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## The Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial protocol; a randomized, blinded, efficacy trial of standard versus intensive hyperglycemia treatment in acute stroke

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### Abstract

**Rationale**—Patients with acute ischemic stroke and hyperglycemia have worse outcomes than those without hyperglycemia. Intensive glucose control during acute stroke is feasible and can be accomplished safely, but has not been fully assessed for efficacy.

**Aims**—The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial aims to determine the safety and efficacy of standard versus intensive glucose control with insulin in hyperglycemic acute ischemic stroke patients.

**Design**—SHINE is a randomized, blinded, multicenter, Phase III trial of approximately 1400 hyperglycemic patients who receive either standard sliding scale subcutaneous insulin (blood glucose range 80–179 mg/dL, 4.44–9.93 mmol/L) or continuous intravenous insulin (target blood glucose 80–130 mg/dL, 4.44–7.21 mmol/L), starting within 12 hours of stroke symptom onset. Study treatment lasts for up to 72 hours. The acute treatment phase is single-blind (for the patients), but the final outcome assessment is double-blind. The study is powered to detect a 7% absolute difference in favorable outcome at 90 days.

**Study outcomes**—The primary outcome is a baseline severity adjusted 90 day modified Rankin Scale (mRS) score. Favorable outcome is defined as mRS=0 if the baseline NIH Stroke Scale

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<sup>1,2</sup>The amount contributed by these authors is indistinguishable

#### Conflicts of interest:

Dr. Rattan Juneja receives royalties from commercial sales of the GlucoStabilizer® tool.

(NIHSS) is 3–7, or mRS 1 if the baseline NIHSS is 8–14, or mRS 2 if the baseline NIHSS is 15–22. The primary safety outcome is the rate of severe hypoglycemia (<40 mg/dL, <2.22 mmol/L).

**Discussion**—This trial will provide important novel information about preferred management of acute ischemic stroke patients with hyperglycemia. It will determine the potential benefits and risks of intensive glucose control during acute stroke.

### Keywords

acute ischemic stroke; cerebral infarction; clinical trial; ischemic stroke; protocols; stroke; hyperglycemia; diabetes

## Introduction and rationale

Hyperglycemia is seen in approximately 40% of acute ischemic stroke patients<sup>1, 2</sup> and is associated with worse clinical outcomes.<sup>1–3</sup> Preclinical and clinical data suggest a potential clinical benefit of intensive glucose control in the setting of acute cerebral ischemia. However, hypoglycemia, especially severe or prolonged hypoglycemia, is of greatest concern with insulin therapy.<sup>4–7</sup> A protocol minimizing severe and prolonged hypoglycemia while controlling hyperglycemia has the potential to improve outcomes in acute stroke patients. Intensive glucose control with IV insulin therapy has been found to improve clinical outcomes in some non-stroke acute illnesses.<sup>8, 9</sup> However, there remains clinical equipoise about how best to treat hyperglycemia during acute ischemic stroke. Results from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) funded Treatment of Hyperglycemia in Ischemic Stroke (THIS)<sup>10</sup> and the Glucose Regulation in Acute Stroke Patients (GRASP)<sup>11</sup> trials demonstrated safety and feasibility of insulin infusion therapy for intensive glucose control in acute ischemic stroke patients. No previous trial has fully assessed the efficacy of intensive glucose control and current stroke guidelines therefore emphasize the need for definitive clinical trials to determine optimal management of hyperglycemia in acute stroke.<sup>12</sup>

As improved glucose control protocols decreased the risk of hypoglycemia, determining the efficacy and safety of intensive versus standard glucose control in acute ischemic stroke patients became a priority. Numerous previous glucose control trials informed the SHINE trial design.<sup>10, 11, 13–15</sup> The SHINE trial was designed to address key questions about hyperglycemia management in acute stroke. The primary aim of the SHINE trial is to determine the efficacy of intensive versus standard glucose control. The secondary aim is to assess safety and therefore determine an overall risk/benefit profile for the intensive insulin intervention versus the standard treatment. The results of this trial will likely clarify the preferred treatment and guide clinical decision making.

