Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial

Treatment Protocols

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Protocol PI

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Agenda

- General protocol for control group/ intervention group
- Discussion of meals
- Hypoglycemia protocol
- Pauses of study protocol

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SHINE Synopsis

- Acute ischemic stroke <12 hrs of symptom onset and within <3 hrs arrival
- Baseline blood glucose
  - >110 mg/dL if known type 2 diabetes
  - ≥ 150 mg/dL if not a known diabetes
- Baseline NIHSS 3-22
- Randomized, initially single blind – final outcome double blind
  - Control group: IV saline and SQ insulin (80-179 mg/dL)
  - Intervention group: IV insulin drip and SQ insulin or saline (80-130 mg/dL)
- Final outcome - 3 month mRS

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Treatment Groups - General Concepts

- Two groups: both glucose control, both insulin
- All patients get IV drip & SQ injections
- Frequent glucose checks
- 60 gram carbohydrate diet
- Document in medical record and study laptop
- NIHSS & AE assessments q 24 hrs
- 72 hr treatment (starts at time of randomization)
- Early d/c per clinical team OK

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Control Group

Control Group- General Concepts

- **BG target**: 80-179 mg/dL
- **Glucose checks:** q1-q3 hours (+/- 15 min)
- **Drip**: IV saline drip – 0, 4 or 5 cc/hr
- **SQ injections:** SQ insulin (human regular per sliding scale) and basal insulin (only at 48 hrs if indicated)

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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 ... n Regular Insulin (Humulin R or Novolin R) Sliding Scale
Start ... e indicated below and adjust if ... ted each time glucose is checked.	Start at Leve... t the end of the first 24 hours, ... evious two glucose levels remain ≥ 180mg/dL, advance to Level 2. If after 24 hours on Level 2, the previous two glucos... s remain ≥ 180mg/dL, proce... vel 3. In Level 3, give a one-time subcutaneous basal insulin injection (Glargine) at a dose equal to 40% of b... 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

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Control Group- Initiating Treatment

- Capillary BG (FSBG)
  - Check at enrolling hospital ASAP
  - Re-check post randomization when study treatments are ready and initiate based on this glucose level
- Start IV saline infusion per control treatment screen
- Only give SQ insulin at designated dosing times

Control Group- Continuing Treatment

- Glucose checks q1 hr for 1st 4 hrs then q3 hr sched
  - If hourly check is within 30 mins of next dosing time, give dose
  - If 4th hourly check within 1 hr of non-dosing scheduled check, skip
  - If 4th hourly check is within 1 hr of next scheduled dose, give dose
  - Call PI on call with these transitions!!!!
- Adjust IV saline if needed with each glucose check
- Though checking q3 hrs, dosing is q6 hrs as below:

	Time								
Activity	Glucose check & IV saline adjustment	03:00	**6:00**	9:00	**12:00**	15:00	**18:00**	21:00	**24:00**
	SQ insulin dosing		**6:00**		**12:00**		**18:00**		**24:00**

