1. Introduction

1.1 Study Overview

There is an increasing need for improved treatments for stroke patients as stroke is the most common cause of serious long term adult disability and the third most common cause of death in the United States.[1] Hyperglycemia is seen in approximately 40% of acute ischemic stroke patients[2,3] and has been associated with worse clinical outcomes.[4,5] Intravenous (IV) insulin therapy with tight glucose control has been found to improve clinical outcomes in some non-stroke acute illness trials.[6,7] Current stroke guidelines emphasize the need for definitive clinical trials to determine best practice for managing hyperglycemia in acute stroke patients.[8] A clear determination of the risk and benefit of glucose control with IV insulin would have a dramatic impact on acute ischemic stroke patient therapy.

This Phase III multicenter, randomized, controlled trial will determine the efficacy of and provide further safety data on glycemic control in stroke patients. The hyperglycemic acute ischemic stroke patients that meet all eligibility criteria will receive up to 72 hours of hyperglycemia control with IV insulin therapy or control therapy with subcutaneous (SQ) insulin. Treatment will be started within 12 hours of symptom onset and is recommended, but not required, to begin within 3 hours of arrival to the emergency department (ED). The primary efficacy outcome to be assessed at 90 days will be the severity adjusted difference in favorable outcome between the groups. Favorable outcome will be defined by a previously described baseline severity adjusted dichotomized modified Rankin scale (mRS).[9-11] Outcome success will depend on the severity of the initial stroke (per NIH Stroke Scale Score (NIHSS)). The primary safety outcome will be the severe hypoglycemic event rate. Secondary outcomes will assess additional neurological and functional status using stroke severity, functional and quality scales[12-14] as well as glucose control success and adherence to the protocol dosing recommendations of the computerized decision support tool. This trial launches a highly collaborative model for stroke research providing a foundation for maximally generalizable results based on performance at academic, community, urban, rural, large and small hospitals throughout North America to produce a highly representative national population sample. A validated computer decision support tool will guide delivery of IV insulin therapy. A baseline severity-adjusted dichotomized outcome analysis (responder analysis)[9] will adjust for variability of individual patient characteristics to allow detection of the true clinically relevant treatment effect. In this setting **an absolute 7% treatment effect is recognized as a threshold at or above which a profound effect on a large stroke population would be realized**.

1.2 Study Objectives

Specific Aim 1

To determine the efficacy of tight glucose control to a target range of 80-130 mg/dL with IV insulin infusion in hyperglycemic acute ischemic stroke patients within 12 hours of symptom onset as measured by mRS at 90 days after stroke.

- Hypothesis 1: Tight glucose control (target 80-130 mg/dL) with IV insulin infusion therapy using a validated computerized decision support tool will increase the severity adjusted 90 day favorable outcome on the mRS by an absolute 7% or more, as compared to the control group.

Specific Aim 2
To determine the safety of tight glucose control with IV insulin infusion in hyperglycemic acute ischemic stroke patients treated for up to 72 hrs.

- Hypothesis 1: Tight glucose control with IV insulin infusion therapy using a decision support tool is safe as determined by a severe hypoglycemia (< 40 mg/dL) rate that does not exceed that of the control group by more than 4%.

2. Study Process Flowchart