## Design

SHINE is a randomized, blinded, multicenter, controlled phase III trial of continuous intravenous insulin versus standard subcutaneous insulin in acute ischemic stroke with hyperglycemia. Additional treatments constituting usual care are allowed; including intravenous (IV) tissue plasminogen activator (tPA), intraarterial tPA, and United States Food and Drug Administration cleared endovascular devices. Throughout the study period, current American Heart Association guideline for the early management of adults with ischemic stroke will be followed.<sup>12</sup>

Enrollment must be within 12 hours of stroke symptom onset. Also, to maximize early treatment, enrollment should be within 3 hours of arrival to the Emergency Department. The

12 hour window for enrollment is based on a combination of supporting animal model data, feasibility, and generalizability considerations.

The trial is single blind during treatment and double blind for the functional outcome assessment. Blinding the treating team during treatment was felt to impose excessive risk, and having an unblinded investigator manage the study treatment for 72 hours on an hourly basis is not feasible.

At 6 weeks serious adverse events and early follow-up information are assessed by telephone. At 3 months the primary and secondary outcomes are assessed in-person. Subjects unable to return in-person at 3 month are assessed by telephone. The sliding dichotomy that assesses the primary outcome allows individual patients to have favorable outcomes according to their initial stroke severity, based on the NIHSS.<sup>16</sup> This design maximizes the generalizability of the results by enrolling a broad range of stroke severities, and increases the use of individual patient data that are often lost with single dichotomized outcome definitions. The sliding dichotomy has been successfully used in a previous stroke trial<sup>17</sup> and is described under primary outcome.

Recruitment is aimed at capturing a broad patient population from across the United States with expected suitable representation of women and minorities (see appendix). Only adults aged 18 years or older are included. To optimize recruitment, the SHINE research team includes a Recruitment PI (CEH) and a NINDS Recruitment Specialist whose focus is to maximize timely recruitment across all sites. This team has developed individualized screening and recruitment goals and a monitoring plan for each site. The recruitment plan is designed to promptly and accurately estimate the number of sites required to complete recruitment on schedule.

The limitations of this design include potential bias due to the single-blind acute treatment period. The double-blind primary outcome assessment is designed to eliminate this bias. Potential measured and unmeasured confounders include all treatments and care outside the study treatment protocol through the 90 day outcome assessment. The secondary analysis will attempt to adjust for pre-specified confounds.

## Patient population

The primary target population for the SHINE trial are acute ischemic stroke patients likely to have persistent hyperglycemia during hospitalization, and who can be enrolled within 12 hours of symptom onset (Table 1). Patients receiving standard IV tPA are stratified at randomization to prevent confounding of treatment effect.

Previous data indicate that patients with history of type 2 diabetes or those with baseline blood glucose at or above 150 mg/dL (8.32 mmol/L)(even without diabetes) are likely to have persistent hyperglycemia, unless treated with insulin.<sup>10, 11, 13, 18</sup> Patients who do not meet these criteria typically have self-limited hyperglycemia that resolves early and spontaneously during hospitalization.<sup>10, 13, 19</sup> Thus, the SHINE eligibility criteria attempt to exclude patients with self-limited hyperglycemia.

Previous data show that patients with the mildest strokes generally have good outcomes and those with the most severe strokes generally have poor outcomes. Therefore, the mildest (NIHSS <3) and most severe (NIHSS >22) stroke patients are excluded from the SHINE trial to avoid obscuring a treatment difference between the groups. Also, excluded are patients for whom clinical equipoise for treatment is absent (e.g., those with type 1 diabetes or pregnancy), those at excessive risk from either intervention (e.g., receiving renal dialysis), those at risk for loss to follow up (inability to return), and those with confounding that

would preclude accurate estimation of treatment effect (other experimental interventions, substantial pre-existing neurological or psychiatric disease) (Table 1).

Additionally, since with the sliding dichotomy some patients require a 90 day mRS of 0 to classify as having favorable outcome, those with residual symptoms from prior stroke, or who are unable to live independently due to pre-existing disabilities, are excluded from this trial.

