3. Screening

3.1 Subject Identification

Each site will be responsible for identifying and recruiting participants into the study. It is known that screening methods vary across sites. It is, however, important to have multiple recruitment strategies to reach all potential patients (e.g., overnight, weekends, and holidays). The site PI, coordinator, and other support staff will agree to a screening plan before being eligible to enroll patients. Once potential participants are identified, the site will collect information about them to make a determination of their eligibility for the study. The determination of eligibility will be made using the data collected from patient history, assessments and examinations performed as part of the potential participant's routine care. Potential participants who are eligible for and are interested in the study will be asked to sign an informed consent with subsequent enrollment into the study. The site will track potential participants from the time they are identified until they are enrolled or not enrolled. Each site will document and report a summary of recruitment and enrollment progress.

The methods used for recruitment of subjects in the study will be devoid of any procedures that may be construed as coercive. The recruitment process will not involve any restrictions on sociodemographic factors including gender or racial and ethnic characteristics of the patient population. However, the composition of the study population will depend on patient sources available to the enrolling sites.

Patients will be recruited by members of the research teams at enrolling sites. Stroke teams and Emergency Medicine teams involved in the immediate evaluation and management of acute stroke patients will be trained to recognize potentially eligible candidates and to rapidly refer them for formal screening by appropriate study team personnel. When a patient is found eligible, they or their Legally Authorized Representative (LAR) as appropriate to the situation will be approached for discussion of the trial and informed consent.

Recruitment and enrollment will usually occur at the acute portal of entry to the enrolling site. Most often this will be in the Emergency Department, but this could also occur in a hospital inpatient unit directly receiving an acute stroke patient in transfer from another facility as long as arrival is within the specified enrollment window (12 hours from symptom onset and is recommended within 3 hours from arrival to the hospital).

Specifically randomization must be within 12 hours of onset and treatment must be started as soon as possible after enrollment AND is recommended to begin within 3 hours of arrival to the designated enrolling center.

3.2 Screening Overview

Screening is defined as any procedure done solely for the purpose of determining a potential subject's eligibility or to enter a subject into a research study. Federal regulations and institutional policy must be followed when screening subjects to determine potential eligibility. Potential subjects may be identified by neurologists, local emergency department, or clinic staff in conjunction with study personnel. The patient with "suspected stroke" could include both Acute Ischemic Stroke (AIS) and Intracerebral Hemorrhage (ICH) as the etiologies have a similar clinical presentation. When a potential candidate is identified, the site PI and/or the study coordinator (or their designee as clearly delineated by a call schedule system) should be contacted to begin the screening process. Patients should be screened and enrolled as quickly as possible

after presentation to the acute portal of entry. All acute ischemic stroke patients arriving within 12 hours of onset with glucose identified >110 must be referred to the study team for formal screening and must be captured in the Screen Failure Log.

In “FDA Information Sheets” dated 01 October 1995, the following specifications are made: *Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent.*

For the SHINE study there is no activity required in the screening process that could not reasonably be considered routine care for acute stroke patients. Therefore, unless required by local IRB, patients would be approached for consent only after the clinical screening process had established eligibility.

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

(1) Age 18 years or older

(2) Clinical diagnosis of ischemic stroke defined as acute neurological deficit occurring in one or more cerebral vascular territories. Neuroimaging must be done to exclude intracranial hemorrhage (ICH).

(3) Protocol treatment must begin within 12 hours after stroke symptom onset and is recommended, but not required, to begin within 3 hours after hospital arrival. If time of symptom onset is unclear or patient is awakening with stroke symptoms, the time of onset will be the time the patient was last known to be normal.

(4) Known history of type 2 diabetes mellitus and glucose >110 mg/dL OR admission blood glucose ≥150 mg/dL in those without known diabetes mellitus

(5) Baseline NIHSS score of at least 3 but no more than 22

(6) Pre-stroke modified Rankin Scale score = 0 for patients with an NIHSS score of 3-7. Pre-stroke modified Rankin Scale score = 0 or 1 for patients with an NIHSS score of 8-22.

(7) Able to provide a valid informed consent to be in the study (self or their authorized legally accepted representative).

