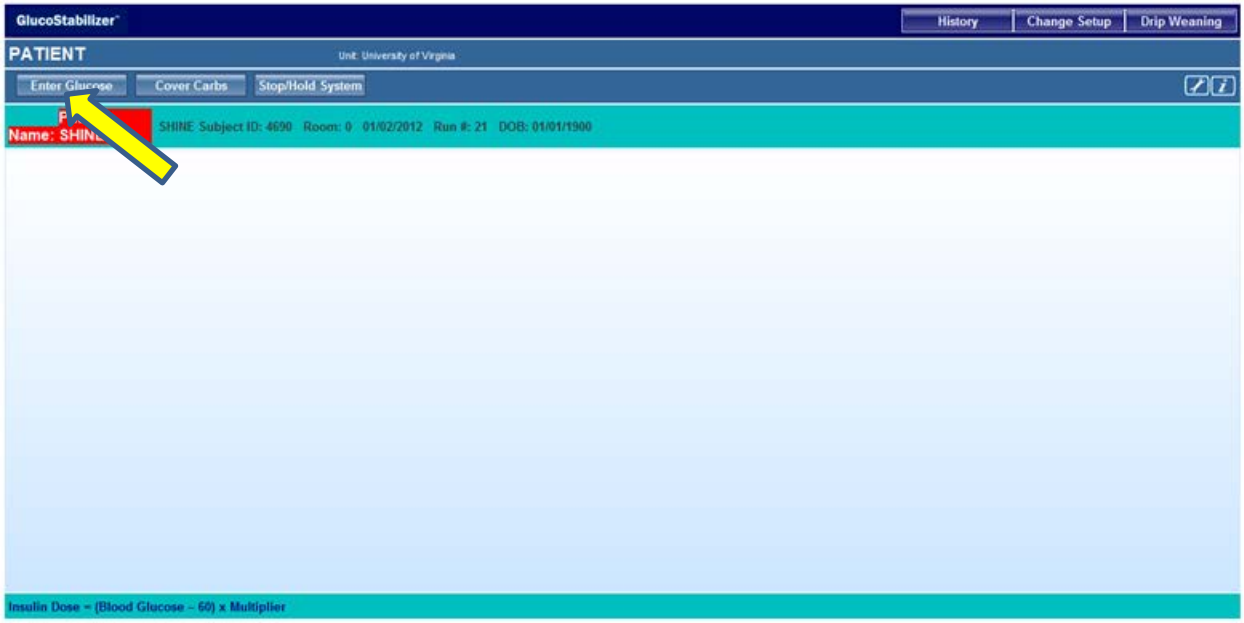
(xi) Remember that the study patient is blinded to his or her treatment group. Care should be taken to maintain the blind. Note that GlucoStabilizer® will display dosing recommendations for IV insulin. Use the lock program option if the study laptop will remain in the patient room so that this will only be visible to the treating and study teams and not the study patient and his or her family/friends.

(xii) Once the IV insulin infusion is ready to be started, check the POC glucose immediately prior to starting infusion. This value will be entered into the GlucoStabilizer® tool.

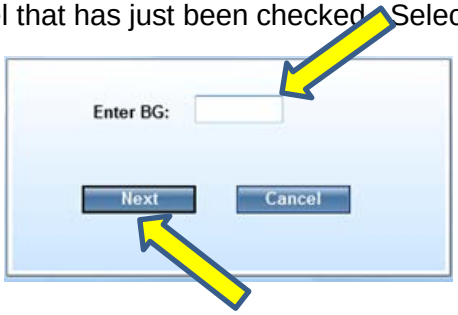
(d) IV insulin initiation

(i) A new finger stick glucose measurement will be checked just prior to initiation of therapy.

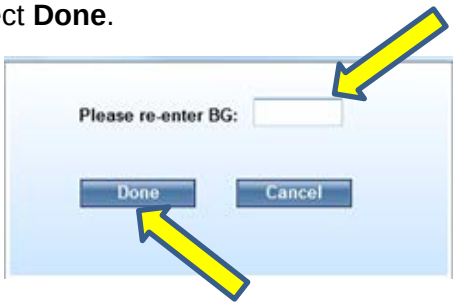
(ii) On the GlucoStabilizer® main page, select **Enter Glucose**.



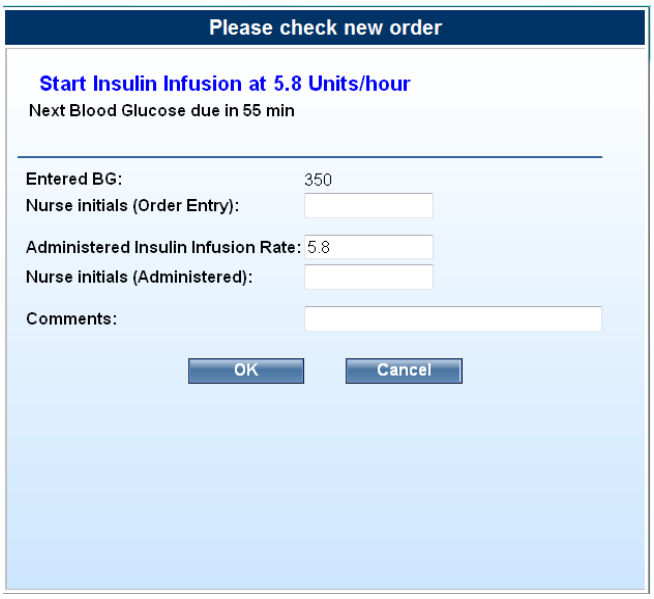
(iii) A pop up will display "**Enter BG**". Type the result of the POC glucose level that has just been checked. Select **Next**.



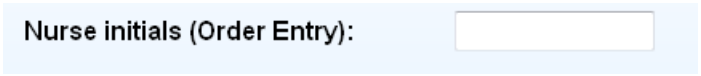
(iv) A prompt will display "**Please re-enter BG**". Type in the result again and select **Done**.



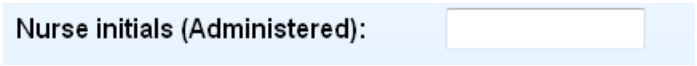
(v) A pop-up will display "**Please check new order**". The nurse will be instructed to **Start Insulin Infusion at __ Units/hour**. GlucoStabilizer® has calculated an individualized insulin infusion rate based on the glucose level just entered.



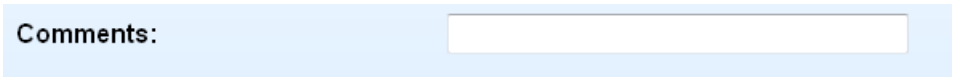
(vi) The nurse will enter his or her initials in the box for **Nurse initials (Order Entry)** to confirm the POC glucose result.



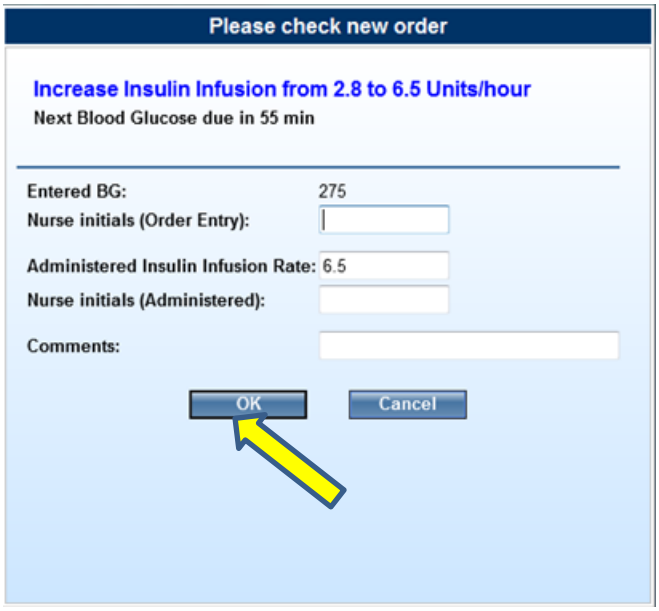
(vii) The nurse will enter his or her initials again in the box for **Nurse initials (Administered)** to acknowledge the rate of the insulin infusion and to confirm that the rate was adjusted.



(viii) A Comments box allows the nurse to make notes as needed. For example, treatment on hold for MRI or patient being discharged.



(ix) Select **OK**.



(x) The GlucoStabilizer® will display current orders with the date and time. The time that the next blood glucose is due will initially be 55 minutes and count down will display on the screen. The display will countdown from 15, 55, or 115 minutes (usually from 55).

(xi) The details of the treatment will also be displayed, including the current rate of infusion and multiplier, the time the next blood glucose check is due, the latest blood glucose result, the target BG range and carbohydrate ratio.

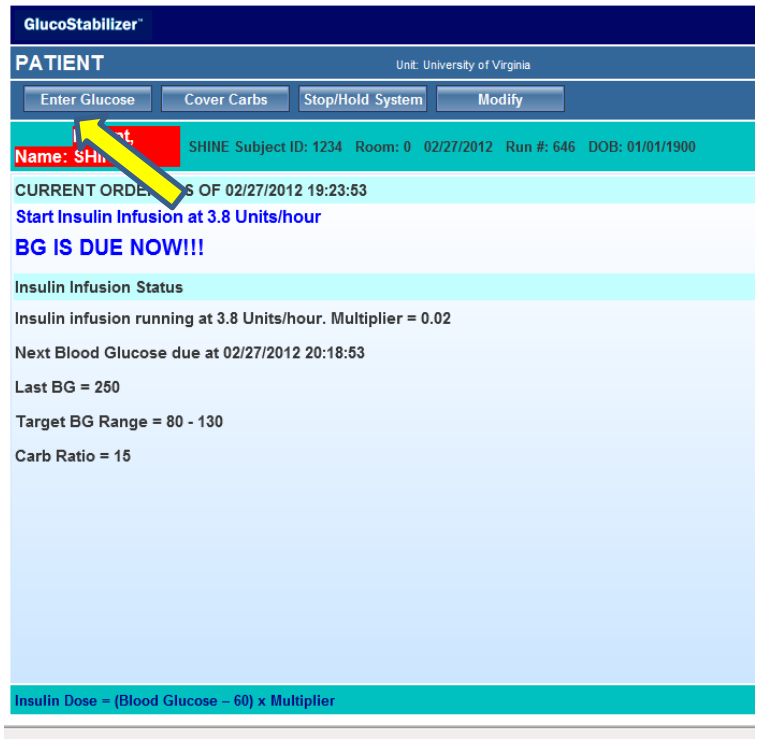
(xii) The second blood glucose check will be due in 60 minutes, but the after will sound after 55 minutes.

(4) **GlucoStabilizer® continuing infusion for the intervention group**

(a) 55 to 115 minutes after the previous BG entry, the GlucoStabilizer® screen will display a blinking message "**BG IS DUE NOW**!!!". An audible alert will accompany this message. Neither visual nor auditory alerts can be disabled.

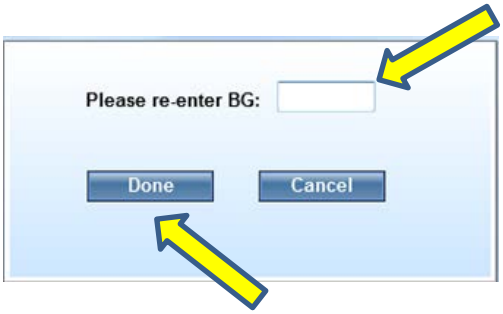
(b) The nurse will check the patient's blood glucose at the time of the alert using a POC glucose test to assure that the new infusion rate is initiated on time.

(c) Select **Enter Glucose** on the GlucoStabilizer® screen.



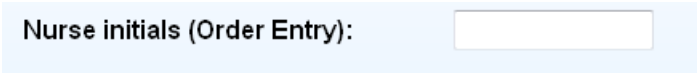
(d) Again, a pop up will prompt the nurse to "**Enter BG**". Type the result of the POC glucose check. Select **Next**.

(e) The nurse will be asked to "**Please re-enter BG**". Type in the result again and select **Done**.

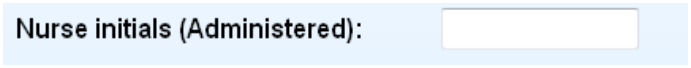


(f) A pop-up will display "**Please check new order**". The new rate for the Insulin Infusion will be displayed based on the glucose entered.

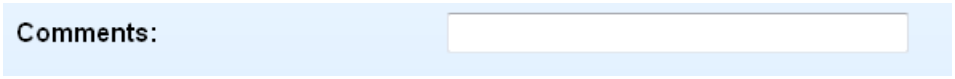
(g) The nurse will enter his or her initials in the box for **Nurse Initials (Order Entry)** to confirm the POC glucose.



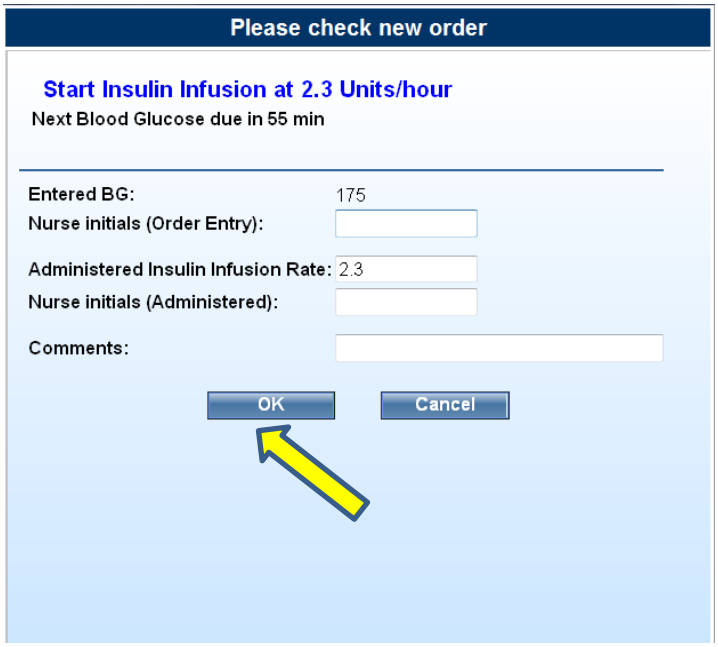
(h) The nurse will enter his or her initials again in the box for **Nurse initials (Administered)** to acknowledge the rate of the insulin infusion and that the rate was adjusted.



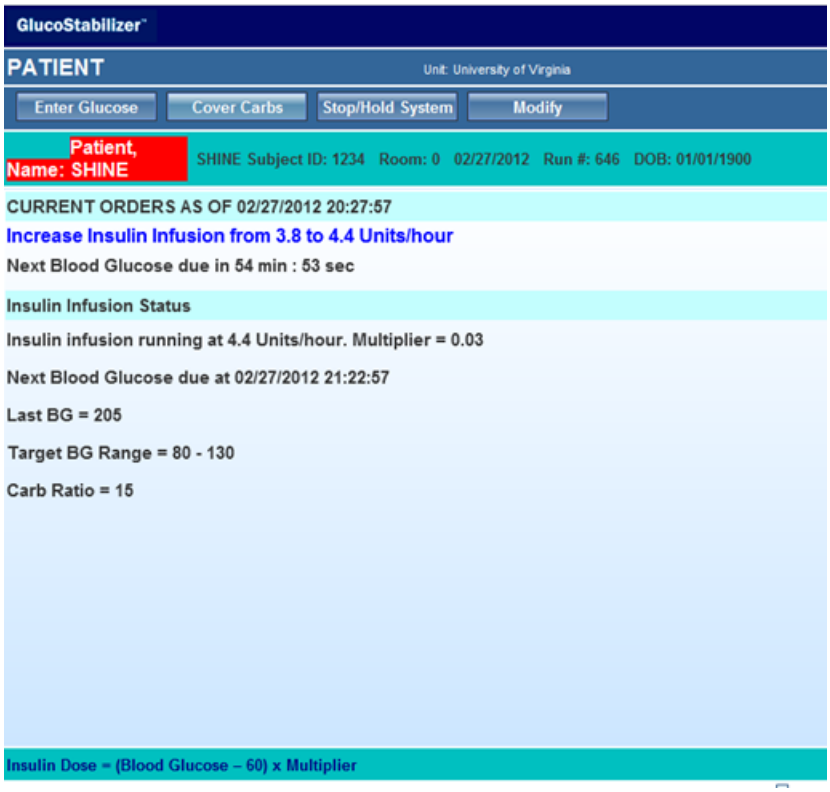
(i) Enter notes in the Comments box as needed.