## Randomization

The SHINE trial utilizes a web-based central randomization system that employs a combination of covariate balance<sup>20</sup> and response adaptive randomization (RAR)<sup>21</sup> methods. The prognostic variables considered at the time of randomization include baseline NIHSS strata (3–7, 8–14, 15–22), use of IV tPA thrombolysis (yes/no), and clinical center. Randomization is initially 1:1, but as the trial progresses this ratio may change based on two factors, the prevention of serious imbalances in the pre-specified prognostic variables and the favorable outcome rate in each treatment group. This randomization design is aimed to preserve the randomness of treatment assignment, prevent serious imbalance in important baseline prognostic variables, and promote subject recruitment while preserving the statistical test power.

## Treatment

There are two treatment groups in the SHINE trial (Table 2). One group receives continuous IV insulin infusion to maintain blood glucose 80–130 mg/dL (4.44–7.21 mmol/L). An FDA cleared computerized decision support tool, GlucoStabilizer®,<sup>22</sup> (Alere Informatics Solutions [AIS], Charlottesville, VA) recommends the insulin drip rate to maintain the glucose in the target range. The other group receives only subcutaneous (SQ) insulin to maintain blood glucose 80–179 mg/dL (4.44–9.93 mmol/L)(Table 2). The glucose values are based on point of care capillary glucose testing. All patients are treated with a combination of IV and SQ study medications, some of which are insulin and some are normal saline to maintain the blind (Table 2). All pre-stroke anti diabetes medications are held throughout the treatment period. All patients are treated in hospital units that support IV insulin infusion. At the completion of the 72 hour study treatment period, the treating team determines the subsequent standard care regimen. For patients who are ready for discharge prior to 72 hours, the study medications are discontinued at least 6 hours prior to discharge. If study treatment must be temporarily interrupted for standard care reasons, procedures for pausing and restarting the study treatment are provided.

The treating nurses enter all glucose levels and insulin treatments in both groups into laptop computers, which are instantly transmitted to an AIS server in Charlottesville, VA. AIS transfers all study data to the Statistical and Data Management Center every 24 hours.

Hypoglycemia is defined as blood glucose <70 mg/dL (<3.88 mmol/L), and severe hypoglycemia as <40 mg/dL (<2.22 mmol/L), but to prevent hypoglycemia, study medications are held and IV glucose is given in both groups whenever the blood glucose levels fall to <80 mg/dL (<4.44 mmol/L). In the control group, patients receive 25 ml of 50% dextrose (D50), glucose level is rechecked every 15 minutes and additional D50 is given after each check until the glucose is 80 mg/dL ( 4.44 mmol/L). In the intervention group, the GlucoStabilizer® program recommends a calculated dose of D50 based on the blood glucose level.<sup>22</sup> The computer sounds an alarm to recheck the glucose level every 15 minutes and recommends additional D50 doses until the glucose is 80 mg/dL ( 4.44 mmol/L).

When blood glucose is  $<70$  mg/dL ( $<3.88$  mmol/L) in either group, a confirmatory blood sample is sent to the laboratory. Additionally, a hypoglycemia symptomatic questionnaire<sup>23</sup> and a neurological examination are done every 15 minutes until resolution.

## Primary outcome

The primary efficacy outcome is baseline severity adjusted 90 day mRS assessed using a sliding dichotomy to identify favorable outcomes, also known as responder analysis.<sup>16</sup> The responder analysis dichotomizes mRS scores as favorable or unfavorable based on the baseline NIHSS measured at enrollment and the 90 day mRS, and was chosen to provide a more sensitive measure of clinical effect. Patients in the lowest baseline severity tertile (NIHSS 3–7) need to have a 90 day mRS score of 0 to achieve favorable outcome. Patients with baseline NIHSS 8–14 can have a 90 day mRS score 0–1 for favorable outcome, and those with baseline NIHSS 15–22 can have a 90 day mRS score 0–2 for favorable outcome, as used in previous trials.<sup>17</sup>

## Secondary outcomes

Secondary outcomes include favorable outcome as measured by the NIHSS, Barthel Index and the Stroke Specific Quality of Life scale<sup>24</sup> at 90 days. Blood glucose control and protocol adherence will also be analyzed.