3.3.2 Exclusion Criteria

(1) Known history of type 1 diabetes mellitus

(2) Substantial pre-existing neurological or psychiatric illness that would confound the neurological assessment or other outcome assessment

(3) Having received experimental therapy for the enrollment stroke. IV tPA (up to 4.5 hrs) or IA tPA are allowed as are IA therapies including use of FDA cleared devices. Non FDA cleared devices are considered experimental and are excluded.

(4) Known to be pregnant or breast-feeding at the time of study entry

(5) Other serious conditions that make the patient unlikely to survive 90 days

(6) Inability to follow the protocol or return for the 90 day follow up

(7) Renal dialysis, including hemo- or peritoneal dialysis

3.4 Justification and Explanation of Eligibility Criteria

Inclusion Criteria

Age 18 years or older

Only ≥ 18 year old ischemic stroke subjects will be included since ischemic strokes in the pediatric population are substantially different from adult strokes. The population under age 18 is excluded to avoid confounding the results.

Diagnosis of ischemic stroke

Ischemic stroke is defined as acute neurological deficit occurring in one or more cerebral vascular territories. Neuroimaging must be done to exclude intracranial hemorrhage (ICH). Primary ICH is excluded, but primary ischemic stroke with hemorrhagic conversion is not excluded.

If the diagnosis was ischemic stroke at the time of randomization but the diagnosis changes during the 72 hour treatment period, follow instructions in Section 5.1.2 (12) - stopping study treatment when there is a change in diagnosis of ischemic stroke/stroke mimic. TIA is not considered a stroke mimic, and the study protocol should be followed.

Protocol treatment recommended within 3 hours of hospital arrival & required within 12 hours of stroke symptom onset

The 12-hour eligibility requirement was chosen as this is almost universally before the development of maximum edema in acute ischemic stroke patients, but is a wide enough time window to be inclusive of most patients allowing generalizable results and is supported by the preliminary data. Treatment is recommended but not required to begin within 3 hours of arrival to the Emergency Department to assure the avoidance of treatment delays in hopes of maximizing treatment effect as suggested by much of the animal and human data in acute ischemic stroke. This will also allow the patients to be treated with standard IV tPA as per published eligibility criteria and then enrolled in the trial.

The start time of protocol treatment is defined as the time of randomization. To be eligible, randomization is recommended to occur within 3 hours of hospital arrival and must be within 12 hours of symptom onset.

Glucose >110 mg/dL in patients with type 2 diabetes or ≥150 mg/dL in patients without diabetes

An enrollment blood glucose >110 mg/dL in patients with type 2 diabetes or ≥150 mg/dL in patients without diabetes is based on our preliminary data and other data suggesting this group is most likely to benefit. As demonstrated by GIST-UK[15], THIS[16], GRASP[17], Walters[18] and Kriesel[19] hyperglycemia frequently resolves spontaneously in most patients without diabetes. Thus, patients without diabetes mellitus or admission

hyperglycemia will be excluded. Both THIS[16] and GRASP[17] trials and an observational study[20] demonstrated that most patients enrolled with hyperglycemia ≥150 mg/dL remained hyperglycemic during hospitalization unless they received intravenous insulin. The vast majority of patients with admission glucose ≥150 mg/dL have undiagnosed diabetes or impaired glucose metabolism (insulin resistance) as has been reported,[21-23] thus making them good subjects for this trial.

The admission blood glucose is the first finger stick point of care (POC) glucose measurement at the enrolling hospital. The most recent POC glucose at the time of randomization will be used to confirm eligibility. It is not necessary for study purposes to re-check glucose prior to randomization. Only finger stick POC glucose measurements (not serum laboratory glucose measurements) are used for randomization. Glucose measurements from outside hospitals or EMS cannot be used to determine eligibility.

A diagnosis of type 2 diabetes will be based on the medical history provided and the medical record. Patients with current or past treatment with an oral agent with or without insulin therapy and/or a previous diagnosis of type 2 diabetes mellitus will be defined as having type 2 diabetes. Reports of 'borderline diabetes mellitus' will require clarification as to presence or absence of true diabetes mellitus. Patients determined to have a history of diagnosed type 2 diabetes must have a glucose level greater than 110 mg/dL to be eligible. Patients with no known history of type 2 diabetes must have a glucose level of greater than or equal to 150 mg/dL to be eligible. If there is documentation in the medical record of a HbA1c of $\geq$ 6.5%, the patient will be assumed to have a diagnosis of diabetes mellitus.