(j) Select **OK**.



(k) GlucoStabilizer® will display the current orders with the date and time. The next blood glucose check will initially be due in 55 minutes and then may be due up to 115 minutes later. This is determined by the GlucoStabilizer®, and the countdown will display on the screen. The details of the treatment will also be displayed, including the current rate of infusion and multiplier, the time the next blood glucose is due, the latest blood glucose result, the target BG range and the carb ratio.



(l) 55 to 115 minutes after the previous BG entry, the GlucoStabilizer® screen will display blinking message "**BG IS DUE NOW**!!!". An audible alert will accompany this message.

(m) At the time of the alert, the nurse will check the patient's blood glucose using a POC test to assure that the new infusion rate is initiated on time.

(n) For each glucose check and insulin infusion rate adjustment (if indicated) throughout the protocol, these steps will be repeated.

(o) If the glucose drops below 80 mg/dL at any time, GlucoStabilizer® will direct the nurse to follow specific hypoglycemia prevention and management instructions.

The clinical nurse or study team may choose to decline the GlucoStabilizer® infusion recommendation. To do so, document the actual infusion rate in the Administered Infusion Rate field and enter a comment to explain. A pop up box will display "The administered insulin infusion rate is different from the ordered rate. Would you like to continue?" Click OK. The SHINE Study Hotline should be notified when rate recommendations are declined by calling 800-915-7320 (ext.1).

FAQ Q: We have a patient in the intervention arm and just did a glucose check. GlucoStabilizer is recommending that the insulin infusion rate is decreased to 0.3 u/hr. The pump doesn't go any lower than 0.5 u/hr.

A: In any case when the GlucoStabilizer recommendation is lower than the lowest infusion rate of the pump, decline the recommendation. Enter 0 for the infusion rate when confirming the blood glucose and administration rate. Turn off the drip and document that the infusion was stopped in the medical record. The GlucoStabilizer will continue to count down to next check, and the visible alert will appear and the audible alert will sound when the glucose check is due. Check the glucose, enter and re-enter the value, and if the recommended rate is one that your infusion pump can accommodate, restart the infusion at that rate. If the recommended rate continues to be lower than the lowest rate for your infusion pump, repeat the steps above to decline the recommendation and check again per GlucoStabilizer.

(5) **Hypoglycemia prevention and management**

(a) The hypoglycemia prevention and management protocol will be initiated for any patient whose glucose concentration drops below 80 mg/dL.

(b) Definitions

(i) Blood glucose < 80 mg/dL → initiate hypoglycemia prevention and management protocol

(ii) Hypoglycemia: defined as a blood glucose < 70 mg/dL

(iii) Severe hypoglycemia: defined as a blood glucose < 40 mg/dL

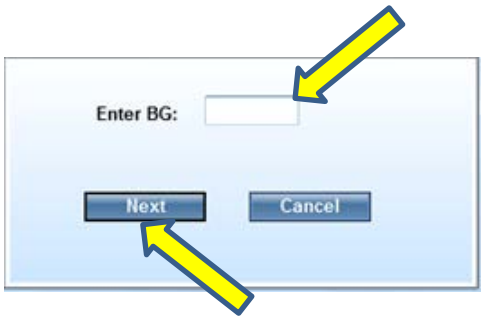
(c) **Hypoglycemia protocol for intervention group**

(i) If the blood glucose drops to < 80 mg/dL the GlucoStabilizer® will automatically instruct the nurse to follow special hypoglycemia prevention instructions (stop all insulin treatments, give an individualized IV dose of 50% glucose (D50).

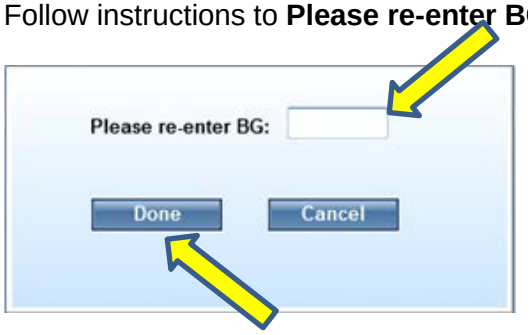
(ii) **Stop the insulin infusion and hold all subcutaneous insulin/saline injections when the glucose is < 80 mg/dL!** Meal insulin should not be given when glucose is < 80 mg/dL at any point during the meal.

(iii) To record the glucose measurement and receive D50 dose recommendation, select **Enter Glucose**.

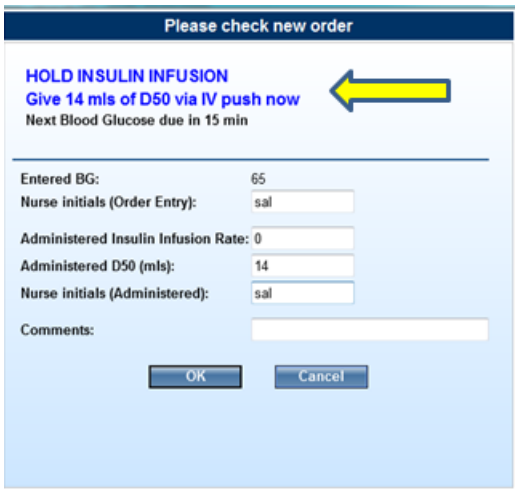
(iv) A pop up will prompt the nurse to "**Enter BG**". Type the result of the POC glucose check. Select **Next**.



(v) Follow instructions to **Please re-enter BG** and select **Done**.



(vi) A pop-up will display "**Please check new order**". When the blood glucose is <80 mg/dL, a message will display **HOLD INSULIN INFUSION**. The nurse will be instructed to "Give an individualized dose of D50 via IV push now". This dose will be based on the glucose level just entered.

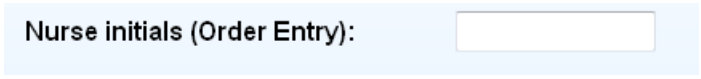


(vii) Confirm that the **INSULIN INFUSION IS STOPPED AND ALL SUBCUTANOUS INSULIN/SALINE INJECTIONS ARE BEING HELD**.

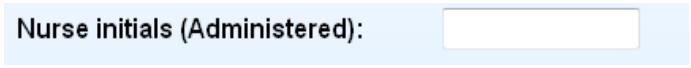
(viii) D50 and syringes with graduated marks for volume (mL) will be readily accessible.

(ix) Give individualized dose of D50 slow IV push (over 1-2 minutes).

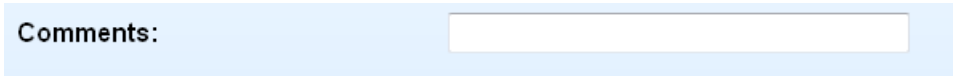
(x) The nurse will enter his or her initials in the box **for Nurse initials (Order Entry)** to confirm the POC glucose result.



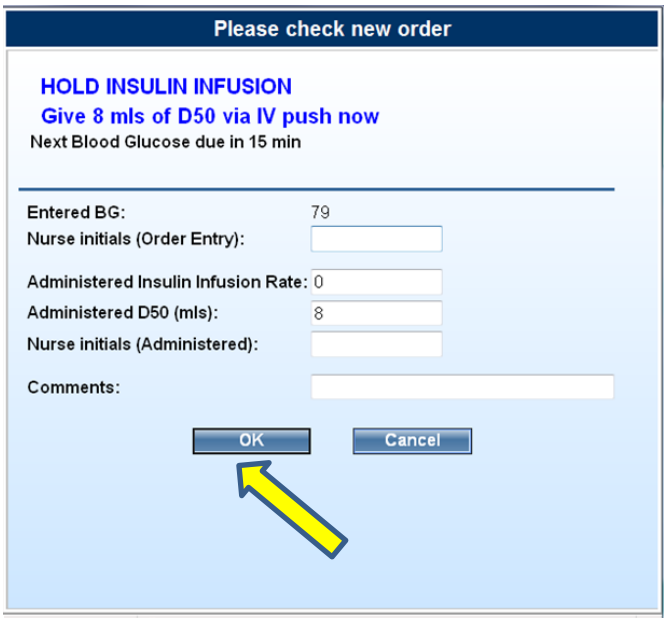
(xi) The nurse will enter his or her initials again in the box **(Order Entry)** and **Nurse initials (Administered)** to acknowledge that the D50 was administered.



(xii) A Comments box allows the nurse to enter notes as needed. For example, treatment on hold for MRI or patient being discharged.



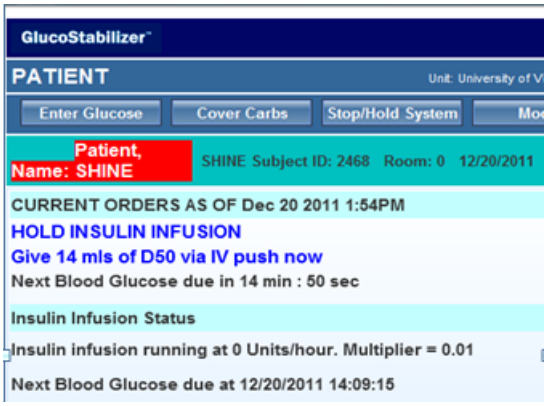
(xiii) Enter OK.



(xiii) **<u>GlucoStabilizer® will not capture the information unless OK is selected</u>**. If this screen times out, repeat the steps to enter the BG and accept the recommendation.

(ix) The next glucose check will be **due in 15 minutes**. This time will countdown on the GlucoStabilizer® main page.

(xv) POC glucose measurements will be checked and recorded every 15 minutes when the glucose is < 80 mg/dL. GlucoStabilizer® will show verbal and sound audible alarms every 15 minutes until a BG of > 80 mg/dL is entered.



(xvi) At the completion of the countdown, which is 15 minutes after the previous BG entry for blood glucose < 80 mg/dL, the GlucoStabilizer® screen will display blinking message "**BG IS DUE NOW**!!!". An audible alert will accompany this message.

(xvii) The nurse must check the POC glucose at the time of the alert. These steps will be repeated for every glucose measurement that is < 80 mg/dL.

(xviii) If the glucose drops below 70 mg/dL, additional steps are required and described below in Section 6 below (Additional steps for blood glucose < 70 mg/dL).

(xix) 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).

(6) Additional steps for blood glucose < 70 mg/dL

If the blood glucose drops < 70 mg/dL, the following additional actions are required:

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

(ii) Draw a STAT laboratory serum glucose measurement but do not delay treatment with D50 by waiting for this blood draw result. Only the results from POC glucose checks should be used for study treatment dosing. The study coordinator will document the result of the serum glucose measurement.

(iii) Screen the patient for hypoglycemia symptoms using Hypoglycemia Symptomatic Questionnaire.

1. The worksheet and instructions will be available on paper and on the desktop of the laptops.
2. The Hypoglycemia Symptomatic Questionnaire must be repeated every 15 minutes when glucose is < 70 mg/dL.
3. Once the glucose is ≥ 70 mg/dL, no additional assessments with the Hypoglycemia Symptomatic Questionnaire are required
4. Once the glucose is ≥ 80 mg/dL, the timing of glucose checks and insulin infusion rate will again be determined by the GlucoStabilizer®.

(iv) Screen the patient for neurological worsening.

1. An assessment of neurological change is required per site standard care (“neuro check”) every 15 minutes when glucose is < 70 mg/dL even if there are no new neurological findings

2. The **SHINE study definition of neurological worsening** is any clinical change that is associated with a ≥ 4 point increase from baseline on the NIHSS score. (Baseline is considered to be the most recent daily NIHSS.)
3. Any patient with neurological worsening will be assessed for hypoglycemia and for relatedness of the hypoglycemia to neurological worsening if present.
4. If the patient has not returned to neurological baseline within 24 hours, a NIHSS assessment is required within 24 (+/-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.
5. If neurological worsening (persists for ≥ 24 hours) is associated with a glucose concentration < 55 mg/dL, an SAE form is required.

(v) If the glucose falls below 40 mg/dL at any time, an SAE form and a call to the SHINE safety hotline are required.

FAQ Q: Our subject in the intervention group had a worrisome hypoglycemia of 49 mg/dL, which corrected with D50. Is there anything that we can do to help avoid additional episodes of hypoglycemia?
A: Perhaps yes. Sometimes a reason can be identified, such as errors in insulin dosing (too much), taking non-study antidiabetic medications by mistake, sneaking in high sugar snacks that can mislead the Glucostabilizer program into recommending too much insulin, or a change in medical status that can affect insulin sensitivity (e.g. infection). Consider whether any protocol deviations occurred as they can be corrected. Call the SHINE hotline for instructions on hypoglycemia related to protocol deviations (might be best to start a new drip). Also, some patients on the Glucostabilizer protocol occasionally do have recurrent hypoglycemia episodes (<70 mg/dL) for no apparent reason. Remember to call the SHINE hotline for 3 episodes of hypoglycemia (<70 mg/dL) within any 24 hour period, or for a single measurement of <40 mg/dL.

(7) Meal insulin for the intervention group

(a) General concepts-SHINE protocol-recommended diet

1. For patients who are cleared for a PO diet, a 60 grams/meal carbohydrate diet will be ordered for breakfast, lunch and dinner as part of standard care. Meals will be encouraged, but not required, to be delivered at approximately 06:00, 12:00 and 18:00.
2. Patients receiving tube feeds may receive bolus or continuous tube feeds per standard care. Bolus tube feeds will also be encouraged to be given at around 06:00, 12:00 and 18:00.
3. Dietary teams should be involved in assuring that the 60 grams/meal carbohydrate diets are maintained throughout the study protocol.
4. About twenty minutes after the initiation of a meal estimate meal consumption. If the patient is not finished eating, an estimate of the likely total consumption is required.
5. Estimate the proportion of the meal consumed by the patient. This estimate is based on the entire meal irrespective of its subparts or food groups.
    i. Full or near full consumption → 60 grams carbohydrates

ii. No or nearly no consumption → 0 grams carbohydrates (no entry should be made in GlucoStabilizer ® and no meal insulin should be administered)
iii. Partial consumption →30 grams carbohydrates

6. Note that only 30 grams or 60 grams can be entered into GlucoStabilizer®. No other values should be entered or GlucoStabilizer® will recommend an incorrect meal insulin dose.
7. If no or nearly no consumption is estimated, no meal insulin (carb coverage) is required. Because no meal insulin is required, no entry in GlucoStabilizer® should be made. No injection is given.
8. Patients should not consume additional food not included on the meal tray from the hospital kitchen aside from protocol-approved snacks.
9. 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.

FAQ Q: What do we do if the glucose check is due at the same time we're getting ready to enter the carb coverage in GlucoStabilizer?