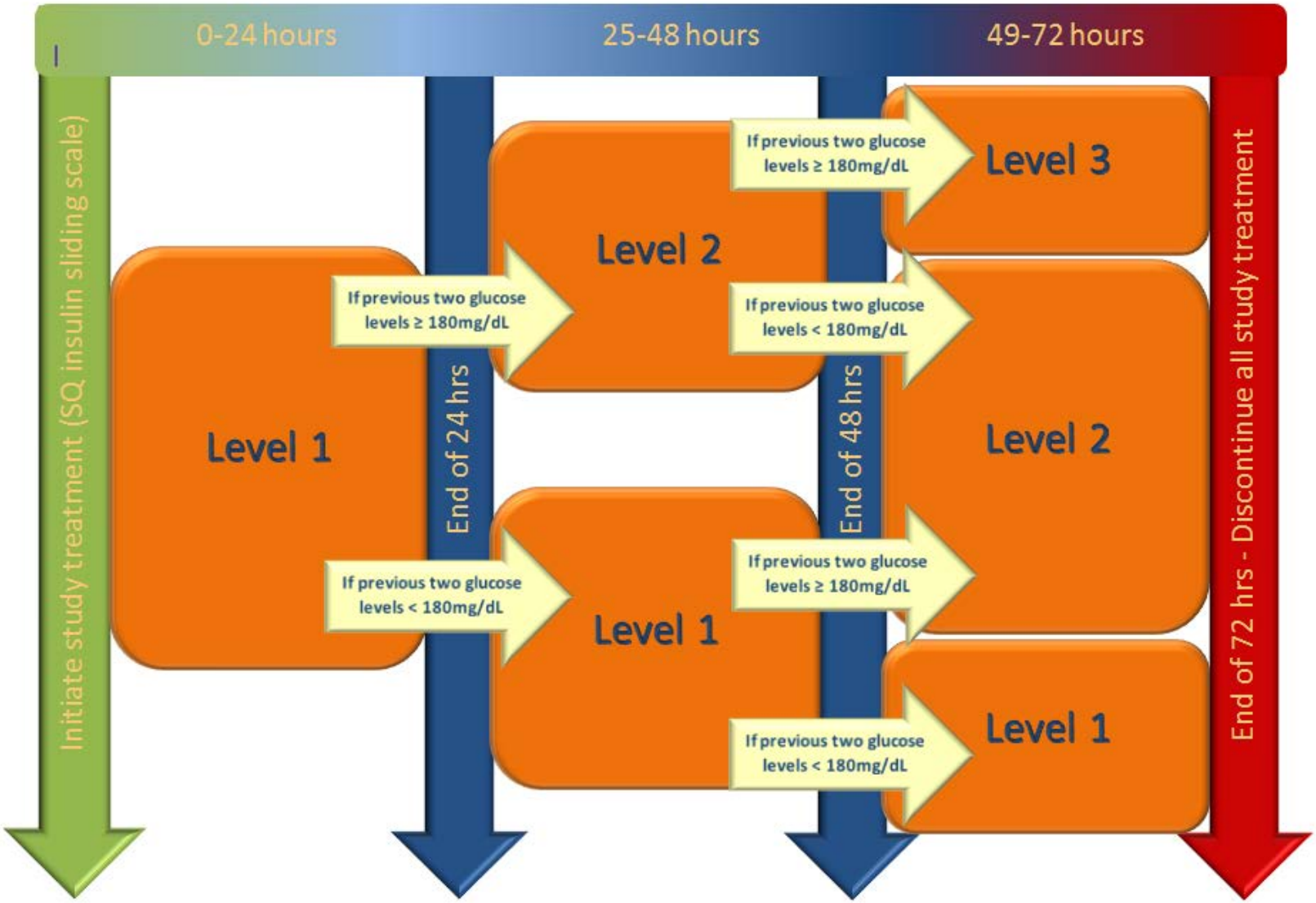
Control Group – Level Changes

- Level changes allow increase in insulin coverage for subjects who need higher dosing

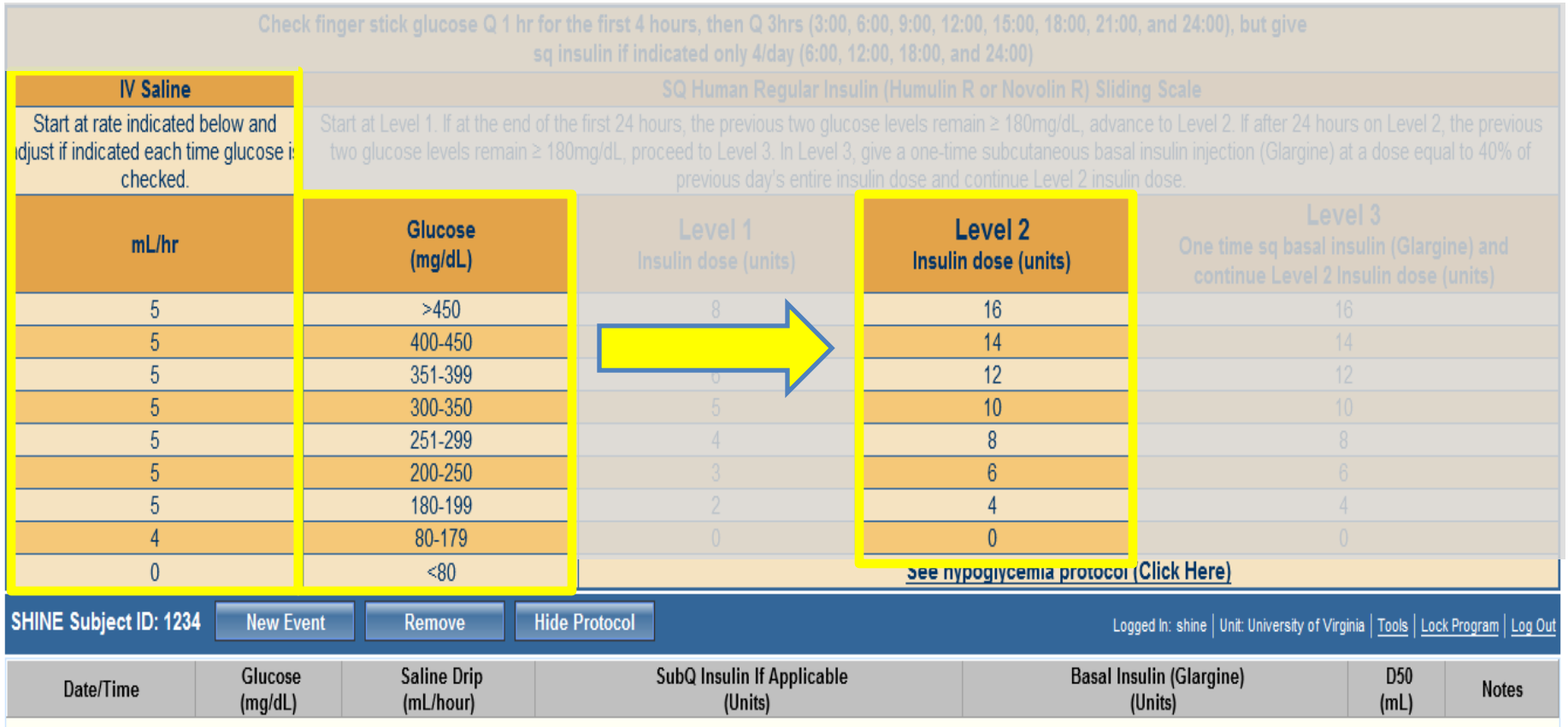
- All patients on Level 1 for first 24 hrs
- Level changes assessed every 24 hrs