## Data and safety monitoring

Adverse events are collected during the study treatment period, and serious adverse events are collected throughout the entire study period. The primary safety outcome is the rate of severe hypoglycemia determined as the percentage of patients in each group having at least one blood glucose measurement  $<40$  mg/dL ( $<2.22$  mmol/L) during the treatment period.

A study appointed independent safety monitor and an NIH-NINDS appointed Data and Safety Monitoring Board (DSMB) oversee safety in the SHINE trial. The DSMB meets every six months to review study progress and accumulated data. Their main responsibilities are to ensure that study participants are not exposed to unnecessary or unreasonable risks, and that the study is conducted with high scientific and ethical standards. The DSMB is assisted by an independent safety monitor who reviews and adjudicates all serious adverse events throughout the study. The independent safety monitor also fields safety concerns from the investigators during study treatment.

## Sample size

The sample size estimate was based on data from the two NIH funded pilot trials,<sup>10, 11</sup> as well as other relevant acute stroke trials.<sup>25, 26</sup> These data supported an estimate of 25% favorable outcome rate in the control group. The minimal clinically relevant absolute difference in favorable outcome between the two treatment groups was estimated to be 7% (control group = 25%; intervention group = 32%). The study is therefore powered to detect an absolute 7% difference in favorable outcome between the groups. The study design includes four interim analyses for both efficacy and futility of the primary outcome (after 500, 700, 900, and 1,100 patients complete the study) and a final analysis for a total of five planned analyses of the primary outcome. Including a 3% non-adherence rate and the four interim analyses, approximately 1400 randomized patients are needed to provide 80% power with a two-sided type I error rate of 0.05.

In the event that the control group favorable outcome rate is higher than 25% a blinded sample size re-estimation will be done prior to the first interim efficacy/futility analysis

using the approach of Gould and Shih.<sup>27</sup> The overall favorable outcome rate of the study population will be estimated using the interim data for the sole purpose of sample size re-estimation (not for interim testing of a treatment effect).

## Statistical analysis

The primary analysis for the SHINE trial will compare the proportion of subjects in each treatment group with favorable outcome after controlling for baseline NIHSS and standard IV tPA. Outcome differences will be analyzed under the intention-to-treat principle (all randomized participants included) and adjusted relative risks will be reported with two-sided 95% confidence intervals. Additional analyses will identify potential prognostic variables as covariates for secondary analyses of the primary outcome. Specific variables include age, gender, race, ethnicity, admission blood glucose, previous stroke, lacunar stroke subtype, and time from stroke onset to randomization.

The four interim analysis plans described above use the error spending function method with O'Brien and Fleming (OBF) type stopping guidelines.<sup>28, 29</sup> The OBF-type boundary is considered conservative as its boundaries make it unlikely to terminate a study early by requiring overwhelming early evidence of efficacy or futility. It spends smaller amounts of alpha at the first look and gradually increases the spending as more information is acquired while maintaining the overall type I and II error rates. For example, under the null hypothesis of no difference between the two treatment groups, there is a 4% chance of stopping the trial for futility at the first look, 10% at the second, 25% at the third, and 35% at the fourth. Overall, there is approximately a 75% chance of stopping the trial early for futility, if there is no difference. Under the alternative hypothesis, there is an 11% chance of stopping the trial early for overwhelming efficacy at the first look, and a 66% chance overall of stopping early. These analyses will begin once final outcome data are available from roughly one-third of the study population.

## Trial organization and funding

The SHINE trial is funded by the NIH/NINDS. Recognizing the effort and skill needed to successfully run the various aspects of a large acute clinical trial, the SHINE trial has three principal investigators, each with a specified focus. The administrative PI (KCJ) is the main contact person for SHINE and chairs the executive committee. The protocol PI (AB) oversees the treatment protocols. The recruitment PI (CH) is focused on patient recruitment and retention. A study endocrinologist (RJ) oversees the insulin treatments and all relevant metabolic issues. The SHINE trial is conducted primarily in collaboration with the NINDS funded Neurological Emergencies Treatment Trials (NETT) Network, as well as numerous ancillary (non-NETT) sites for patient enrollment. The NETT includes 22 hub and spoke complexes (Appendix) (NETT PI is WB). The Clinical Coordinating Center for the NETT, and therefore SHINE, is at the University of Michigan. The Statistical and Data Management Center for the NETT and for SHINE is the Medical University of South Carolina Data Coordinating Unit, directed by the SHINE Statistical PI (VLD). A total of approximately 60 sites are expected to participate in this trial.