A: When you make an entry in the 'Cover Carbs' function in GlucoStabilizer, the timing of the next check is automatically pushed out to 1 hour later (even if the clock has been counting down and a glucose check is almost due). If a glucose check is almost due and you enter the carb consumption, you will not be prompted to check the glucose for another hour. If you have a patient who is on the q2 hour schedule for checks, this means that it could be nearly 3 hours between glucose checks. Because we want to avoid this, clinical nurses are encouraged to use the +/-15 minute window for glucose checks to ensure that a check is done at the time that it is due. If the clock is counting down and the meal has arrived, make every effort to hold the meal until the glucose check is due (+/-15 minutes). Once you have entered the glucose and received the insulin infusion rate recommendation, the patient can begin the meal. This will help to avoid a gap in glucose checks.

(b) Protocol-approved snacks

SHINE patients may also consume up to 2 low carbohydrate snacks (< 5 grams carbohydrates per serving) from the list below between meals (up to 6 low carbohydrate snacks daily). The study protocol diet does not limit the consumption of sugar free foods and drinks listed in the unlimited category below. Patients should only consume food included on the meal tray from the hospital kitchen or the protocol approved snacks during the 72 hour treatment period.

For patients in the intervention group, there is NO estimate of consumption for snacks, NO entry in GlucoStabilizer® and NO insulin coverage. Snacks must be documented in the medical record. The study protocol should be followed for meal consumption estimates and meal insulin dosing only for breakfast, lunch and dinner.

<u>Low carbohydrate snack options (up to 2 between meals)</u>

5 celery sticks + Tablespoon peanut butter
5 baby carrots
5 cherry tomatoes + 1 Tablespoon ranch
1 hard-boiled egg
½ cup raw broccoli + 1 Tablespoon ranch
1 cup cucumber slices + 1 Tablespoon ranch dressing

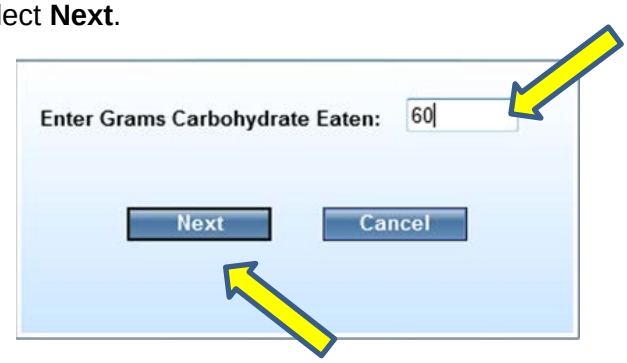
¼ cup of fresh blueberries
1 cup of salad greens, 1/2 cup of diced cucumber, and with vinegar and oil
2 saltine crackers
1 piece of string cheese stick
½ cup of egg salad, tuna salad or chicken salad
3 oz of deli ham, chicken or turkey slices
1 serving of cubed or sliced cheese (1 oz)
½ cup cottage cheese
½ cup tofu
1 slice deli ham, chicken or turkey + 1 slice cheese

Unlimited
Bouillon and broth
Club soda, unsweetened
Coffee, unsweetened or artificial sweeteners only
Diet soft drinks
Flavoring extracts
Horseradish
Mineral water
Mustard
Pickles
Soy sauce
Spices
Sugar-free drink mixes
Sugar-free gum
Sugar-free Jell-O
Tabasco or hot sauce
Unsweetened lemon or lime juice
Unsweetened tea
Vinegar

(c) Subcutaneous meal insulin dosing using GlucoStabilizer®

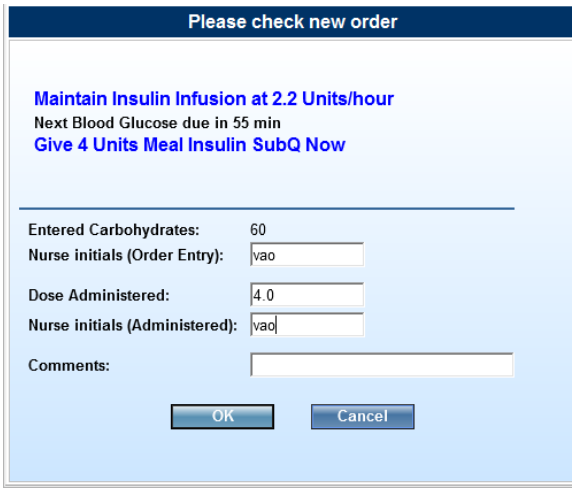
1. The GlucoStabilizer® will indicate the meal insulin dose for patients who are eating based on the quantity of carbohydrates in a meal and the specified insulin to carbohydrate ratio (1:15). This means that one unit of insulin will cover 15 grams of carbohydrates consumed.
2. Only rapid acting analog insulin (Humalog, Novolog, and Apidra are all acceptable rapid acting analog insulins) will be used to cover meal carbohydrates. Human regular insulin (Humulin R or Novolin R) **MUST NOT** be used for subcutaneous injections in the intervention group. (See Section 12- Pharmacy Manual)
3. Follow study site protocol for obtaining rapid acting analog insulin and syringes for subcutaneous injections.
    a. Nurses will prepare and inject the rapid acting analog insulin according to the recommendation of the GlucoStabilizer®.
    b. The meal insulin will be given after assessment of consumption.
    c. The GlucoStabilizer® will determine the meal insulin dose. If the patient has consumed part or all of the meal, select the option to **Cover Carbs** on the GlucoStabilizer® main page.

d. A pop up will display "**Enter Grams Carbohydrate Eaten**"
e. Based on the estimated portion of the meal eaten, enter the following in GlucoStabilizer®:
f. Partial consumption→Enter **30**. Full or near full consumption → Enter **60**, No or nearly no consumption → **No entry should be made,**
g. Select **Next**.



h. A pop up will display "**Re-enter Grams Carbs Eaten**". Re-enter and select **Done**.

i. A pop-up will display "**Please check new order**". This will include instructions to maintain insulin infusion and to give an individualized dose of subcutaneous meal insulin.



j. The nurse will enter his or her initials in the box for **Nurse initials (Order Entry)** and **Nurse initials (Administered)** to confirm the entered carbohydrates, to acknowledge the maintenance of the insulin infusion rate (this will NOT change) and the administration of the subcutaneous meal insulin. Select **OK**.

k. **Note that the nurse must select OK within 2 minutes or this pop-up box will time out and the meal consumption and rapid acting insulin dose will not be captured**, and the time of the next glucose check will not update as needed. The nurse must confirm that the order is accepted by clicking OK.

n. Upon acceptance of the recommendation and clicking OK, the GlucoStabilizer® will display the current orders for the insulin infusion rate and if applicable the dose of the subcutaneous insulin injection.

o. The time that the next blood glucose is due will continue to count down on the screen. The details of the treatment status will also be displayed, including the current rate of infusion and multiplier, the time the next blood glucose is due, the last blood glucose result, the target BG range and carb ratio.

p. The nurse will give the subcutaneous injection of the rapid acting insulin.

xii. 60 grams carbohydrates consumed = 4 units of SQ rapid acting analog (meal) insulin will be recommended

xiii. 30 grams carbohydrates consumed =2 units of SQ rapid acting analog (meal) insulin will be recommended

q. Continue the steps described in GlucoStabilizer® continuing infusion for the intervention group (Section 5.1.2, (4).

4. If a glucose check is due at nearly the same time as the meal, check the glucose first and adjust the infusion prior to giving the meal.

FAQ Q: Should meal insulin be given if a study patient was hypoglycemic at the beginning of the meal?

A: When the blood glucose is < 80mg/dL, the hypoglycemia prevention and management protocol indicates that the insulin infusion should be stopped and all subcutaneous insulin injections should be held. Any time that any portion of the meal occurs at the same time that the BG < 80mg/dL and the hypoglycemia protocol has been initiated, the meal insulin should not be administered for that meal. An example of the way that this could occur is that if a glucose check happens to be due at the same time the meal is delivered. If the glucose is < 80mg/dL, the hypoglycemia protocol will be initiated. If the patient starts eating while the glucose is known to be < 80mg/dL, no meal insulin should be given. Because no meal insulin should be administered, no entry in GlucoStabilizer should be made, and no injection is given. Consumption should be documented on the study CRF (Form 20: Daily Care Log). The questions, 'Was meal insulin given?' should be answered "No", and the reason should be listed as "Other". Specify that the reason that no meal insulin was given and "Other" was selected was due to the "Hypoglycemia protocol".

The D50 should always be given per the recommendation of GlucoStabilizer - even if the patient is just starting to eat at the same time. Questions about the hypoglycemia protocol and meal insulin dosing can be directed to the SHINE PI on call, and concerns about safety should be directed to the Independent Safety Monitor.

(c) Bolus tube feeds

(i) For patients receiving bolus tube feeds, a 60 grams/meal carbohydrate bolus feed is recommended.

(ii) Bolus tube feeds will also be encouraged to be given at around 06:00, 12:00 and 18:00.

(iii) The nurse will estimate the proportion of the bolus given.

1. 50-60 grams carbohydrates/bolus → Enter 60 grams carbohydrates in GlucoStabilizer®
2. 0-9 grams carbohydrates/bolus → No entry in GlucoStabilizer® is indicated.
3. 10-49 grams carbohydrates/bolus →Enter 30 grams carbohydrates in GlucoStabilizer®

(iv) If a glucose check is due at nearly the same time as the bolus tube feed, check glucose first and adjust the infusion prior to giving the bolus.

(d) NPO or Continuous tube feeds

(i) **Continuous tube feeds** - For patients receiving continuous tube feeds**, no meal insulin is given**. Patients who are receiving continuous tube feeds will receive placebo saline subcutaneous injections TWO times per day. Continuous tube feeds should include approximately 180 grams of carbohydrates per day. Special instructions are provided on the study protocol when there are interruptions in continuous tube feeds (see Section 9 - Procedure for interruptions in continuous tube feeds below).

(ii) **NPO** – For patients who are NPO, **no meal insulin is given**. Patients who are NPO will receive placebo saline subcutaneous injections TWO times per day.

(iii) **Subcutaneous saline injections (only for patients who are not eating AND in intervention group of study)**

Patients who are not eating or are receiving continuous tube feeds will receive placebo saline subcutaneous injections TWO times per day (at approximately 9:00 and 21:00 associated with a glucose check).

The clinical/research nurses will prepare and inject subcutaneously 0.05 ml of sterile saline using 1cc syringes. The subcutaneous saline injections are needed to maintain the blind and simulate the 0-4 subcutaneous insulin injections in the control group.

Only patients that are NPO (nothing by mouth) or on full continuous tube feeds AND in the intervention group should get the saline injections.

FAQ Q: We enrolled a patient who was cleared for a PO diet as soon as she was admitted to the stroke unit. At each meal, however, she has eaten none or nearly none of the food on the tray. Do we need to be giving her the SQ saline injections at 09:00 and 21:00 since she is not eating?

A: SQ saline should only be ordered for patients who are NPO or on continuous tube feeds. SQ meal insulin should be ordered for patients who have been cleared for a PO diet or are on bolus tube feeds. If a patient is cleared to eat but is not eating, do NOT give SQ saline. The decision about which SQ study treatment is appropriate in the intervention group should be based on the active diet order.

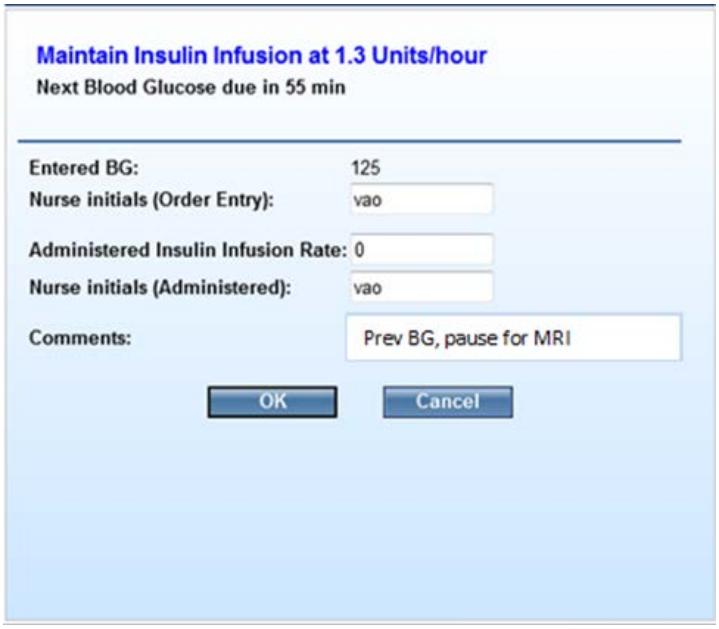
		SHINE TREATMENT GROUP	
		INTERVENTION GROUP	**CONTROL GROUP**
NUTRITIONAL STATUS	**Eating PO meals or Bolus Tube Feeds**	**IV insulin** plus **Subcutaneous meal insulin injections** **How much IV Insulin?** Per GlucoStabilizer recommendation **How many units SQ meal insulin?** Per GlucoStabilizer recommendation based on proportion of meal consumed given 20 minutes after start of meal 3x/day @ **0600, 1200, & 1800**	**IV saline** plus **Subcutaneous sliding scale insulin injections** **How much IV saline?** Per Sliding Scale Control Treatment Screen **How many units SQ insulin?** Per Sliding Scale Control Treatment Screen Finger stick glucose check @ 0300,**0600**,0900,**1200**,1500,**1800**,2100,**2400** (Insulin dosing only @0600, 1200, 1800, & 2400)
	NPO or Continuous Tube Feeds	**IV insulin** plus **Subcutaneous saline injections** **How much IV Insulin?** Per recommendation of GlucoStabilizer **How much SQ saline?** 0.05 mL of SQ saline @ time of glucose check nearest 0900 and 2100	**IV saline** plus **Subcutaneous sliding scale insulin injections** **How much IV saline?** Per Sliding Scale Control Treatment Screen **How many units of SQ insulin?** Per Sliding Scale Control Treatment Screen Finger stick glucose check @ 0300,**0600**,0900,**1200**,1500,**1800**,2100,**2400** (Insulin dosing only @0600, 1200, 1800, & 2400)

(8) Pauses in intervention treatment

(a) When a SHINE intervention treatment is temporarily interrupted for any reason (e.g. patient needing to go off the care unit and the clinical nurse cannot accompany the patient to maintain the SHINE study procedures), the IV insulin drip should be stopped.

(b) In the GlucoStabilizer®, click the tab “Enter Glucose”. Enter the previous glucose value. Re-enter the glucose value, and click OK.

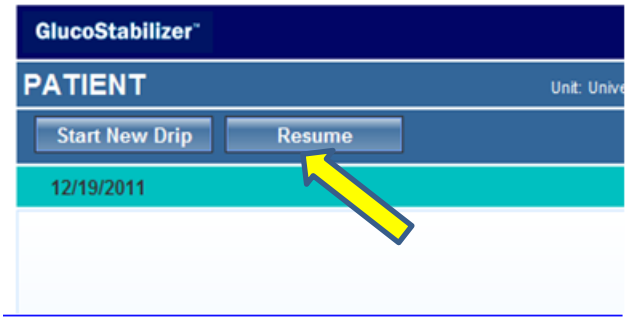
(c) Change the recommended infusion rate to “0”. The nurse will enter his or her initials in the box for Nurse Initials (Order Entry) and Nurse initials (Administered) to confirm that this infusion rate is 0. In the Comment field, document the pause and that the glucose value entered is from the previous check (Ex. “Previous BG, pause for MRI). Select OK. A pop up box will appear asking, “The administered insulin infusion rate is different from the ordered rate. Would you like to continue?” Select OK.