- Level 2
  - Advance to Level 2 at 24 hrs if latest two glucose results are $\geq$ 180mg/dL
  - Also, possible to advance to level 2 at 48 hrs

Sliding Scale - Level Changes



Control Group – Level 2



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

Control Group - Level 3

- Advance to Level 3 at 48 hrs if latest two glucose results are $\geq$ 180mg/dL
- Level 3 includes a one-time dose of basal insulin SQ (glargine/Lantus) at 48 hrs
- Calculating basal insulin dose
  - Add all insulin requirement in previous 24 hrs (all 4 doses)
  - 40% of that total is the dose of basal insulin
- Basal insulin given SQ now (at 48 hrs)
- Continue SQ sliding scale insulin- Level 3

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Control Group – Level 3

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

Start at rate indicated below and adjust if indicated each time glucose is checked.

SQ Human Regular Insulin (Humulin R or Novolin R) Sliding Scale

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.

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

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When subjects resume eating

Control Group - Meals

- NPO until cleared to swallow
- 60 grams carbohydrates per meal when start meals
- Dysphagia diet/bolus tube feeds must also be 60 grams carbohydrate
- Protocol-approved snacks between meals available upon request

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Protocol approved snacks

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
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

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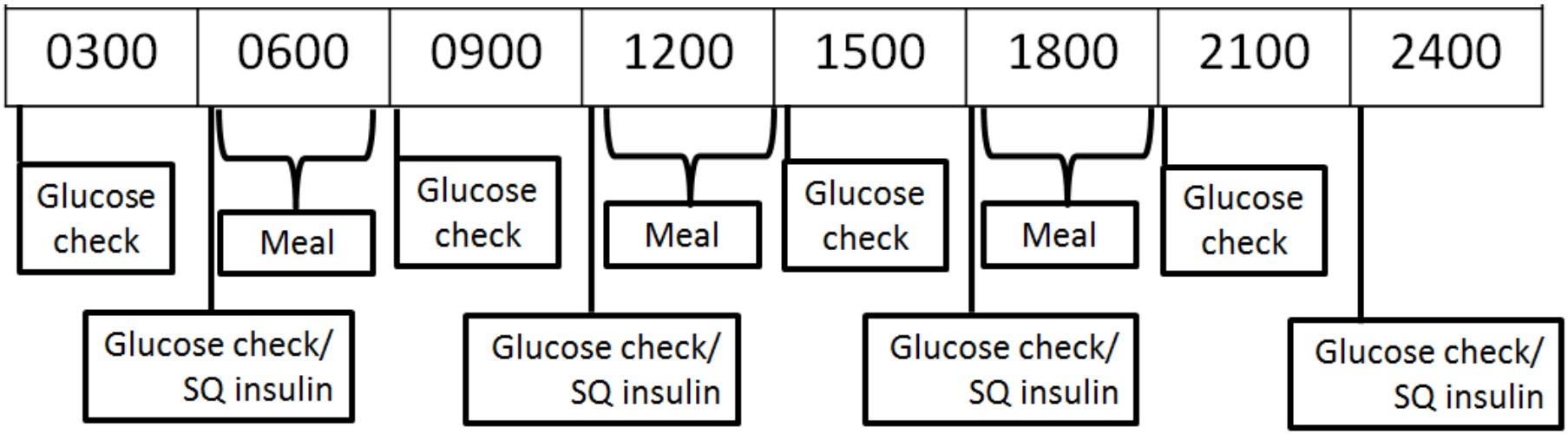
Considering timing of meals/checks



<u>Note</u>: The glucose check precedes the meal

- 6 AM check should precede breakfast (any time from 6AM to 9AM)
- Noon check should precede lunch
- 6PM check should precede dinner

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Questions on Control Protocol?