Baseline NIHSS score of at least 3 but no more than 22
Previous data suggest that patient with an NIHSS score of < 3 have overwhelmingly good recovery and those with an NIHSS score of > 22 have overwhelmingly poor recovery. The intervention of glucose control was not felt to be likely to alter these extreme outcomes.

The NIHSS score used to determine eligibility must be completed by a certified investigator. The NIHSS score that is closest to the time of randomization should be used and must have been done within **30 minutes** before the time of randomization.

Patients who do not have a complete NIHSS are not eligible (e.g. untestable item per NIHSS scoring criteria).

Based on the NIHSS scoring instructions, untestable is only considered for the following:
Question 5: Motor Arm (UN: Amputation or joint fusion)
Question 6: Motor Leg (UN: Amputation or joint fusion)
Question 7: Limb Ataxia (UN: Amputation or joint fusion)
Question 10: Dysarthria (UN: Intubation or other physical barrier)

This only includes patients who are intubated or who have other physical barriers to assess the NIHSS during the entire screening period. If the NIHSS cannot be scored for any of these reasons within 30 minutes prior to randomization, the patient is not eligible. Urgent or emergent intubation during the screening period will be exclusionary if the NIHSS cannot be assessed with 30 minutes of randomization or if medications or neurologic worsening are confounding neurological assessment.

Prestroke mRS of 0 or 1
Patients with an NIHSS of 3-7 who do not have pre-stroke mRS score of 0 will be excluded as they may be unable to reach the success criteria defined by the stratified dichotomy outcome. Patients with an NIHSS of 8-22 will be eligible if they have a pre-stroke mRS score of 0 or 1. Note that only patients with a prior stroke can have a mRS score of 1. Use SHINE instructions for scoring the pre-stroke modified Rankin Scale found in Section 6.

Able to provide a valid informed consent
Informed consent is to be obtained from the patient or patient's Legally Authorized Representative (LAR). Eligibility of a person to serve as a subject's LAR is determined in accordance with local law at the study site. Consent from non-English speaking patients must be obtained according to site IRB procedures.

Exclusion Criteria
Patients with type 1 diabetes
Patients with type 1 diabetes mellitus are excluded for safety reasons. Usual care for type 1 diabetes patients during acute illness usually includes intravenous insulin infusion accompanied by dextrose otherwise these patients would be at risk of diabetic ketoacidosis. Since withholding standard care is unacceptable, these patients are excluded. The number of subjects excluded based on this criterion is likely to be very small given that only 2% of all patients with diabetes mellitus are classified as type 1.

During the stress of hospitalization, type 1 diabetics and pregnant women routinely require IV insulin. Type 2 diabetics who are insulin dependent may be enrolled in the study. It will be per the discretion of the enrolling investigator to determine if the potential subject is one that could be safely randomized to either treatment group.

Patients with type 1 diabetes will be identified based on medical history which may include patient/family report, medical records or conversations with treating medical personnel a HbA1c of $\geq$ 6.5% is diagnostic of diabetes mellitus in the SHINE trial, and with no evidence of type 1 diabetes, these patients will be assumed to be eligible. If there is any uncertainty regarding type 1 or type 2, those having been started on insulin treatment without first being treated with any oral agent will be defined as having type 1 diabetes.

Neurological or psychiatric illness likely to confound the final outcome assessment
Patients with a neurological or psychiatric illness likely to confound the final outcome assessment will be excluded since their baseline deficits and outcomes cannot be accurately obtained. Any patient deemed by the enrolling physician to have any condition that confounds the enrollment neurological exam will be excluded. This includes diagnoses other than neurological or psychiatric illnesses (i.e. medication effect during the entire screening period).

Experimental therapies
Patients receiving experimental stroke therapies will be excluded due to uncertain effects of such therapies on outcomes. Experimental stroke therapies include any therapies that are being studied in an interventional research program.

Patients who are enrolled in SHINE must not be enrolled in another experimental trial during the entire period of enrollment (Baseline to End of Study). If the other study has an intervention/treatment arm and a control arm, even if the patient would be in the control arm, enrollment during the time that the patient is in SHINE is not permitted. Participation in observational trials of standard care would not be cause for exclusion but would require approval prior to enrollment both by the overall SHINE leadership team and the PI of the other trial..