## Summary

The SHINE trial is designed to address key questions about the management of hyperglycemia during acute ischemic stroke. This trial has the potential to impact the management of a substantial proportion of acute stroke patients. This trial design is scientifically rigorous, including response adaptive randomization and baseline severity adjusted double-blind primary outcome assessment. Continuous intravenous insulin infusion based on a computerized decision support tool will be compared to a standard subcutaneous

insulin sliding scale. Recruitment started in April 2012 and is expected to be completed in 2016.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Addendum

After enrolling 57 patients, the SHINE DSMB approved a protocol modification allowing enrollment of patients with a pre-stroke mRS of 0 or 1 if their baseline NIHSS is 8–22. However, patients with baseline NIHSS 3–7 must have a pre-stroke mRS of 0 to permit reaching a potential favorable outcome that is based on a sliding dichotomy of the mRS according to the baseline NIHSS score.

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**Table 1**

## Eligibility criteria

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<u>Inclusion</u>	
1	Age 18 years or older
2	Clinical diagnosis of ischemic stroke. Neuroimaging must be done to exclude intracranial hemorrhage.
3	Protocol treatment must begin within 3 hours after hospital arrival and within 12 hours after stroke symptom onset. If time of symptom onset is unclear or patient is awakening with stroke symptoms, the time of onset will be the time that the patient was last known to be normal.
4	Known history of type 2 diabetes mellitus and admission blood glucose >110 mg/dL (>6.10 mmol/L) OR admission blood glucose 150 mg/dL ( 8.32 mmol/L) in those without known diabetes mellitus.
5	Baseline NIHSS score 3–22.
6	Pre-stroke modified Rankin Scale score = 0 (able to walk, look after own affairs, and no residual symptoms from prior stroke).
7	Able to provide a valid informed consent to enroll (self or legally authorized representative).
<u>Exclusion</u>	
1	History of type 1 diabetes mellitus.
2	Substantial pre-existing neurological or psychiatric illness that could confound the neurological or other outcome assessment.
3	Having received experimental therapy for the enrollment stroke. IV tPA up to 4.5 hours or IA tPA are allowed as are endovascular therapies using FDA cleared devices. Non-FDA cleared devices are considered experimental and are excluded.
4	Known to be currently pregnant or breast-feeding.
5	Unlikely to survive 90 days due to another serious condition.
6	Inability to follow the protocol or return for the 90 day follow up.
7	Renal dialysis, including hemo- or peritoneal.

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**Table 2**

Outline of subcutaneous and intravenous study treatments in the SHINE protocol.

	<b>Control Group</b>	<b>Intensive Treatment Group</b>
<b>Subcutaneous treatments</b>	Regular human insulin at 6:00, 12:00, 18:00 and at 24:00 according to sliding scale; At 24 and 48 hours advance to the next treatment level if the latest 2 glucose levels are $\geq 180$ mg/dL; <u>Level 1 sliding scale</u> : 2–8 units for glucose 180 to $>450$ mg/dL; <u>Level 2 sliding scale</u> : 4–16 units for glucose 180 to $>450$ mg/dL <u>Level 3 sliding scale</u> : same as level 2 plus long acting basal insulin (glargine <sup>*</sup> ) at 48 hours	If not eating or continuous tube feeding, normal saline (placebo) at 9:00 and 21:00, or If eating or bolus tube meals, rapid acting analog insulin with meals
<b>Intravenous treatments</b>	Normal saline (placebo) with periodic rate adjustments	Continuous regular human insulin according to a computerized tool, GlucoStabilizer®.
<b>Capillary blood glucose monitoring</b>	Every 1 hour for the first 4 hours, then 3:00, 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00 (before meals if patient is eating)	Every 1–2 hours according to GlucoStabilizer® instructions

\* dose of glargine insulin is 40% of the total insulin given in the prior 24 hours;