Intervention Group

Intervention Group- General Concepts

BG target: 80-130 mg/dL

Glucose checks: Timing -q1-q2 hrs recommended by GlucoStabilizer® (+/- 15 min)

Drip: IV insulin per GlucoStabilizer®

SQ injections: SQ meal insulin (or saline if NPO)

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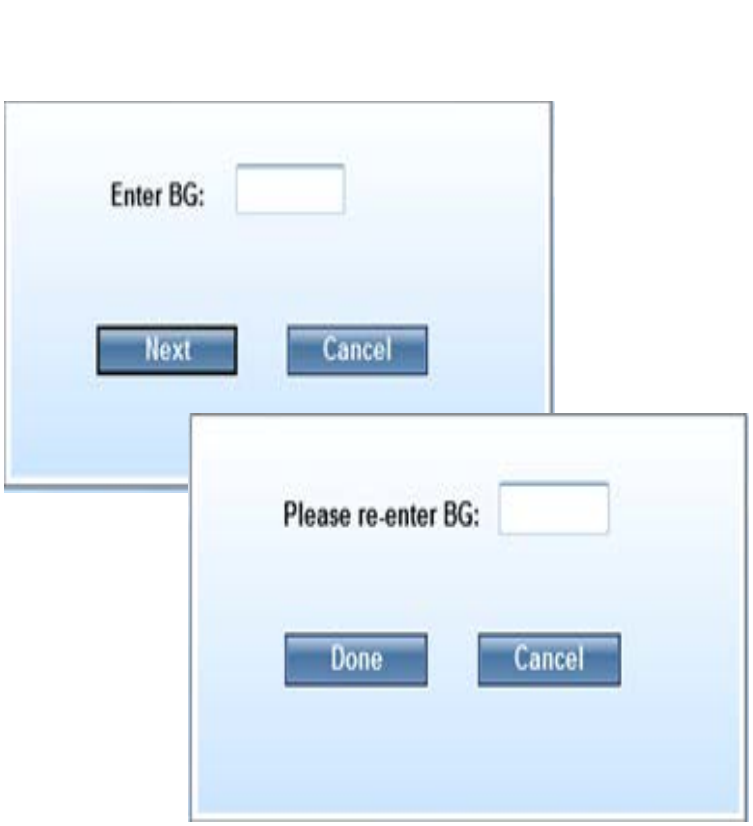
Intervention Group – Initiating Treatment

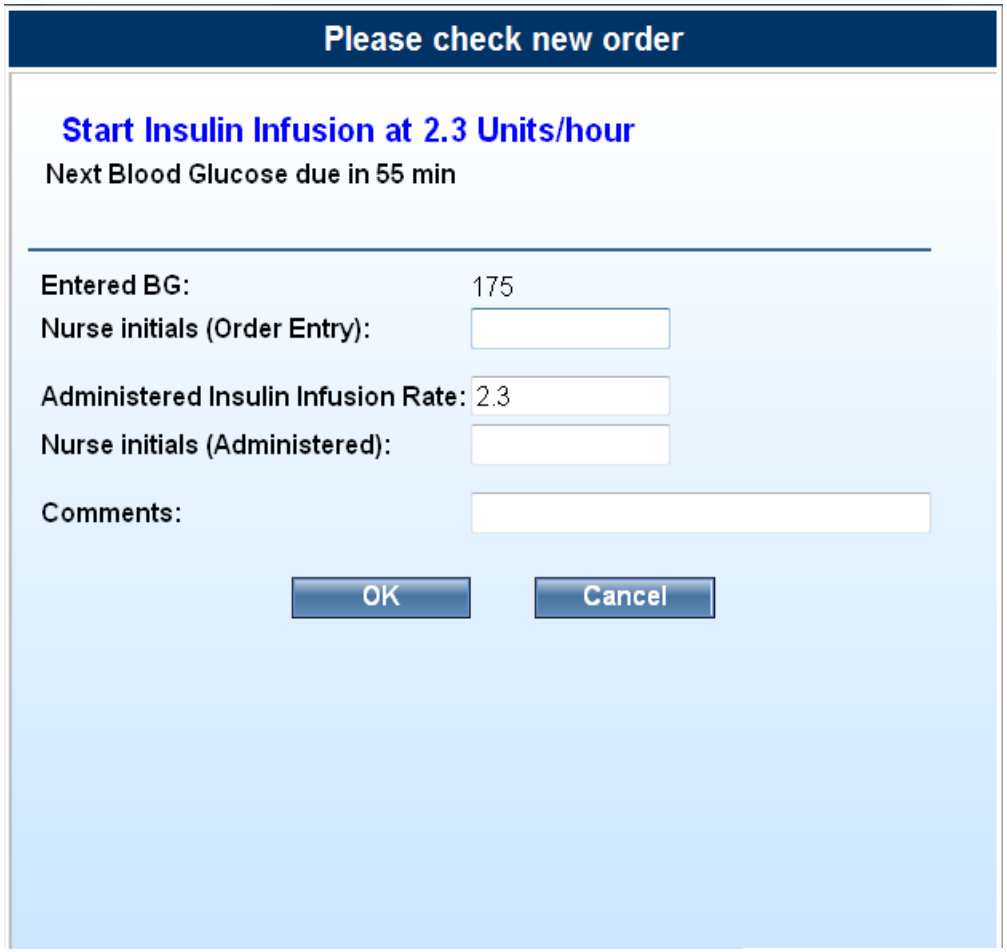
- Capillary BG (FSBG)
  - Check at enrolling hospital ASAP
  - Re-check post randomization when study treatments are ready and initiate based on this glucose level