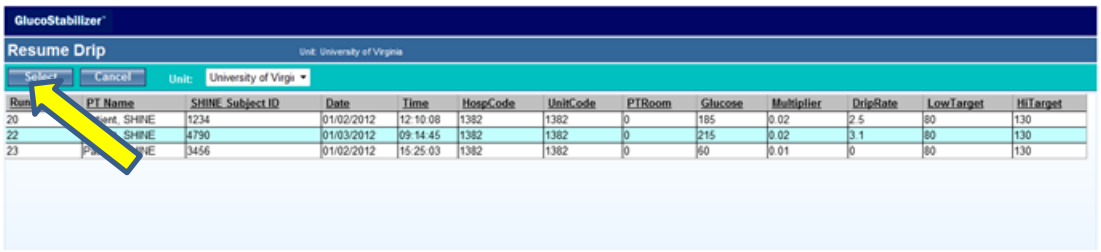
(d) Select “Stop/Hold System”. A pop up box will appear asking “Would you like to Stop/Hold System?” click OK.

(e) Upon return to the unit, follow the instructions below to return to the study protocol.If the IV insulin infusion has been off for < 3 hours; follow the instructions below to **resume the drip**.

1. Select **Resume**.

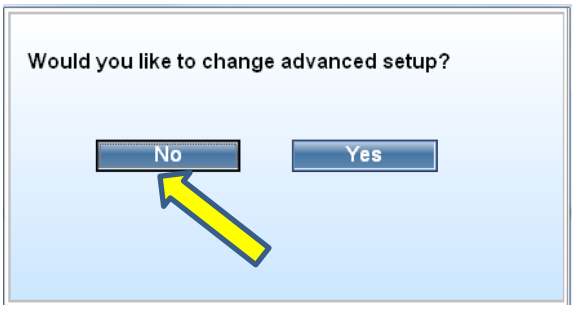


2. Put cursor in the row for the study patient and choose **Select**.



3. Review the Drip Setup, confirming the SHINE Subject ID. Select **Save**.

4. Select **No** for changing to advanced setup.

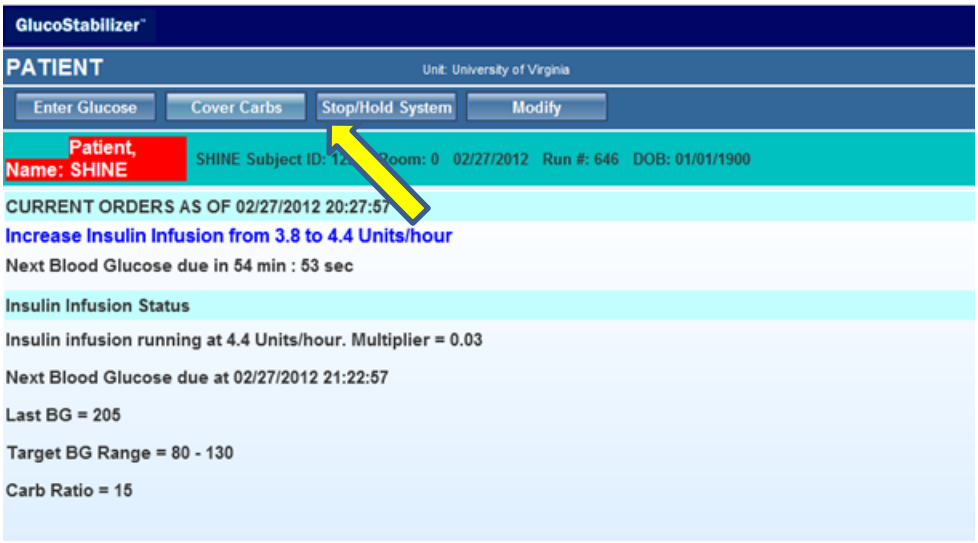


5. The home screen of the GlucoStabilizer® will display with the current countdown ongoing.
6. Follow instructions in Section 5.1.2 (4)-GlucoStabilizer® Continuing Infusion to repeat the glucose check and insulin dosing adjustments per protocol.

(i) If the IV insulin infusion has been off for ≥ 3 hours, follow the instructions as described above to **start a new drip** (Section 5.1.2 (3) GlucoStabilizer® and IV insulin initiation).
(ii) For patients that are NPO or on continuous tube feeds, if a scheduled SQ saline injection was missed during the pause, give the dose immediately after the glucose check to restart the insulin infusion.

(9) Procedure for interruptions in continuous tube feeds

(a) When there is a pause in the continuous tube feeds for patients in the intervention group, subcutaneous saline injections will continue per protocol unless the patient is cleared for PO diet or bolus tube feeds.
(b) When there is an interruption in continuous tube feedings in the intervention group, the insulin drip will be stopped, and the option to stop/hold GlucoStabilizer® will be selected.



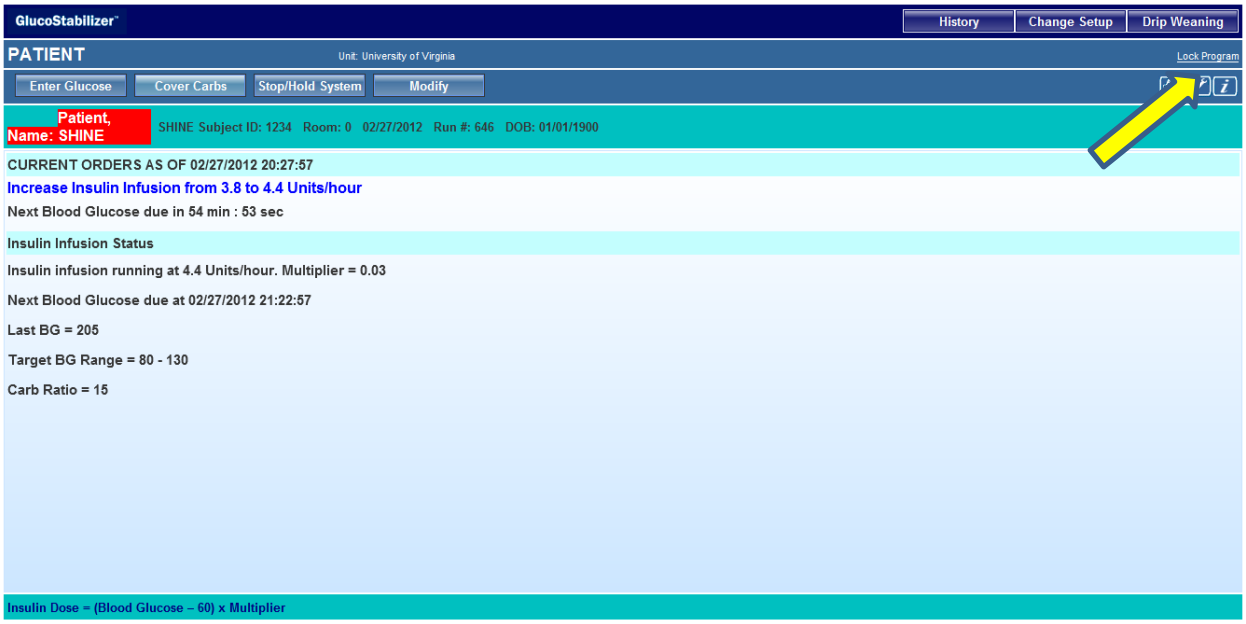
(c) If the continuous tube feeds are **restarted within 1 hour** after the drip was stopped, the nurse will select the GlucoStabilizer® option to '**Resume'** and check the glucose and re-start the insulin drip per recommendation of GlucoStabilizer®.

If the continuous tube feeds have not been restarted within 1 hour, the nurse will select the GlucoStabilizer® option to '**Start a New Drip'**, check the glucose and re-start the insulin drip at the rate recommended by GlucoStabilizer®.

(10) Locking the GlucoStabilizer® Program

When the nurse leaves the bedside, the GlucoStabilizer® should be locked.

(i) Choose lock program



(i) Upon return to the bedside, unlock the GlucoStabilizer® by entering the username and password (shine/shine). The Lock Program feature is designed to help maintain the blind.

(12) Stopping study treatment when there is a change in diagnosis of ischemic stroke/stroke mimic

(a) In the event that there is a change in the diagnosis of ischemic stroke during the 72 hour treatment period, all study treatments should be stopped at the time that the study team receives knowledge of the new diagnosis.

(b) The clinical care team will determine glucose control therapy after the SHINE treatment protocol is discontinued.

(c) Instructions for completing CRFs when the study treatment is stopped due to a change in diagnosis of ischemic stroke

(i) The Day 1-Day 3 visits should be completed only during the period of time that the patient was receiving study treatment.

(ii) The final diagnosis will be captured on the Study Treatment CRF (Form 15) as: Migraine, Seizure, Brain tumor/mass, Psychogenic, Anamnestic syndrome, CNS Infection (abscess, meningitis, encephalitis), Toxic/metabolic (encephalopathy) and Other: specify).

(iii) A brief narrative explaining the change in diagnosis is required. This narrative should include sufficient information to demonstrate that the new diagnosis is most likely including appropriate imaging and laboratory data. A brief narrative template is included in WebDCU: [On _____(full date), the diagnosis was changed to _____. This diagnosis was based on _____(lab/imaging results) and _____(clinical information).]

(iv) On the Study Treatment CRF (Form 15), the study treatment status should be captured as: Started but discontinued prior to 72 hours of study treatment

(d) The End of Study Visit must be completed. Unless consent is withdrawn, patients whose treatment ends early are still in the study and the 6 week and 90 day follow up visits must be completed in addition to the End of Study Visit.

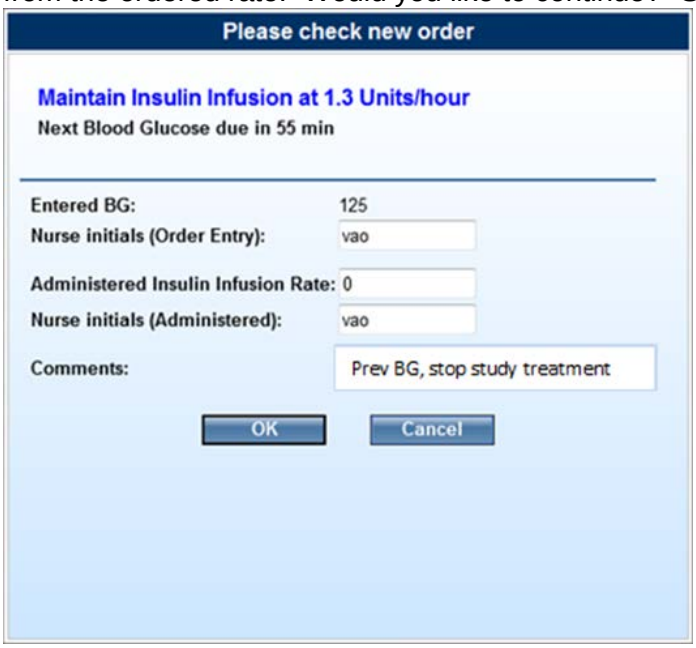
(13) Transition from study treatment

(a) The start time for the study treatment period is the time of randomization. The treatment period will be 72 hours or until the time of discharge from the hospital, whichever comes first.

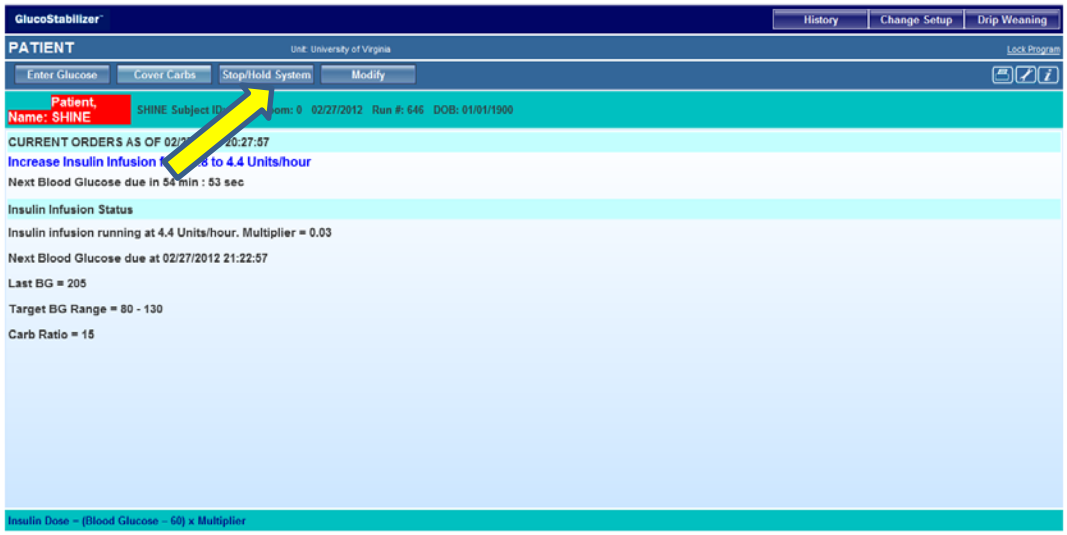
(b) At the end of the treatment period, the clinical nurse should chart that the study infusion was stopped in the medical record and follow these steps to document the end of study treatment in GlucoStabilizer®.

(i) In the GlucoStabilizer®, click the tab "Enter Glucose". Enter the previous glucose value. Re-enter the same value, and click OK.

(ii) Change the recommended infusion rate to "**0**". The nurse will enter his or her initials in the box for **Nurse initials (Order Entry)** and **Nurse initials (Administered)** to confirm that this infusion rate is 0. In the Comment field, document the pause and that the glucose value entered is from the previous check (Ex. "Previous BG, pause for MRI). Select OK. A pop up box will appear asking, "The administered insulin infusion rate is different from the ordered rate. Would you like to continue?" Select **OK**.



(iii) Select “Stop/Hold System” in GlucoStabilizer®.



(iv) Select the option to “Log out” and shut down the study laptop.

(c) Patients who discontinue study treatment are required to do so 6 hours prior to actual discharge from the hospital.

(d) After the SHINE protocol ends, the clinical care team will determine inpatient and outpatient glucose control therapy. The treatment should be based upon on ADA/AACE guidelines and individual patient needs.[28]

(e) The table below offers information to consider for hospitalized patients requiring glucose control. These guidelines are not part of the SHINE protocol and are not required actions.

Considerations for the transition from study treatment to standard clinical care	
Option	**Comment**
Intravenous insulin drip	Consider IV insulin therapy in some critically ill patients per ADA guidelines.
SQ insulins, including regular, rapid-acting analog, and long-acting basal	Per ADA guidelines scheduled subcutaneous insulin that delivers basal, nutritional, and correction components is preferred. • An example of basal insulin is Lantus (glargine) SQ QD calculated based on previous 24 hour insulin requirements and given when the drip is being discontinued as suggested below. • An example of nutritional insulin (for patients who are eating) is rapid acting analog SQ insulin dosing based on meal carbohydrate consumption. • An example of correction insulin is regular SQ insulin dosing based on blood glucose level per sliding scale protocol. ADA guidelines caution against hyperglycemia escape when a patient is transitioned from intravenous to subcutaneous insulin therapy. An option to consider after stopping the SHINE insulin infusion, depending on individual patient needs, may be to give basal insulin right after the IV insulin is stopped. Check blood glucose in 30-60 minutes, and give SQ insulin to correct hyperglycemia as needed. Then consider continuing with a standard SQ insulin protocol.
Oral agents and injectable noninsulin therapies	Consider that oral agents are not recommended in hospitalized patients, but may be initiated or resumed in anticipation of discharge per ADA guidelines.
Hospital discharge education and instructions	Consider individualized discharge planning per ADA guidelines.