Standard care IV tPA or IA tPA according to the AHA/ASA guidelines will be allowed.[24] The pilot trials demonstrated safety in the population treated with IV tPA. The increased risk of symptomatic hemorrhagic transformation of infarcts observed in IV tPA treated stroke patients with hyperglycemia[25, 26, 27] may be reduced with glucose control. Intra-arterial (IA) treatments that are standard care, including the use of FDA cleared devices, will be allowed. FDA cleared devices must be employed according to their Instructions for Use. Non FDA cleared devices or other experimental interventions will not be allowed. No clear data are available on the risk/benefit ratio of these interventions and they could confound the results.

Pregnant or breastfeeding
Pregnant women will be excluded since the standard care for this population often includes IV insulin treatment for hyperglycemia.

Other serious conditions that make the patient unlikely to survive or unable to return at 90 days
Patients with conditions other than the enrolling stroke who are unlikely to survive for 90 days will be excluded.

Inability to follow the protocol or return for the 90 day follow up
Patients known to be unable or unwilling to follow the protocol will be excluded. Patients unlikely to return at 90 days will be excluded since the primary efficacy outcome is measured at that time.

Renal dialysis
Renal dialysis patients will be excluded including those requiring hemodialysis and peritoneal dialysis due to inability to accurately follow glucose levels and variability in insulin requirements that would put patients at risk. Only patients requiring dialysis will be excluded.

3.5 Screen Failure Log

To maintain compliance with recruitment procedures, a Screen Failure Log will be completed for all NON-RANDOMIZED patients who were screened for the SHINE study. All patients diagnosed with ischemic stroke who present within 12 hours of onset with glucose >110 mg/dL will be considered potentially eligible. All potentially eligible subjects that were not randomized into the SHINE trial will be recorded on the Screen Failure Log. These data will be entered into WebDCU™ monthly, by the 10th day of the following month. The coordinating center and the recruitment/executive committee will use the data on the screening forms to support the site in screening and recruitment in the trial. Monthly screening data are submitted to the Clinical Coordinating Center on a continuous basis. Information in the SHINE Screen Failure Log will be reviewed by the Recruitment and Executive teams and will be considered in site screening and

recruitment evaluation. See Appendix 8 for the Completion of Specific CRF Guidelines for instructions on completing the Screen Failure Log.

The Screen Failure Log will be maintained to document all patients considered for enrollment but not randomized to provide basic information on this population. This log will allow a better understanding of the population considered, the population enrolled and the reasons for ineligibility. See Appendix 2 for Screen Failure Log and decision tree tool.

3.6 Prohibited Therapy

No other diabetes treatment medications (i.e., oral agents, IV or subcutaneous insulin) besides the assigned protocol treatment will be allowed during the 72-hour treatment period because such medications would confound the study. The use of non FDA cleared devices for IA therapy is not allowed. Patients taking PO diets must eat protocol-specified diets as defined in Section 5.

4. Enrollment Procedures

Enrollment will be overseen by an enrolling investigator as designated on the site Delegation of Authority Log.

4.1 Obtaining Informed Consent

Consent will be obtained by either the Principal Investigator or by a designated member of the study team prior to performing any procedures solely for the purpose of research. In every case, alternative available treatments will be explained and it will be made clear that the patient is under no obligation to participate in any research project being offered. In obtaining and documenting informed consent, each investigator will comply with the applicable regulatory requirements and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent must be the IRB-approved version corresponding to the version of the protocol approved when the screening was initiated. The name of the study team member obtaining consent should be clearly documented, and this person should sign the informed consent document and provide the date of their signature and time as required per local site procedures.

Informed consent is to be obtained from the patient or patient's LAR. Eligibility of a person to serve as a subject's LAR is determined in accordance with local law at the study site. The consent document should include the subject's name, LAR's name and relation to the subject (if a LAR provides consent), as well as the date the consent was signed. This information should be completed by the subject or the LAR. The study team should not fill in the date the consent was signed for the subject or LAR.

Additional informed consent procedures may be required for ancillary studies.

HIPAA consent must be similarly obtained and documented in keeping with local institutional and IRB regulation for form format (i.e. contained in body of ICF or a separate document.)

Sites must follow local IRB procedures when consenting non-English speaking patients. The informed consent process should be clearly documented. This documentation may occur in the patient's medical record or research record. Templates for documenting the informed consent process are located on the SHINE website (www.SHINETrial.org) in the Study Toolbox. The patient or LAR must receive a copy of the signed consent form.