- Start IV insulin infusion per GlucoStabilizer® recommendation

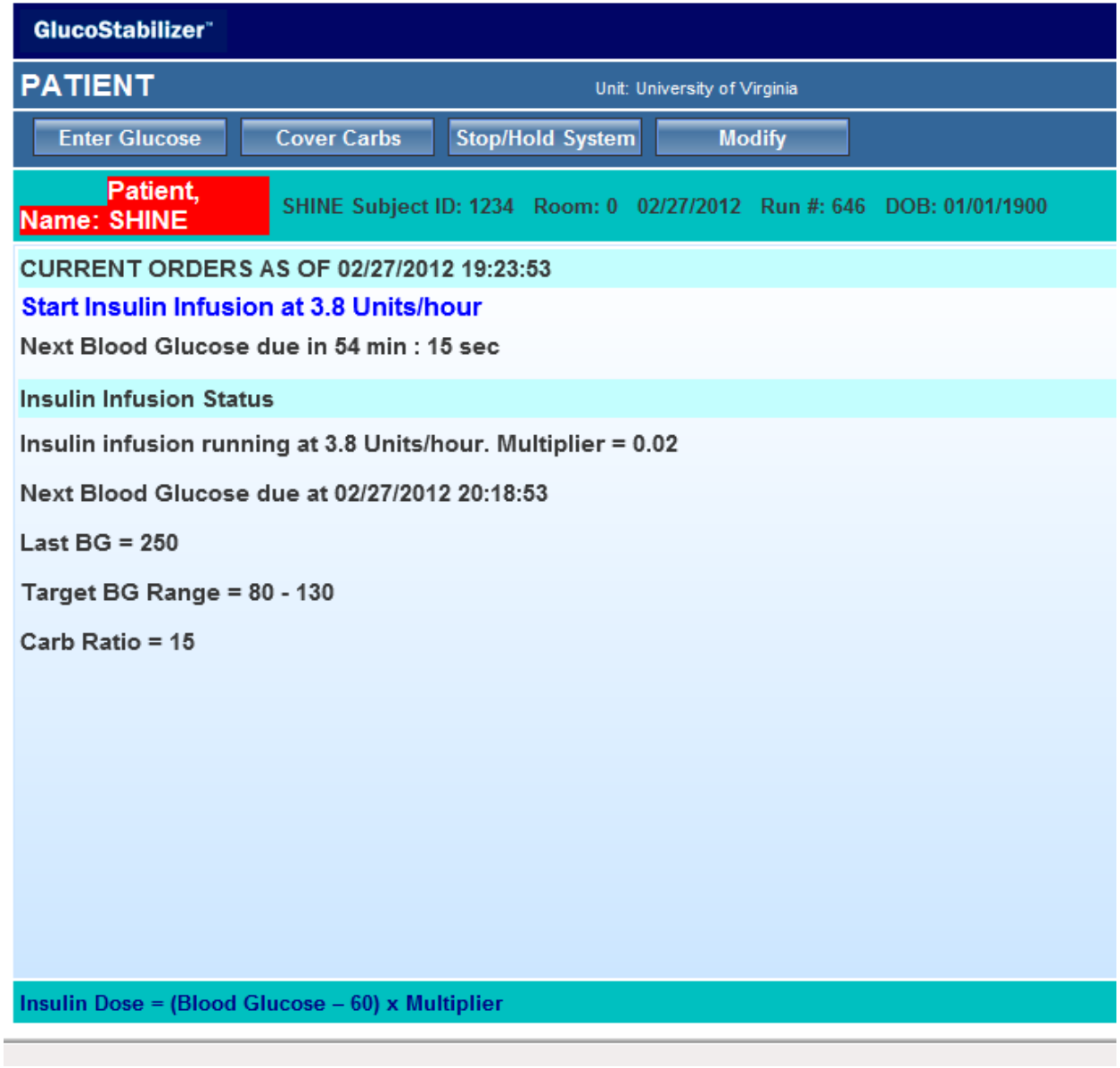
Entry in GlucoStabilizer®

As per previous lap top training…





Entry in GlucoStabilizer ®



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Intervention Group– Continuing Treatment

- Usually q1 hr checks for first 6-8 hrs
- May change to q2 hrs if BG stabilized
- Dose IV insulin per GlucoStabilizer® each time
- SQ injections in intervention group
  - meal insulin SQ if receiving meals

    OR
  - saline SQ if not receiving meals (09:00 and 21:00)

Intervention Group – Meals
PO or bolus tube feeds

- NPO until cleared to swallow
- 60 grams carbohydrates per meal when start meals
- Dysphagia diet/bolus tube feeds must also be 60 grams carbohydrate
- Protocol-approved snacks between meals upon request
- SQ meal insulin (rapid acting analog) based on meal consumption