(ii) **Drip Weaning Report sample**

5.1.3 Control Group Protocol

Study treatment: IV saline + subcutaneous insulin injections
Target blood glucose: < 180 mg/dL

Once randomized to the control group (saline infusion + subcutaneous sliding scale insulin injections with a target blood glucose of < 180 mg/dL), the control treatment screen on the study laptop will be activated. A sliding scale for determination of the IV saline rate and subcutaneous insulin dosing will be provided on the control treatment screen. A schedule for the required timing of the glucose checks will also be displayed on the control treatment screen. Patients will continue on study treatment for 72 hours. Discontinuation prior to 72 hour is allowed when discharge is clinically indicated and requires that all study protocol treatment must be stopped at least 6 hours in advance of scheduled discharge.

(1) **Study treatment preparation**

(a) **Drug preparation**

(i) Upon randomization the SHINE study team will contact the pharmacy to communicate the randomization allocation. Study treatment must begin as soon as possible following randomization.

(ii) Orders for the study treatments are to be entered by the study investigator per site procedures.

(iii) The pharmacy will provide the study IV saline per site procedures.

(b) **Study patient preparation**

(i) The clinical nurse and/or study team will gather supplies for the IV saline infusion (catheter, tubing, infusion pump),) and will follow site procedures for obtaining supplies for the subcutaneous insulin injections.

(ii) Human Regular Insulin (Humulin R or Novolin R) must be used for the subcutaneous insulin injections in the control group.

(iii) If the patient advances to Level 3 on the sliding scale, a one-time dose of basal insulin will be given at 48 hours. Glargine (Lantus) must be used for this one-time subcutaneous basal insulin injection at a dose equal to 40% of previous day's (24 h) entire insulin dose.

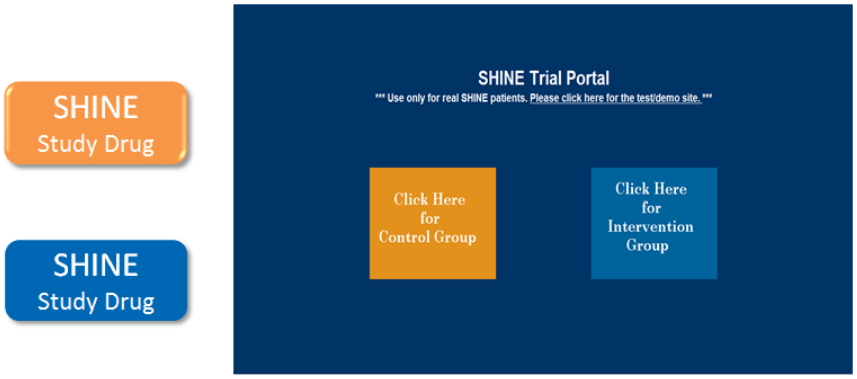
(iv) The D50 will be stored to allow immediate availability at the bedside. If a patient in the control group becomes hypoglycemic (< 80 mg/dL), IV D50 25 mL (1/2 amp D50) will be given.

(v) The nurse will place an IV for study medication only. All other IV medications should be administered separately from the IV for study saline infusion.

(vi) Upon receipt of the IV saline bag from the pharmacy, the clinical nurse will hang it with an infusion pump. The IV pump should be programmed to maintain the blind (e.g. This should read SHINE Study Drug rather than saline).

(vii) The IV saline bag will be labeled with an ORANGE sticker that says SHINE study drug. The label **MUST** only be applied by the pharmacist who is preparing the IV infusion.

(viii) The background for the study laptop screens will be **ORANGE** for the control group. The nurse should verify that the screen and sticker match to assure that the correct study drug has been provided.



(ix) In the control arm of the study, the initial IV saline infusion rate and subsequent rate adjustments will be based on POC glucose levels and displayed on the control treatment screen of the study laptop tool. The subcutaneous insulin dose will be determined using the sliding scale also displayed on the control treatment screen.

(2) Blood glucose monitoring

(a) Blood glucose will be monitored using POC glucose checks. The Accu-Chek System is the SHINE study preferred system. Other blood glucose monitoring systems can also be used per site procedures.

(b) The SHINE protocol recommends the use of capillary blood for the POC glucose tests However, if there is concern about continuing participation in the treatment protocol due to the number of finger stick blood glucose checks or if the number of checks exceeds the number listed in the consent form, non-capillary blood can be used for the POC test.

(c) For patients who are in the control arm of the study, the control protocol will require POC glucose checks at least every 1 hour for the first 4 hours.

Complete one POC glucose test to start the infusion and then check hourly for the next four hours (for a total of 5 checks before transitioning to the schedule for checks approximately every 3 hours; Check to start study infusion:_ _:_ _, ___mg/dL, 1hr:_ _:_ _, ___mg/dL, 2hr: :_ _:_ _, ___mg/dL, 3hr:_ _:_ _, ___mg/dL,4hr:_ _:_ _, ___mg/dL). After the hourly checks for the first four hours on the study infusion, transition to q3hr checks. The schedule for the q3 hour checks is 03:00, 06:00, 09:00, 12:00, 15:00, 18:00, 21:00 and 24:00 and should be maintained for the remainder of the study treatment period.

(d) Glucose must be checked with 15 minutes of the scheduled time for a regular check and within 5 minutes of the scheduled time when a patient is hypoglycemic.

(e) Only the results of POC glucose should be recorded in the control treatment screen of study laptop. Lab glucose levels should **NOT** be entered!

(f) In the control group, the timing of POC glucose monitoring is displayed on the control treatment screen of the study laptop for the duration of the study treatment period.

(g) If the blood glucose drops < 80 mg/dL, the hypoglycemia prevention and management protocol will be initiated.

(3) Control treatment protocol

(a) **Overview**

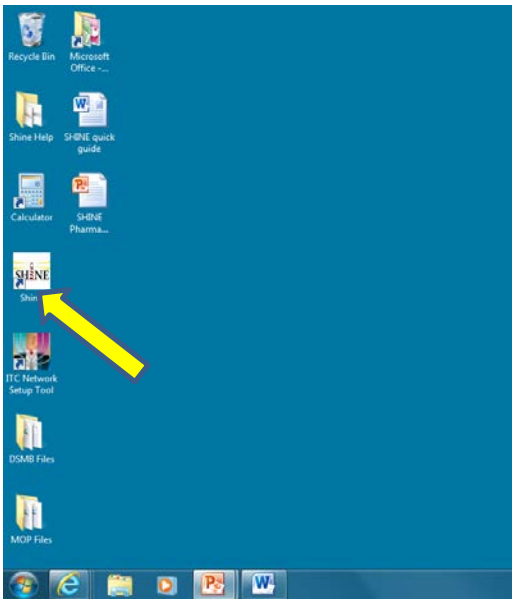
(i) SHINE study laptops will be supplied to all participating sites and must be used to access the control treatment screen. The icon for the SHINE portal will be located on the desktop of the laptop. Study laptops are to remain powered on and open throughout the treatment period. The screens for the control group will allow the clinical nurses to see the sliding scale table and timing for glucose checks. The glucose levels, subcutaneous insulin administered and saline infusion rates will be entered in the control treatment screen. The sliding scale table will have three levels of dosing (Level 1, Level 2 and Level 3). Changes in the level of dosing will occur only if indicated and only at 24 and 48 hours after the initiation of study treatment (time of randomization).

(ii) **Administrative set up instructions**

1. Retrieve the study laptop and ensure internet connectivity per site procedures.
2. The initial setup for each subject will be done by the site study team.
3. The login for the computer is the **SHINE** user profile, and the password is **shine.**
4. The GlucoStabilizer® login will be **User ID: shine**, **Password: shine** for all personnel and all sites. Contact the study team with questions about the login.
5. The SHINE subject ID is a unique identification number for each randomized patient. This will be provided by the study team after the patient has been randomized in WebDCU™.

(iii) **Initiating IV saline/subcutaneous insulin**

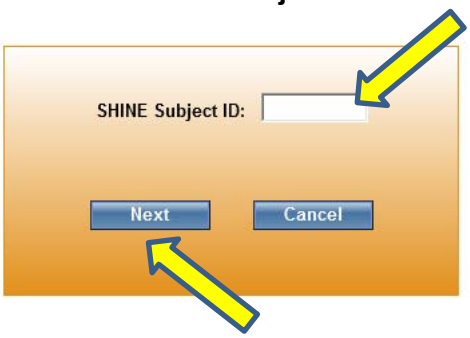
1. Select the icon for the SHINE Trial Portal on the desktop.



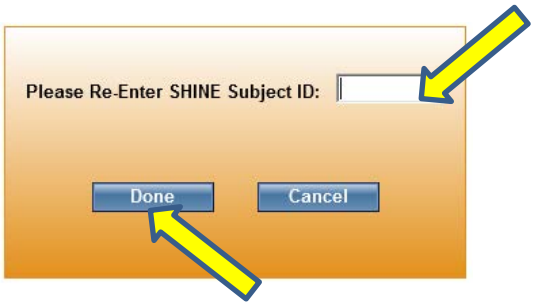
2. The SHINE Trial Portal will open.
3. Check the hard copy of the randomization to confirm that the patient is in the control group.
4. Click on the orange box that says "**Click Here for Control Group**".

5. Enter **User ID and Password (shine/shine)**. Click on **Log In** button.

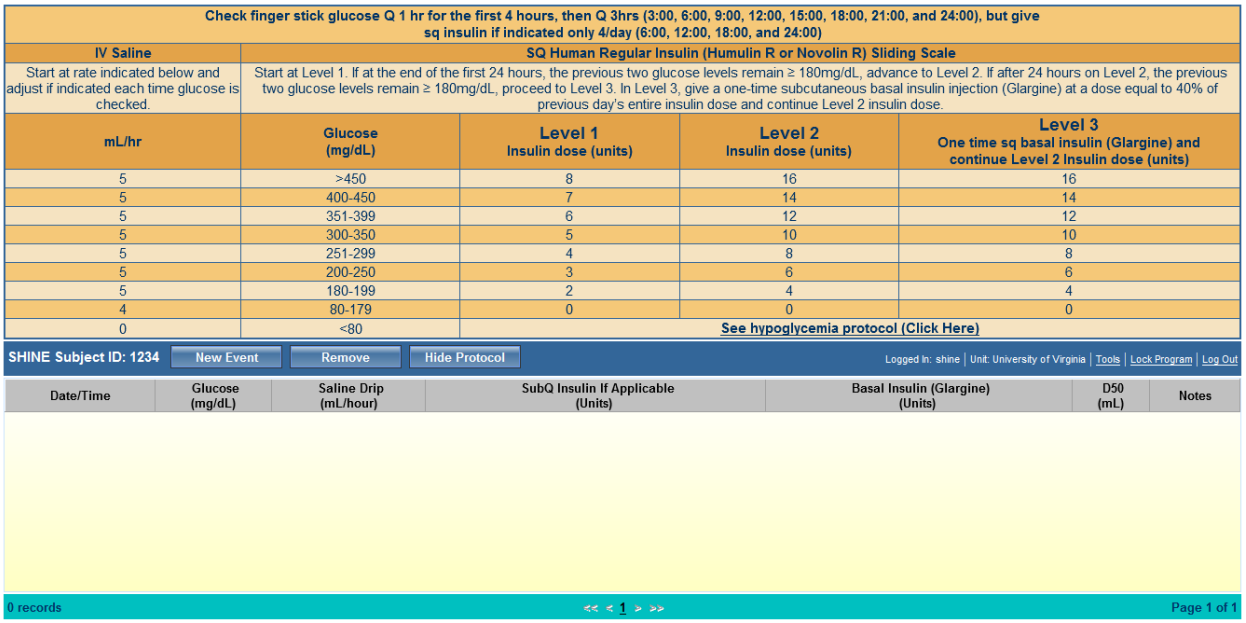
6. Enter the **SHINE Subject ID**. Select **Next**.



7. Re-enter the **SHINE Subject ID**. Select **Next**.



8. The Subcutaneous Insulin Sliding Scale and IV Saline (Placebo) Table for SHINE Control Group will be displayed.



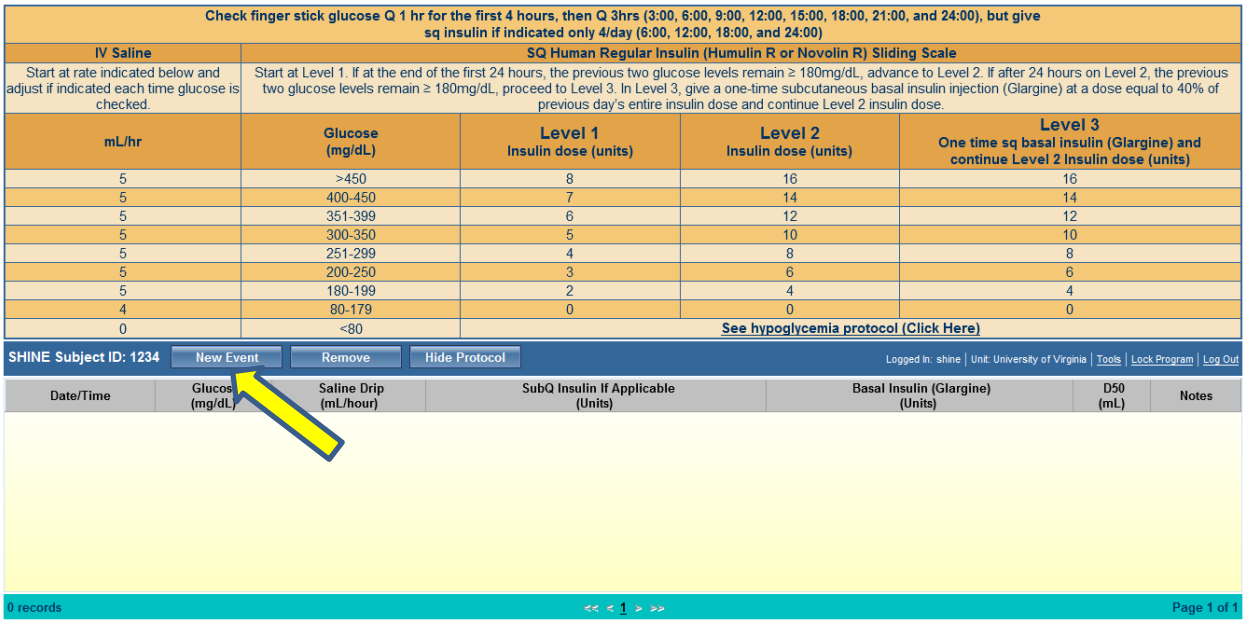
Check finger stick glucose Q 1 hr for the first 4 hours, then Q 3hrs (3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00), but give sq insulin if indicated only 4/day (6:00, 12:00, 18:00, and 24:00)				
IV Saline	**SQ Human Regular Insulin (Humulin R or Novolin R) Sliding Scale**			
Start at rate 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)		

(xiii) Remember that the study patient is blinded to his or her treatment group. Care should be taken to maintain the blind. Note that the control treatment screen displays the IV saline and subcutaneous sliding scale. Use the lock program option if the study laptop will remain in the patient room so that this will only be visible to the treating and study teams and not the study patient and his or her family/friends.

(xiv) Check the POC glucose immediately prior to starting infusion.

(b) Initiating study treatment

Once the IV saline infusion is ready to be started, check the POC glucose immediately prior to starting infusion. Choose New Event on the control treatment screen.



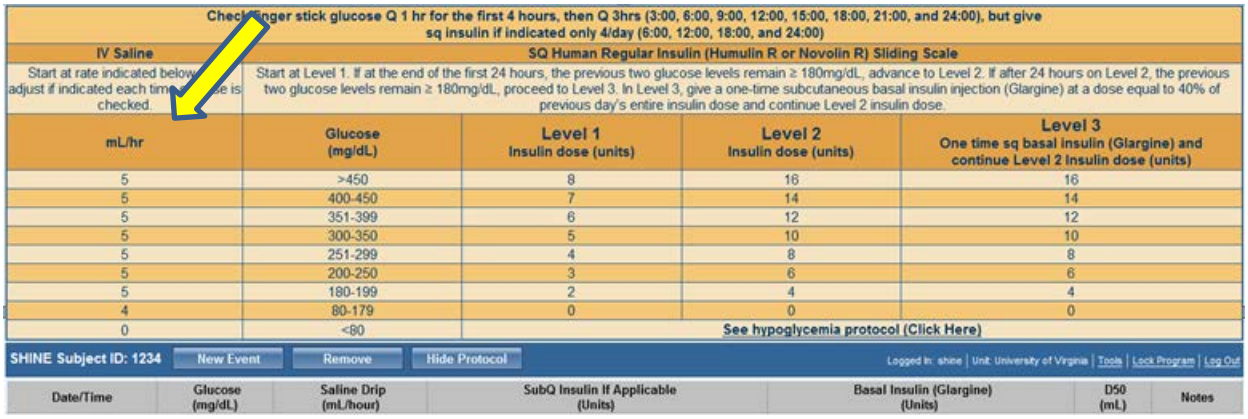
Check finger stick glucose Q 1 hr for the first 4 hours, then Q 3hrs (3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00), but give sq insulin if indicated only 4/day (6:00, 12:00, 18:00, and 24:00)				
IV Saline	**SQ Human Regular Insulin (Humulin R or Novolin R) Sliding Scale**			
Start at rate 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)		

SHINE Subject ID: 1234 | New Event | Remove | Hide Protocol | Logged In: shine | Unit: University of Virginia | Tools | Lock Program | Log Out

Date/Time	Glucose (mg/dL)	Saline Drip (mL/hour)	SubQ Insulin If Applicable (Units)	Basal Insulin (Glargine) (Units)	D50 (mL)	Notes

0 records << < 1 > >> Page 1 of 1

1. **IV saline initiation**
   a. The control treatment screen will display the rate of infusion in the column **IV Saline** regardless of the level of sliding scale subcutaneous insulin dose (Levels 1, 2 and 3). The control screen is a static screen, and the nurse must identify the appropriate rate of IV saline based on the glucose level.



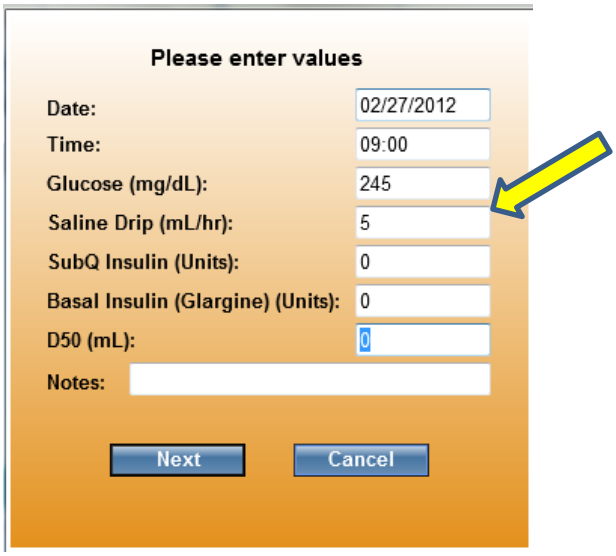
Check finger stick glucose Q 1 hr for the first 4 hours, then Q 3hrs (3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00), but give sq insulin if indicated only 4/day (6:00, 12:00, 18:00, and 24:00)				
IV Saline	**SQ Human Regular Insulin (Humulin R or Novolin R) Sliding Scale**			
Start at rate 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)		

SHINE Subject ID: 1234 | New Event | Remove | Hide Protocol | Logged In: shine | Unit: University of Virginia | Tools | Lock Program | Log Out

Date/Time	Glucose (mg/dL)	Saline Drip (mL/hour)	SubQ Insulin If Applicable (Units)	Basal Insulin (Glargine) (Units)	D50 (mL)	Notes

   b. The nurse will use the result from the POC glucose to find the corresponding rate of infusion for the IV saline. (For example, if the glucose is 162 mg/dL, start the saline at 4mL/hr.)
   c. Start the IV saline drip at the recommended rate.
   d. To record the glucose result and saline drip rate, select **New Event** on the control treatment screen.

e. A pop up will display to enter the result for the POC glucose (mg/dL).
f. The date and time will be pre-populated with the current values when New Event is selected. These can be cleared and a different date/time entered. Do **NOT** change the pre-populated date and time unless incorrect. If incorrect, a 24 hour clock must be used when entering the correct time (03:00, 06:00, 09:00, 12:00, 15:00, 18:00, 21:00 and 24:00).
g. Enter the **Glucose (mg/dL)** result and **Saline Drip (Units/hour)** rate.

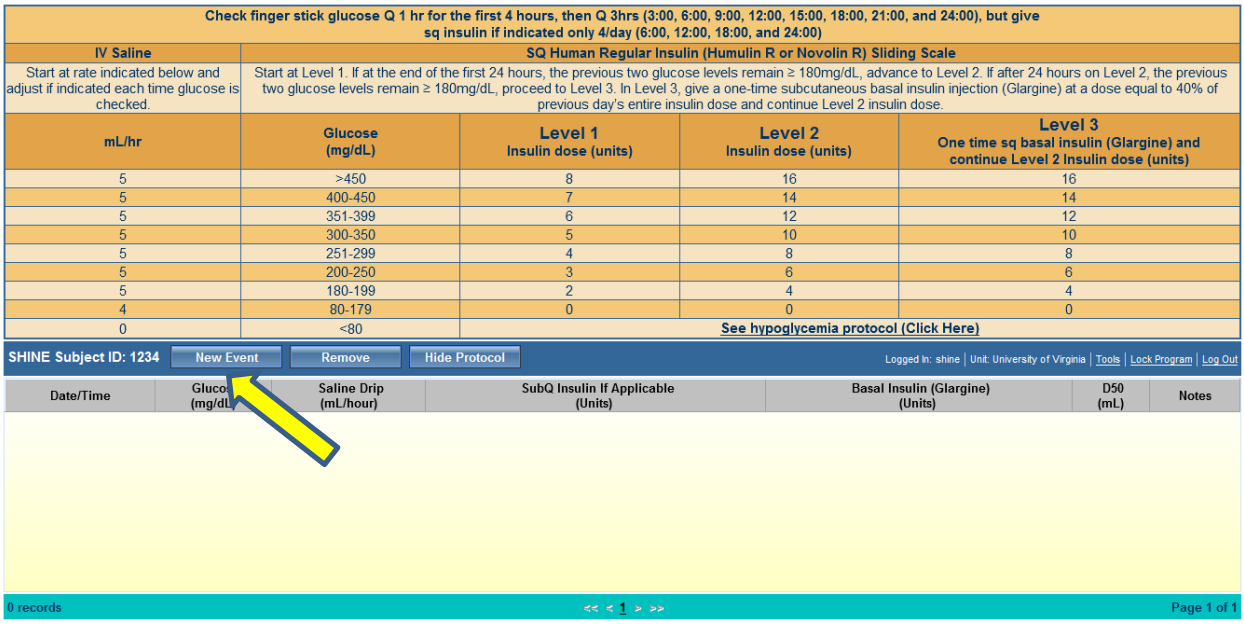


h. Enter 0 for basal insulin or D50.
i. For most patients, the saline drip will start and the subcutaneous insulin dosing will not occur (if not 06:00, 12:00, 18:00 or 24:00). If no subcutaneous insulin, basal insulin or D50 given, enter 0 in each box.
j. Select **Next**. A pop up will display **Please re-enter values to validate**. Re-enter and select **Done**. A new row under the table will display the data just entered. .
k. Use the table on the control treatment screen to adjust the rate of infusion for the IV saline, if indicated, each time the glucose is checked.
l. Recheck the POC glucose every 1 hour for the first 4 hours of study treatment. Note that **subcutaneous insulin** is NOT given at each of these times but **is only given at 06:00, 12:00, 18:00 or 24:00 if indicated**. If a q1 hour check is within 30 minutes of dosing time, the SQ insulin dose should be given at that time (slightly early or slightly late) so that the dose is NOT missed.
m. After the first 4 hours of treatment, glucose will be checked approximately every 3 hours. The schedule for these checks is 3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00.
n. The first Q3 hour check should be skipped if it falls less than one hour from the time of the previous check unless it is a scheduled

dosing time. Also, if one of the scheduled dosing times (06:00, 12:00, 18:00 or 24:00) falls within one hour of the previous glucose check due to a pause, the POC test should be done and SQ insulin dosed per protocol

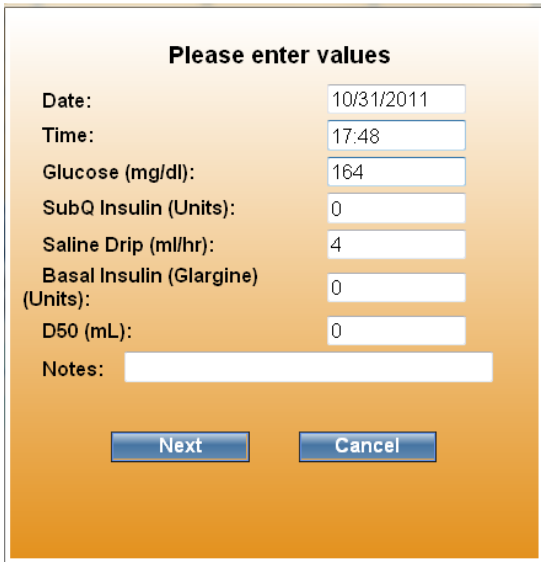
o. The saline drip instructions remain the same regardless of Level 1, 2 or 3 subcutaneous insulin dosing.

2. **Subcutaneous insulin initiation**
   a. The sliding scale table that is displayed on the control treatment screen to determine subcutaneous insulin dosing for patients in the control arm of the study.
   b. The control screen is a static screen used to determine the appropriate dose of subcutaneous insulin based on the glucose level.
   c. A POC glucose check is required to start the study infusion, and then the glucose should be checked at least every 1 hour for the first 4 hours. After the first four hours on the study infusion, the glucose will be checked approximately every 3 hours for the remainder of the study treatment period. The schedule for the checks after the first 4 hours is 3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00.
   d. The **subcutaneous insulin should only be given (if indicated based on the POC glucose result) four times per day** at **6:00, 12:00, 18:00, and 24:00.**
   e. At each POC glucose check the glucose level needs to be entered into the SHINE study portal. When the glucose is > 80 mg/dL there is a +/- 15 minute window to enter the data, when glucose is < 80 mg/dL there is a +/- 5 minute window to enter the data to remain protocol compliant.
   f. Select **New Event** on the control treatment screen.



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)		

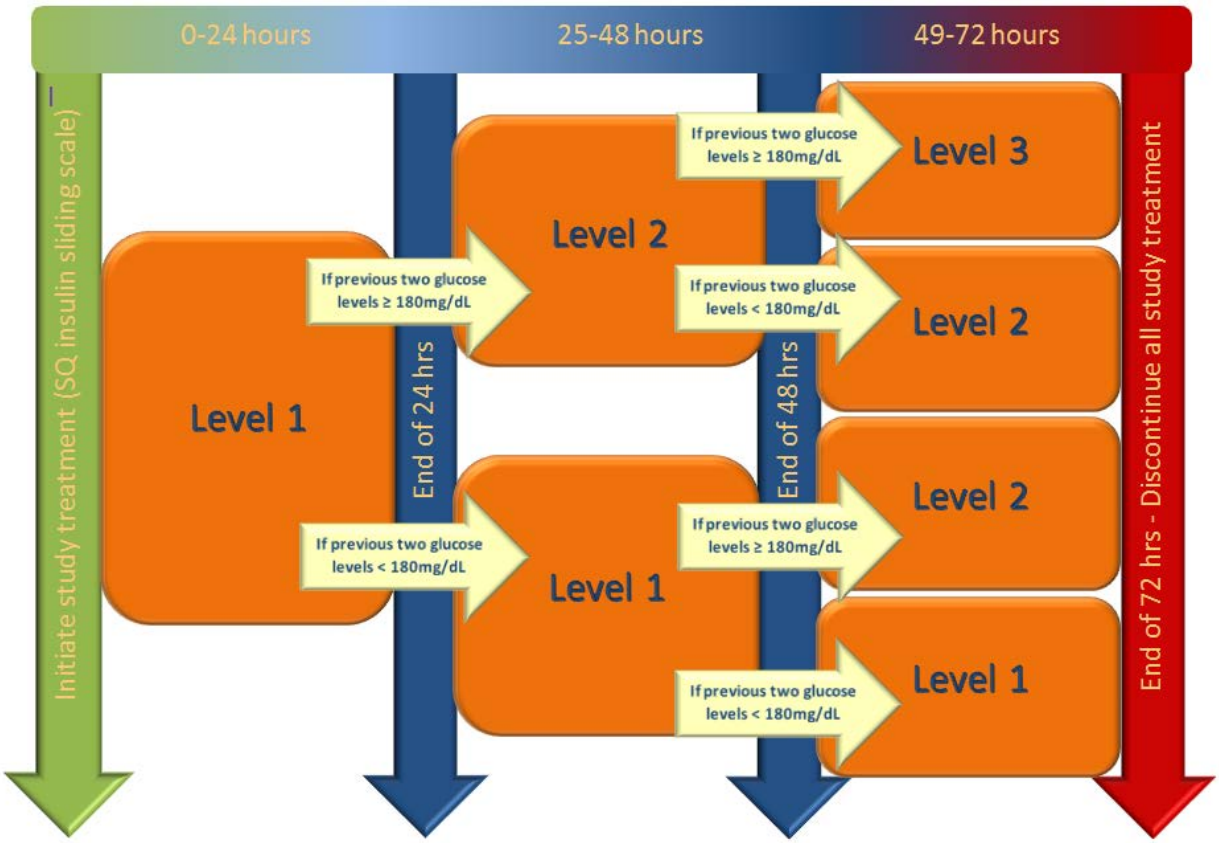
g. A pop up will display to enter the result for the POC glucose (mg/dL).
h. The date and time will be pre-populated with the current values when New Event is selected. These can be cleared and a different date/time entered. Do **NOT** change the pre-populated date and time unless they are incorrect. If incorrect, a 24 hour clock must be used when entering the correct time (03:00, 06:00, 09:00, 12:00, 15:00, 18:00, 21:00 or 24:00).
i. Type in the glucose level.
j. Enter 0 for basal insulin or D50.
k. For most patients, the saline drip will start and the subcutaneous insulin dosing will not occur (if not 06:00, 12:00, 18:00 or 24:00). If no subcutaneous insulin, basal insulin or D50 given, enter 0 in each box.



l. Select **Next**.
m. At the first scheduled time for subcutaneous insulin dosing (6:00, 12:00, 18:00, and 24:00), use the sliding scale to determine the insulin dose.
n. All patients will start at Level 1 on the sliding scale at initiation. Level adjustment decisions will only be made at 24 and 48 hours in consultation with the study team.
o. The nurse will use the sliding scale to determine the insulin dose in units in Level 1 that corresponds to the POC glucose level.
p. If an insulin dose is indicated, Human Regular Insulin (Humulin R or Novolin R) should be used for the subcutaneous insulin injections. DO NOT USE ANALOG RAPID ACTING INSULIN (HUMALOG/NOVOLOG/APIDRA) IN THE CONTROL GROUP.
q. The nurse will administer the indicated dose of subcutaneous Human Regular Insulin and record in control treatment screen.

r. For each glucose check, saline infusion rate adjustment (if indicated) and subcutaneous insulin injection (if indicated) throughout the protocol will be repeated.
s. If glucose is < 180 mg/dL, per the sliding scale, no insulin will be given.
t. If the glucose drops < 80 mg/dL at any time, initiate the hypoglycemia prevention and management protocol.