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Intervention Group
Estimating Meal Consumption

- Nurse assesses meal tray ~20 minutes after start of meal
- Estimating PO meal consumption
  - All or nearly all→ Enter 60
  - None or nearly none→ **No entry** in GlucoStabilizer®
  - Partial→ Enter 30
- Do NOT enter any numbers other than 30 or 60 or will get wrong dose
- Dose immediately based on computer rec

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Intervention Group
Estimating Bolus Tube Feeds

- Nurse assesses bolus tube feed ~20 minutes after start
- Estimating bolus tube feeds
  - All or nearly all (50-60 grams)→ Enter 60
  - None or nearly none (0-9 grams)→ **No entry** in GlucoStabilizer®
  - Partial (10-49) grams→ Enter 30
- Do NOT enter any numbers other than 30 or 60 or will get wrong dose
- Dose immediately based on computer recommendation

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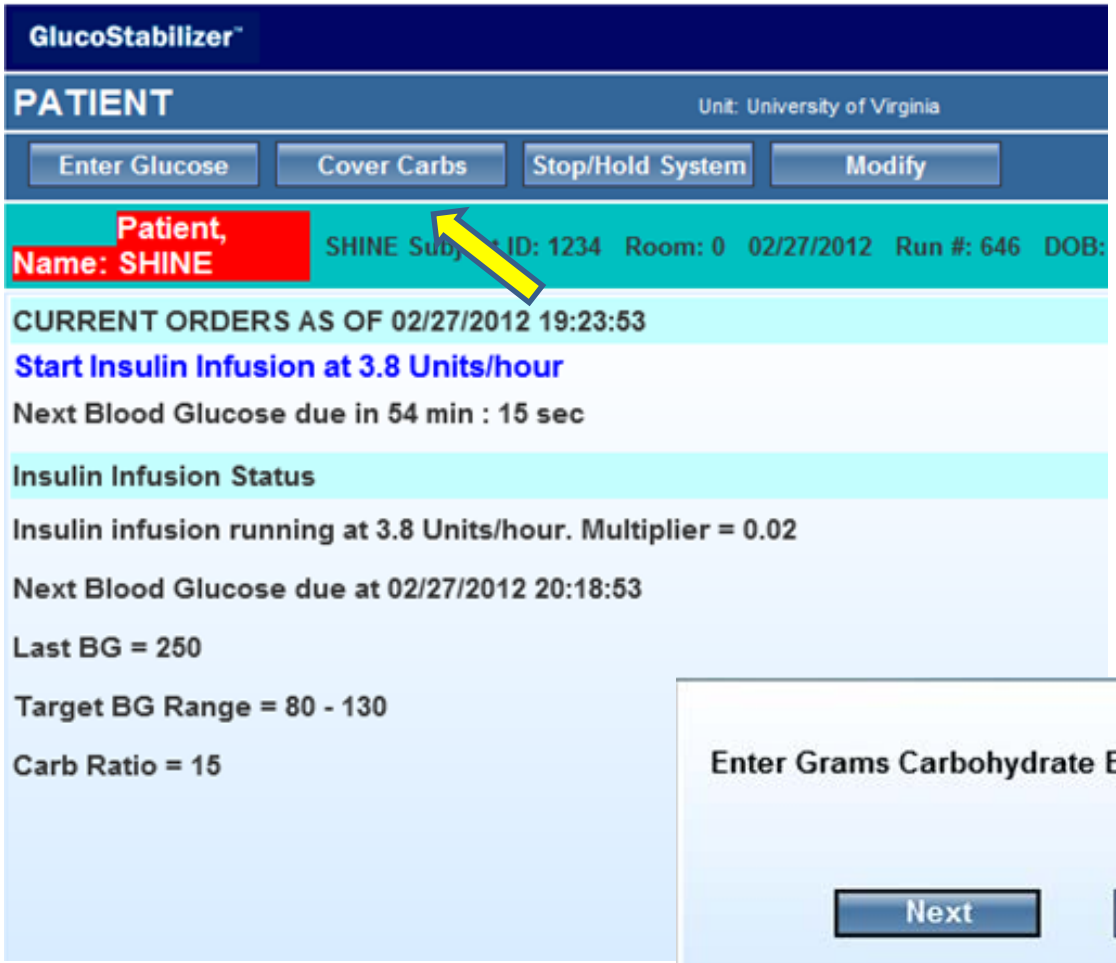
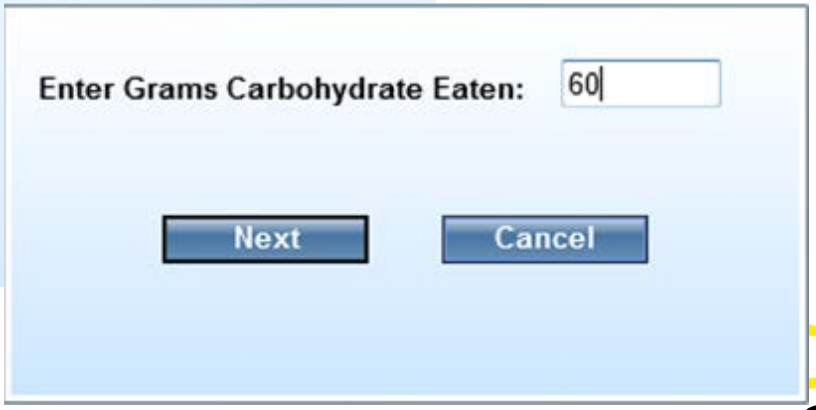
Intervention group