3. **Changing subcutaneous sliding scale levels (control group only)**
   a. Levels of the subcutaneous sliding scale



Levels in the Control Subcutaneous Sliding Scale: The sliding scale has three levels. All patients will begin at Level 1 at the start of the study treatment period (time of randomization). At 24 and 48 hours post-randomization, the results of the previous two glucose checks and episodes of hypoglycemia during the previous 24 hours will be reviewed in consultation with the study team to determine if it is necessary to advance to a higher level in the sliding scale.

(I) Overview of levels

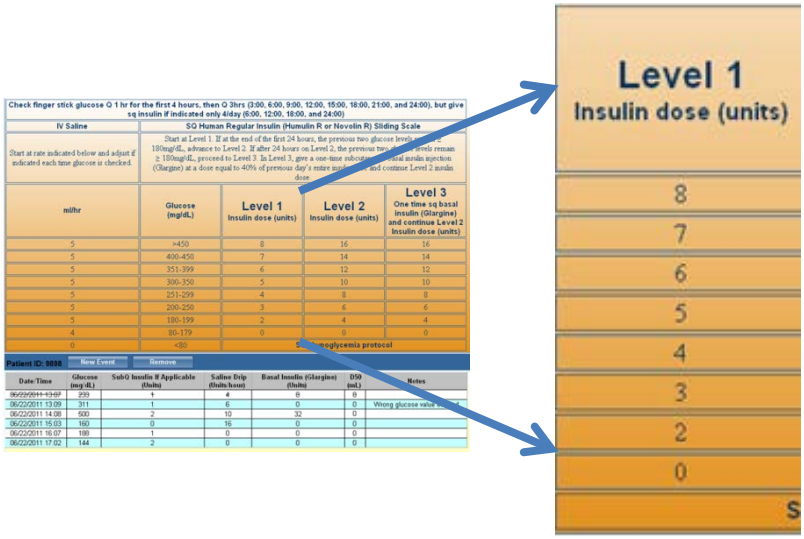
1. The control treatment subcutaneous sliding scale has 3 levels of dosing to provide the opportunity for patients demonstrating sub-optimal glucose control to within their target range to receive higher doses of subcutaneous insulin treatment on succeeding days.
2. All patients start at Level 1. Levels 2 and 3 are also available on the control decision support tool sliding scale display.

3. The opportunity to consider advancing by 1 level occurs only twice during the study treatment: at the time points of 24 and 48 hours of treatment based on time of randomization.
4. At 24 and 48 hours, the results of the previous two glucose checks and episodes of hypoglycemia during the previous 24 hours will be reviewed in consultation with the study team to determine if it is necessary to advance to a higher level in the sliding scale.
5. 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, contact the Shine Safety Hotline. 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.

(c) Navigating the levels of control subcutaneous sliding scale

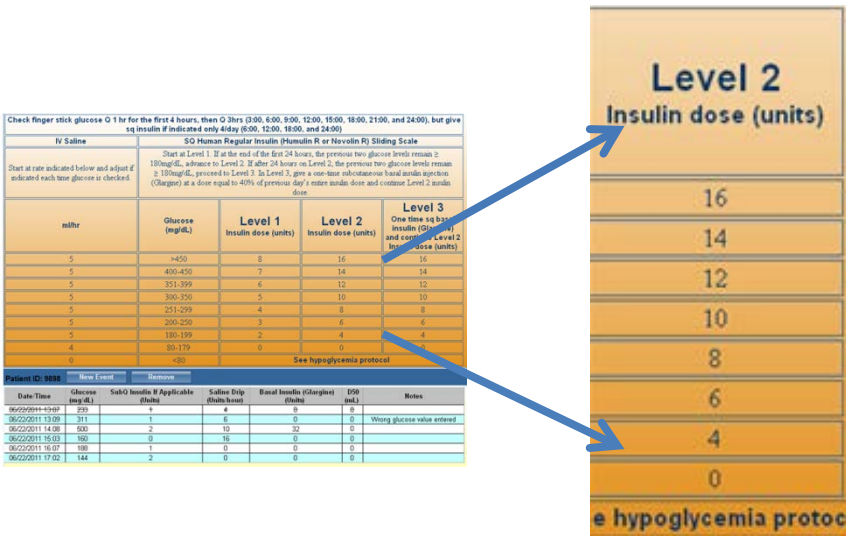
(i) Level 1

1. All patients will be initiated at Level 1.



(ii) 24 hours from the time of randomization:

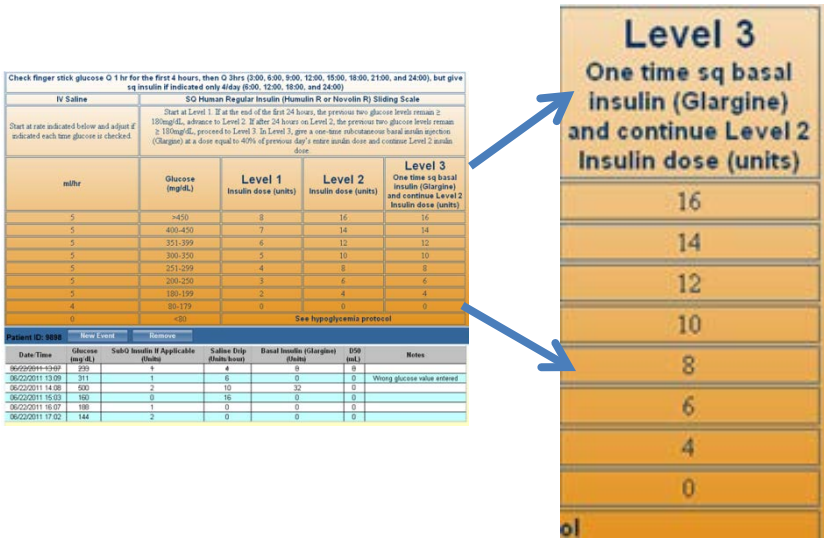
1. If at the end of the **first 24 hours** either of the previous **two glucose levels are < 180 mg/dL**, continue at **Level 1**.
2. If at the end of the **first 24 hours,** both of the previous **two glucose levels are ≥ 180 mg/dL**, advance to **Level 2**.



3. Follow instructions above for glucose checks, saline infusion and subcutaneous insulin injections.
4. No basal insulin should be given at this point.

(ii) 48 hours after randomization:

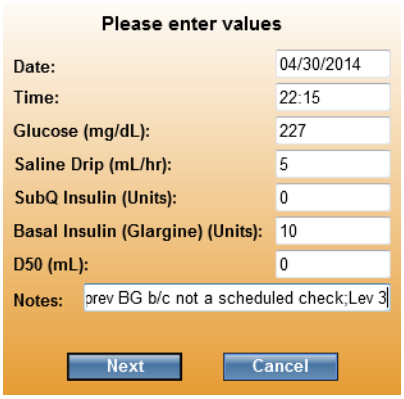
1. If on **Level 1**:
   a. If at the **end of 48 hours,** either of the previous **two glucose levels are < 180 mg/dL**, continue on **Level 1**.
   b. If at the **end of 48 hours**, both of the previous **two glucose levels are ≥ 180 mg/dL**, advance to **Level 2**.
2. If on Level 2:
   a. If at the **end of 48 hours** and either of the previous **two glucose levels are < 180 mg/dL**, continue on **Level 2**.
   b. If at the **end of 48 hours**, both of the previous **two glucose levels remain ≥ 180 mg/dL**, proceed to **Level 3**.



c. Follow instructions above for glucose checks, saline infusion and subcutaneous insulin injections.

(iii) If a patient advances to Level 3:

1. Give a one-time subcutaneous basal insulin injection Glargine (Lantus) at a dose of 40% of previous 24 hours entire insulin dose given.
2. Calculate the dose of basal insulin.
   a. Sum the total insulin given over the past 24 hours.
   b. Multiply this sum by 0.40 to calculate the dose.
   c. Round down if < 0.4 and round up if ≥ 0.5
3. Basal insulin (Glargine) will be requested from pharmacy per site procedures.
4. This dose of basal insulin should be given approximately at the 48 hour point (from time of randomization) regardless of time of day.
5. Record the dose of basal insulin by entering New Event. The pop up will display.
   a. If not a dosing time, enter the following values.
      i. Time: actual time given (do not change unless incorrect)
      ii. Glucose: enter the previous glucose value (because this cannot be blank or 0) and note that this is the previous glucose value
      iii. SQ insulin: If it is not a SQ dosing time, enter 0 as no SQ insulin dose should be administered.
      iv. D50: Enter 0 as no D50 should be administered.
      v. Basal: Enter the dose given.
      vi. Note: Since not a scheduled glucose check time, type 'previous value entered because not a scheduled check time'.
      vii. Select next and re-enter values and select OK.
   b. If it is a dosing time, enter the following values:
      i. If the 48 hour point is within 15 minutes of a glucose check, check POC, give SQ insulin per protocol.
      ii. Time: actual time given (do not change unless incorrect).
      iii. Glucose: enter the POC glucose value.
      iv. SQ insulin: enter the SQ regular insulin dose based on sliding scale if one of the scheduled dosing times **(06:00, 12:00, 18:00 or 21:00**).
      v. D50: Enter 0 as no D50 should be administered.
      vi. Basal: Enter the dose given.
      vii. Note: Note that this was a scheduled glucose check time as well as the time of the 48 hour/glargine (Lantus) dose time.



viii. Select next and re-enter values and select OK.

6. Continue Level 3 of the sliding scale insulin dose.
7. Follow instructions above for glucose checks, saline infusion and subcutaneous insulin injections.

(iv) After 72 hours on study protocol, study treatment should be discontinued.

(4) Hypoglycemia prevention and management protocol

(a) **Hypoglycemia prevention and management (**hypoglycemia protocol)

(i) The hypoglycemia protocol will be initiated for any patient whose glucose level drops below 80 mg/dL.

(ii) Definitions

1. Blood glucose < 80 mg/dL → initiate hypoglycemia prevention and management protocol
2. Hypoglycemia: defined as blood glucose < 70 mg/dL (will require additional steps)
3. Severe hypoglycemia: defined as blood glucose < 40 mg/dL (will require SAE reporting)

(iii) **Hypoglycemia protocol for control group**

1. If the blood glucose drops to < 80 mg/dL, select the link on the control treatment screen to view the hypoglycemia protocol.
   a. **Stop the saline infusion and hold all subcutaneous insulin injections when the glucose is < 80 mg/dL!**
   b. For all POC glucose < 80 mg/dL, the nurse will prepare a dose of IV D50 25 ml (1/2 amp).
   c. D50 will be stored to allow immediate availability at the bedside.
   d. Give 25mL of D50, slow IV push (over 1-2 minutes).
   e. Check glucose again in 15 minutes.
   f. To record the glucose measurement and D50 administration, select **New Event**.

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)		

SHINE Subject ID: 1234 | New Event | Remove | Hide Protocol | Logged In: shine | Unit: University of Virginia | Tools | Lock Program | Log Out

Date/Time	[illegible]	Saline Drip (mL/hour)	SubQ Insulin If Applicable (Units)	Basal Insulin (Glargine) (Units)	D50 (mL)	Notes
02/27/2012 18:15	104	4	0	0	0	
02/27/2012 18:00	79	0	0	0	25	
02/27/2012 15:00	90	4	0	0	0	
02/27/2012 12:00	187	5	2	0	0	
02/27/2012 09:00	245	5	0	0	0	

g. A pop up will display to enter the result for the POC glucose (mg/dL).

h. Enter the **Glucose** result and **D50** administered.
i. As long as the blood glucose is < 80 mg/dL, all insulin treatments and the IV saline will be held.
j. Enter 0 for **SubQ Insulin** and 0 for Saline Drip.
k. Select **Save**.
l. After 15 minutes, the nurse will repeat the POC glucose. Check POC glucose every 15 minutes until glucose is ≥ 80 mg/dL.
m. These steps will be repeated for every glucose measurement that is < 80 mg/dL.
n. If the glucose drops below 70 mg/dL, additional steps are required (described below).

(iv) Additional steps for blood glucose < 70 mg/dL

If the blood glucose drops < 70 mg/dL, the following additional actions are required:

1. Continue to use the hypoglycemia protocol above (e.g. hold saline and SQ insulin, give D50, repeat glucose checks every 15 minutes).
2. Draw a STAT laboratory serum glucose measurement but do not delay treatment with D50 by waiting for this blood draw result. Only the results POC glucose checks should be used for insulin dosing. The study coordinator will document the result of the serum glucose measurement.
3. Screen the patient for hypoglycemia symptoms using Hypoglycemia Symptomatic Questionnaire.
   a. The worksheet and instructions will be available on paper and on the desktop of the laptops.
   b. The Hypoglycemia Symptomatic Questionnaire must be repeated every 15 minutes when glucose is < 70 mg/dL.

c. Once the glucose is ≥ 70 mg/dL, no additional assessment with the Hypoglycemia Symptomatic Questionnaire is required.
d. Once the glucose is ≥ 80 mg/dL, the timing of glucose checks and insulin infusion rate will again be determined by the control treatment screen.

4. Screen the patient for neurological worsening.
   a. An assessment of neurological change is required per site standard care ("neuro check") every 15 minutes when glucose is < 70 mg/dL even if there are no new neurological findings.
   b. The **SHINE study definition of neurological worsening** is any clinical change that is associated with a ≥ 4 point increase from baseline on the NIHSS score. (Baseline is considered to be the most recent daily NIHSS..)
   c. Any patient with neurological worsening will be assessed for hypoglycemia and for relatedness of the hypoglycemia to neurological worsening if present.
   d. If the patient has not returned to neurological baseline within 24 hours, a NIHSS assessment is required within 24(+/-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.
   e. If neurological worsening persists for greater than or equal to 24 hours and is associated with a glucose concentration of < 55 mg/dL, an SAE form is required. If the glucose falls below 40 mg/dL at any time, an SAE form is required.
5. 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), contact the SHINE Safety Hotline (800-915-7320 ext 2). 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.

(5) Meals

(a) Patients who are PO

(i) SHINE protocol-recommended diet for the control group

All patients in the control group who pass a swallow test and are cleared to eat will have a 60 gram carbohydrate diet. The 60 gram carbohydrate diet should be ordered for breakfast, lunch and dinner as a part of standard care. Meals should be delivered at about 06:00, 12:00 and 18:00. Meals will be withheld until subcutaneous insulin is given per the study schedule for glucose checks and sliding scale for insulin dosing occurring at meal time. **Meal insulin will not be given in this group.**

(ii) Protocol-approved snacks

SHINE patients may also consume up to 2 low carbohydrate snacks (< 5 grams carbohydrates per serving) from the list below between meals (up to 6 low carbohydrate snacks daily). The study protocol diet does not limit the consumption of sugar free foods and drinks listed in the unlimited category below. Patients should only consume food included on the meal tray from the hospital kitchen or the protocol approved snacks during the 72 hour treatment period.

Low carbohydrate snack options (up to 2 between meals)

5 celery sticks + Tablespoon peanut butter
5 baby carrots
5 cherry tomatoes + 1 Tablespoon ranch
1 hard-boiled egg
½ cup raw broccoli + 1 Tablespoon ranch
1 cup cucumber slices + 1 Tablespoon ranch dressing
¼ cup of fresh blueberries
1 cup of salad greens, 1/2 cup of diced cucumber, and with vinegar and oil
2 saltine crackers
1 piece of string cheese stick
½ cup of egg salad, tuna salad or chicken salad
3 oz of deli ham, chicken or turkey slices
1 serving of cubed or sliced cheese (1 oz)
½ cup cottage cheese
½ cup tofu
1 slice deli ham, chicken or turkey + 1 slice cheese

Unlimited

Bouillon and broth
Club soda, unsweetened
Coffee, unsweetened or artificial sweeteners only
Diet soft drinks
Flavoring extracts
Horseradish
Mineral water
Mustard
Pickles
Soy sauce
Spices
Sugar-free drink mixes
Sugar-free gum
Sugar-free Jell-O
Tabasco or hot sauce
Unsweetened lemon or lime juice
Unsweetened tea
Vinegar

(iii) Patients receiving tube feedings may receive either bolus or continuous tube feedings per standard care. Bolus tube feedings will be encouraged to be given at around 06:00, 12:00 and 18:00 and will also be 60 gram carbohydrate per feed.

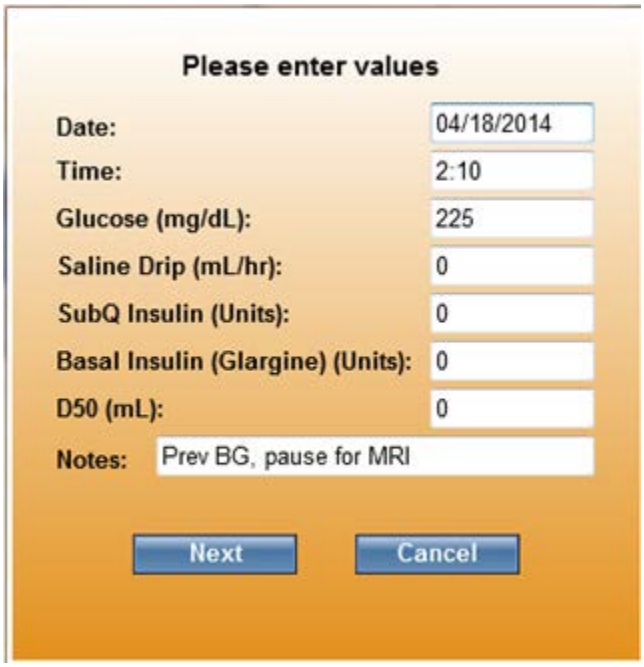
		SHINE TREATMENT GROUP	
		INTERVENTION GROUP	**CONTROL GROUP**
NUTRITIONAL STATUS	**Eating PO meals or Bolus Tube Feeds**	**IV insulin** plus **Subcutaneous meal insulin injections** **How much IV Insulin?** Per GlucoStabilizer recommendation **How many units SQ meal insulin?** Per GlucoStabilizer recommendation based on proportion of meal consumed given 20 minutes after start of meal 3x/day @ **0600, 1200, & 1800**	**IV saline** plus **Subcutaneous sliding scale insulin injections** **How much IV saline?** Per Sliding Scale Control Treatment Screen **How many units SQ insulin?** Per Sliding Scale Control Treatment Screen Finger stick glucose check @ 0300,**0600**,0900,**1200**,1500,**1800**,2100,**2400** (Insulin dosing only @0600, 1200, 1800, & 2400)
	NPO or Continuous Tube Feeds	**IV insulin** plus **Subcutaneous saline injections** **How much IV Insulin?** Per recommendation of GlucoStabilizer **How much SQ saline?** 0.05 mL of SQ saline @ time of glucose check nearest 0900 and 2100	**IV saline** plus **Subcutaneous sliding scale insulin injections** **How much IV saline?** Per Sliding Scale Control Treatment Screen **How many units of SQ insulin?** Per Sliding Scale Control Treatment Screen Finger stick glucose check @ 0300,**0600**,0900,**1200**,1500,**1800**,2100,**2400** (Insulin dosing only @0600, 1200, 1800, & 2400)

(6) Special Situations with the Control Treatment Protocol

(a) **Pauses in control treatment protocol**

(i) When the SHINE control group treatment protocol is temporarily interrupted for any reason (e.g. patient needing to go off the care unit), and the clinical nurse or study team cannot accompany the patient, the IV saline drip should be stopped. Document the pause following the steps below.

1. Select “New Event” on the control treatment screen. Enter the previous glucose value. Enter “**0”** for Saline Drip, SubQ Insulin, Basal Insulin, and D50. In the Notes field, enter a comment documenting the pause and that the glucose entered was a previous value (Ex. Prev BG, pause for MRI).



2. Click “Next”. Re-enter, and select “Done”.

(ii) 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.

(iii) Upon return to the unit, if glucose checks or subcutaneous insulin injections **were missed**, the following procedures should be followed:

1. Immediately check the POC glucose upon return to the unit.
2. Resume the saline infusion according to the sliding scale using the glucose measurement.
3. 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.
4. If indicated per sliding scale, give subcutaneous insulin injection immediately to make up for the missed dose.
5. Return to schedule for glucose checks and subcutaneous insulin injections.
    a. Do not check glucose levels < 1 hour apart unless it is a scheduled dosing time. If the next check is < 1 hour from the check that happened upon return to the unit, skip to the next scheduled check unless it is a scheduled dosing time (06:00, 12:00, 18:00, 24:00). If it is a scheduled dosing time, check and give SQ regular insulin if indicated.
    b. **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.

(b) **Interruptions in Continuous Tube Feeds**

(iii) When there is an interruption in continuous tube feedings in the control group, the saline drip will be stopped.

(iv) The control protocol for subcutaneous insulin dosing does not change if continuous tube feeds are interrupted and the schedule for glucose checks and subcutaneous insulin dosing should be followed.

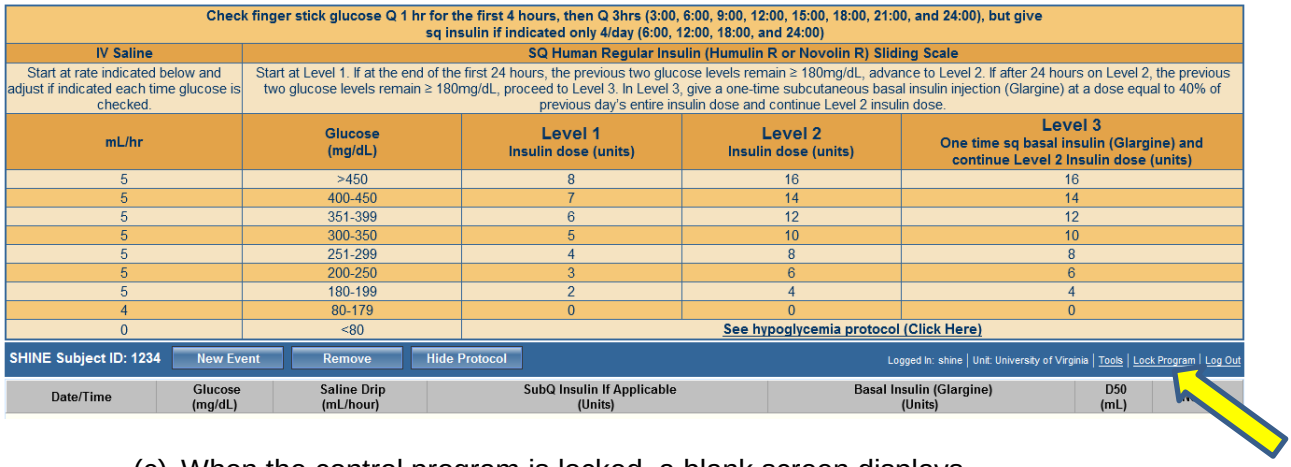
(v) If the continuous tube feeds are restarted less than 1 hour from the time that the saline drip was stopped, the nurse will check the glucose at the time that the continuous tube feeds are restarted. The glucose measurement will be used to restart the saline drip if indicated per the saline sliding scale.

(vi) If the continuous tube feeds are not restarted within 1 hour, the nurse will re-start the saline drip, at the time of the next scheduled glucose check based on the saline sliding scale (0, 4, or 5 ml/hr).

(7) Locking the GlucoStabilizer® Program

When the nurse leaves the bedside, the GlucoStabilizer® should be locked.

(ii) Choose lock program



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)		

(c) When the control program is locked, a blank screen displays.

(d) The User ID is shine, and the Password is shine.

(8) Stopping study treatment when there is a change in diagnosis of ischemic stroke/stroke mimic

(a) In the event that there is a change in the diagnosis of ischemic stroke during the 72 hour treatment period, all study treatments should be stopped at the time that the study team receives knowledge of the new diagnosis.

(b) The clinical care team will determine glucose control therapy after the SHINE treatment protocol is discontinued.

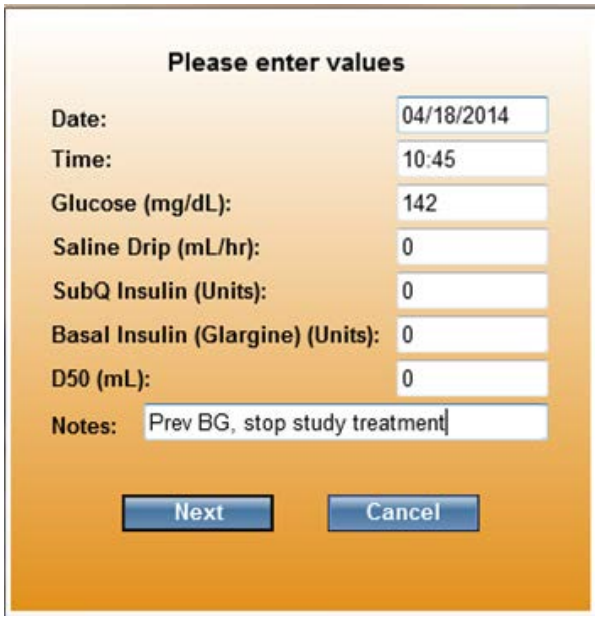
(c) Instructions for completing CRFs when the study treatment is stopped due to a change in diagnosis of ischemic stroke

(i) The Day 1-Day 3 visits should be completed only during the period of time that the patient was receiving study treatment.
(ii) The final diagnosis will be captured on the Study Treatment CRF (Form 15) as: Migraine, Seizure, Brain tumor/mass, Psychogenic, Anamnestic syndrome, CNS Infection (abscess, meningitis, encephalitis), Toxic/metabolic (encephalopathy) and Other: specify).
(iii) A brief narrative explaining the change in diagnosis is required. This narrative should include sufficient information to demonstrate that the new diagnosis is most likely including appropriate imaging and laboratory data. A brief narrative template is included in WebDCU: [On _____(full date), the diagnosis was changed to _____. This diagnosis was based on _____(lab/imaging results) and _____(clinical information).]
(iv) On the Study Treatment CRF (Form 15), the study treatment status should be captured as: Started but discontinued prior to 72 hours of study treatment

(d) The End of Study Visit must be completed. Unless consent is withdrawn, patients whose treatment ends early are still in the study and the 6 week and 90 day follow up visits must be completed in addition to the End of Study Visit.

(9) Transition from study treatment

(a) The start time for the study treatment period is the time of randomization. The treatment period will be 72 hours or until the time of discharge from the hospital, whichever comes first.
(b) Patients who discontinue study treatment are required to do so 6 hours prior to actual discharge from the hospital.
(c) To document stopping study treatment, select "New Event" on the control treatment screen. Enter the previous glucose value. Enter "**0**" for Saline Drip, SubQ Insulin, Basal Insulin, and D50. In the Notes field, document that the glucose entered was a previous value and that study treatment was stopped.



(d) Click “Next”. Re-enter, and click “Done”. Exit the control treatment screen by clicking on the red X in the web browser window and power down the study laptop.
(e) After the SHINE protocol ends, the clinical care team will determine inpatient and outpatient glucose control therapy. The treatment should be based upon on ADA/AACE guidelines and individual patient needs. [28]
(f) The table below offers information to consider for hospitalized patients requiring glucose control. These guidelines are not part of the SHINE protocol and are not required actions.

Considerations for the transition from study treatment to standard clinical care	
Option	**Comment**
Intravenous insulin drip	Consider IV insulin therapy in some critically ill patients per ADA guidelines.
SQ insulins, including regular, rapid-acting analog, and long-acting basal	Per ADA guidelines scheduled subcutaneous insulin that delivers basal, nutritional, and correction components is preferred. • An example of basal insulin is Lantus (glargine) SQ QD calculated based on previous 24 hour insulin requirements and given when the drip is being discontinued as suggested below. • An example of nutritional insulin (for patients who are eating) is rapid acting analog SQ insulin dosing based on meal carbohydrate consumption. • An example of correction insulin is regular SQ insulin dosing based on blood glucose level per sliding scale protocol. ADA guidelines caution against hyperglycemia escape when a patient is transitioned from intravenous to subcutaneous insulin therapy. An option to consider after stopping the SHINE insulin infusion, depending on individual patient needs, may be to give basal insulin right after the IV insulin is stopped. Check blood glucose in 30-60 minutes, and give SQ insulin to correct hyperglycemia as needed. Then consider continuing with a standard SQ insulin protocol.
Oral agents and injectable noninsulin therapies	Consider that oral agents are not recommended in hospitalized patients, but may be initiated or resumed in anticipation of discharge per ADA guidelines.
Hospital discharge education and instructions	Consider individualized discharge planning per ADA guidelines.

5.1.4 Considerations for Study Coordinators during the Treatment Period

Study team should:

1. Communicate with nurses at shift change, meals, end of each 24 hour period during the treatment period
2. Establish site procedures to ensure that study coordinator is notified if any hypoglycemia, severe hyperglycemia or neurologic changes occur.
3. When a study patient experiences study defined neurological worsening, capture the NIHSS score 24 hours (+/-4 hours) after the start of the hypoglycemic event (blood glucose < 70 mg/dL).
4. Be notified if patient planned for discharge. This is particularly important if the patient will be discharged before 72 hours as the study treatment must be discontinued at least 6 hours prior to discharge.
5. Confirm that the NIHSS score is captured each day.
6. Review the Daily Care Log and ensure that data are being captured accurately and that meals are being ordered and recorded per protocol.
7. Control group – assist with transition from hourly checks to q3 hour scheduled check times and
8. Assist in planning the transition to standard care.

FAQ Q: What happens if you check a POC finger stick glucose when it is not due? Do you enter it into the study laptop?

A: If POC glucose is measured when not scheduled (e.g. concern for hypoglycemia, other standard care protocol or test, etc.), only enter in GlucoStabilizer/ control treatment screen if the result is <80mg/dL.

The reason that **values that are <80mg/dL should be entered** is to document the POC glucose levels as they relate to the initiation of the hypoglycemia prevention and management in both treatment groups. Also, importantly, GlucoStabilizer will not know to prompt the hypoglycemia protocol for study patients in the intervention group if a level of <80mg/dL is not entered in the study laptop.

The reason that POC **glucose values should NOT be entered if >80mg/dL** is that this can change the timing of next glucose check and the multiplier which is used to calculated future insulin dosing for study patients in the intervention group. GlucoStabilizer has been programmed and validated based on entering glucose values when due per the programmed schedule for checks recommended by the decision support tool.

All POC glucose values should be documented in the clinical chart per institutional policies.

5.1.5 Concomitant or Ancillary Therapy

Throughout the study period, all AHA guidelines for acute stroke care will be followed. This includes standard care for acute ischemic stroke patients such as swallowing evaluation prior to initiation of PO intake, DVT prophylaxis and secondary stroke prevention therapies. Blood pressure and temperature recommendations also will be followed. Rehabilitation evaluation should be considered for every study patient.