Entering Meals in GlucoStabilizer®





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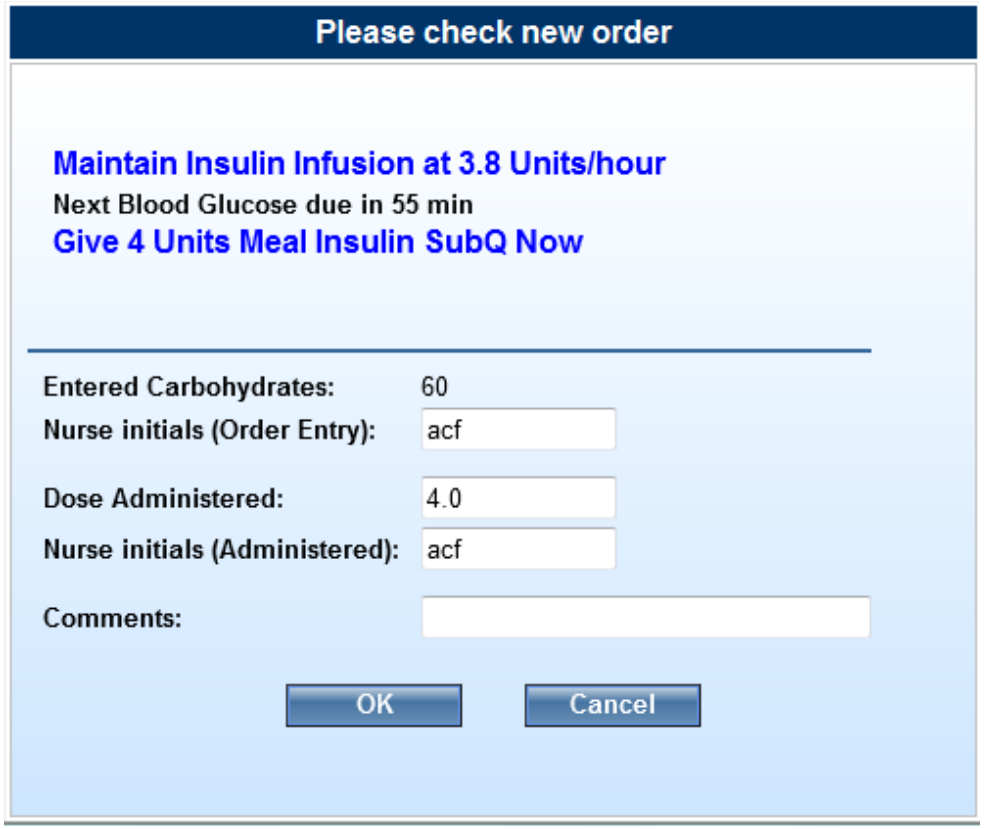
Meal Insulin Dosing



Note: NO entry and NO meal insulin if meal not consumed, 2 unit of insulin if 30 entered, and 4 units of insulin if 60 entered.

Intervention Group
NPO or Continuous Tube Feeds

- Continuous tube feeds – ~180 total grams carbohydrates daily

- SQ injections for NPO or continuous tube feeds
  - 0.05mL Normal Saline (in insulin syringe)
  - Give right after glucose checks at 09:00 and 21:00
  - Document in medical record; no entry in GlucoStabilizer®

Questions on Intervention Protocol?

Hypoglycemia Protocols

Hypoglycemia Prevention & Management

- Hypoglycemia prevention protocol initiated when BG<80 mg/dL

- Definitions
  - Any hypoglycemia is BG <70 mg/dL (AE)
  - Severe hypoglycemia is BG <40 mg/dL (SAE)

Hypoglycemia Prevention & Management General Concepts

- STOP all SQ and IV study treatments if <80 mg/dL
- Give D50 slow IV push (per protocol for each group)
- Recheck glucose q 15 minutes
- Follow neuro exam and symptoms if <70 mg/dL
- Send for serum glucose if <70 mg/dL
- Once BG ≥80 mg/dL resume treatment protocols
- ≥3 BG of <70 mg/dL within 24 hours – required call to independent safety monitor

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Hypoglycemia- Special Situations

- Intervention group – if <80 at any time during meal, don't give meal insulin

- Control group – if 3 episodes of hypoglycemia within 24 hours don't advance to level 2 or level 3 even if last 2 checks >=180 (unless instructed by safety monitor)

Hypoglycemia Prevention & Management

Glucose <70 mg/dL – Additional Steps

- Send a STAT laboratory serum glucose
- Hypoglycemia Symptomatic Questionnaire (q15 min)
  - Once BG ≥ 70mg/dL or symptoms resolve, whichever comes first, one final assessment required
- Neuro checks (q15 min) when <70mg/dL
- Once BG ≥80 mg/dL, resume treatment protocol

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Demonstration of Hypoglycemia Prevention & Management Protocols

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Questions on Hypoglycemia Protocols?

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Pausing the Treatment Protocol

Pauses – Both Groups

- Pausing protocols allow nurses to turn off study treatment for short periods when interruptions are required.

- Both groups should stop IV drip and SQ study treatments

Pauses – Control Group

- Stop drip and document in study laptop and medical record
- Upon return to the unit, restart study protocol based on whether glucose check has been missed:

- No missed check
  - Resume drip
  - Check glucose at next scheduled time/ dose as appropriate

- If a schedule check was MISSED during a pause
  - Check BG immediately, resume drip per protocol
  - If insulin dose missed, give injection now based on current glucose level
    - If next insulin dose is scheduled < 3 hours from a make up dose, skip the next dose
  - Return to scheduled glucose checks

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Pauses - Intervention Group

- Stop drip
- Document in study laptop and medical record
  - Select Stop/Hold in GlucoStabilizer®.
  - Chart the rate change in the med record (rate = 0).

- Upon return to the unit, check BG immediately.
  - If <3 hours since stop drip, Select 'Resume drip' (most recent drip run)
  - If ≥ 3 hours, Select Start a new drip

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Demonstration of Pauses

Loss of IV access

- Replace IV as quickly as possible
- Control group
  - Document drip stopped in medical record and Control Treatment Screen
  - Continue glucose checks and SQ insulin dosing
- Intervention group – call SHINE PI
  - Document drip stopped in medical record and GlucoStabilizer®
  - Continue SQ meal insulin or saline dosing per protocol
  - Document in GlucoStabilizer® by selecting resume, cover carbs, and stop/hold

Questions on Pauses?

Interruption of continuous tube feeds

- Protocol in place for safety in intervention group

- Control group protocol to maintain blind

Interruptions in continuous tube feeds Intervention group

- Stop IV insulin - select stop/hold in GlucoStabilizer®
- If tube feeds restarted in <1 hr, select ‘Resume’, check BG and re-start IV insulin (insulin need is the same)
- If tube feeds not restarted at 1 hr, check BG, select ‘Start a New Drip’, and start IV insulin per rec (insulin need has changed)
- Continue protocol SQ saline if NPO, meal insulin if meals started

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Interruptions in continuous tube feeds
Control group

- Stop IV saline and document in study laptop
- If tube feeds restarted in <1 hr, check BG and re-start IV saline
- If tube feeds not restarted by next scheduled BG check, check BG and re-start IV saline then
- SQ insulin dosing does not change


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Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial

Post Protocol and Outcomes

Karen C. Johnston, MD, MSc

Administrative PI

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Reasons to Discontinue Treatment Protocol

- Common
  - 72 hours complete
  - Clinical team ready for discharge
- Uncommon
  - Safety monitor requires discontinuations
  - Stroke mimic
  - Death

Discontinuing the Treatment Protocol

- Stop all study treatment 6 hrs prior to discharge for patients going home
- GlucoStabilizer® Drip Weaning Report (24 hr insulin total) available for review (intervention group)
- Post-treatment glucose management per clinical team (can't use study protocol/computer)
- Prepare a plan prior to readiness call (e.g. hospital protocol, endocrine consult)
- Discuss transition with medical monitor when required stop for safety

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Transition to Standard Care

- Per ADA guidelines, scheduled subcutaneous insulin that delivers basal, nutritional and correction components as needed
- Consider that oral agents are not recommended in hospitalized patients, but may be initiated or resumed in anticipation of discharge per ADA guidelines.
- Consider individualized discharge planning per ADA guidelines

Case Report Form

- Warning if <3 days (control)
- Reason for early d/c treatment
- Glucose control treatments (standard care)

Summary - Clinical Outcomes

- Primary Study Outcome – 3 month mRS
- Primary Safety Outcome – frequency of severe hypoglycemia (<40 mg/dL) in intervention group versus control group

- Additional Outcomes
  - 6 week phone call – mRS by phone, SAEs
  - 3 month - BI, NIHSS, QOL

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Follow up visits

Outcomes MUST be done by a blinded assessor

- 6 week visit – by phone (15 mins) +/- 14 days
  - mRS and SAEs

- 3 month visit– in person (30-45 mins) +/- 14 days
  - mRS – primary outcome
  - Other clinical/functional/QOL outcomes
  - SAEs

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