**

1. **Study Overview**

Stress hyperglycemia, a state of abnormal metabolism with supra-normal blood glucose levels, is often seen in critically ill patients. Tight glycemic control (TGC) was originally shown to reduce morbidity and mortality in a landmark randomized clinical trial (RCT) of adult critically ill surgical patients but has come under intense scrutiny in the setting of conflicting results of recent adult trials. One pediatric RCT has been published to date that demonstrated survival benefit but was complicated by an unacceptably high rate of severe hypoglycemia. The Heart and Lung Failure – Pediatric Insulin Titration (HALF-PINT) trial is a multi-center, randomized clinical treatment trial comparing two ranges of glucose control in hyperglycemic critically ill children with heart and/or lung failure. Both target ranges of glucose control fall within the range of “usual care” for critically ill children managed in pediatric intensive care units.

HALF-PINT is a multi-center randomized clinical trial that tests the efficacy of a tight glycemic control protocol to reduce mortality and ICU LOS in critically ill children. This nurse-driven protocol has been studied in over 800 children in the cardiac ICU and is safe and manageable in the critical care setting. Study teams at approximately 20 ICUs will enroll patients who meet inclusion criteria (Section D2). Upon developing hyperglycemia (BG ≥150 mg/dL), a consented patient will be randomized to either the TGC-1 group (target BG: 80-110 mg/dL) or the TGC-2 group (target BG: 150-180 mg/dL). Randomized subjects in both groups will be treated for high blood glucose from the time of consent to ICU discharge or Day 28, whichever occurs first. The duration of tight glycemic control depends upon the duration of hyperglycemia.

1. **Patient Selection and Inclusion/Exclusion Criteria**

Study-trained staff will recruit pediatric patients with cardiovascular and/or respiratory failure in participating ICUs according to the following criteria:

***Inclusion Criteria:***

(1) Cardiovascular failure (on intravenous vasopressors or inotropes, i.e., dopamine or dobutamine >5 mcg/kg/min, or any dose of epinephrine, norepinephrine, milrinone, or vasopressin if used to treat hypotension)

*and/or*

Respiratory failure (acute mechanical ventilation via endotracheal tube or tracheostomy anticipated for >24 hours).

(2) Age ≥2 weeks and corrected gestational age ≥42 weeks

(3) Age <18 years (has not yet had 18th birthday)

***Exclusion Criteria:***

(1) Expected to remain in ICU <24 hours

(2) Previously randomized in HALF-PINT

(3) Enrolled in a competing clinical trial

(4) Family/team have decided to limit or redirect from aggressive ICU technological support

(5) Chronic ventilator dependence prior to ICU admission (non-invasive ventilation and ventilation overnight or while sleeping via tracheostomy are acceptable)

(6) Type 1 or 2 diabetes

(7) Cardiac surgery within prior 2 months or during/planned for this hospitalization (extra-corporeal life support (ECLS) or non-cardiac surgery is acceptable)

(8) Diffuse skin disease such that placement of a subcutaneous glucose sensor would be difficult to secure

(9) Pregnancy

(10) Ward of the state

1. **Study devices**

The study employs several devices to enhance safety and improve workflow. These devices are used consistently across study sites but may be new to your center. The risks and benefits of using the study devices are outlined in the study protocol and the devices have been approved by an Institutional Review Board (IRB) before use in subjects. Subjects and/or their legal guardians will give informed consent to allow use of these devices.

FDA-approved drugs or devices are employed during this study with one exception. The CGM device is approved for use in the European Union and bears the CE mark (Conformité Européenne). This device is used in an off-label fashion with the non-significant risk guidelines put forth by FDA. Several devices that are commonly used in ICU practice around the country, but may not be routinely used at each participating institution, are used in HALF-PINT. All bedside HALF-PINT nurses are trained according to manufacturer’s guidelines prior to use in the study. Each institution addresses all administrative and regulatory requirements of that site, using common tools and language distributed by the Clinical Coordinating Center (CCC).

***Continuous Glucose Monitor***

The Guardian REAL-Time® system consists of a subcutaneous glucose sensor, a transmitter that attaches to the sensor, and a pager-sized monitoring device (Medtronic Inc., Northridge, CA). The monitor and transmitter have a formal FDA indication for continuous monitoring of glucose levels in the interstitial fluid under the skin, in children and adolescents (age 7 years and above) with diabetes mellitus, for the purpose of improving diabetes management (<http://www.accessdata.fda.gov/cdrh_docs/pdf/P980022S015A.pdf>). The EnliteTM glucose sensor is composed of a platinum-plated sensor encased in a permeable membrane that is inserted with minimal discomfort into the subcutaneous space of the patient and functions under battery power for up to six days. The EnliteTM is approved for clinical use in the European Union but is not FDA approved to be marketed for clinical use in the United States. It is an improved version of the sensor that is currently FDA approved and marketed for use in the United States (Sof-Sensor). This continuous glucose monitor is used in this trial to help safely achieve a target range of 80-110 mg/dL (TGC-1, 4.4-6.1 mmol/L) vs. a target range of 150-180 mg/dL (TGC-2, 8.3-10 mmol/L). It alerts if a glucose level falls below pre-set values. For the purposes of this trial the low glucose alarm limit is preset to 70 mg/dL. No high alarm is set because of the high rate of false positive alarms. Values are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a meter blood glucose measurement may be required.

***Hospital Glucose Meter***

The NOVA StatStrip® Glucose Hospital Meter (Nova Biomedical Corp., Waltham, MA) is an FDA-approved blood glucose monitor system marketed for in vitro diagnostic use by health care professionals for Point-of-Care quantitative measurement of glucose in whole blood (arterial, venous, or capillary).

***Blood Sampling System***

The Venous Arterial blood Management Protection System, Jr (VAMP Jr®, Edwards Lifesciences, Irvine, CA) blood sampling system is used to reduce blood waste and the risk of iatrogenic anemia due to multiple blood glucose sampling during the study. VAMP Jr is an FDA-approved device and has been used with great success in the SPECS trial, as well as in standard clinical care in the CHB ICUs**.**

1. **Procedures for obtaining study samples**

In an attempt to avoid CVL-associated bloodstream infections, BGs for purposes of the trial will not be drawn from central venous line unless the line is being entered for other reasons, such as replacement of IV fluids. Blood samples will be withdrawn from pre-existing vascular access, such as arterial lines, or via fingerstick. BGs will be measured at the bedside (using a hospital approved glucose meter) and by each site’s clinical laboratory. All other blood tests will be performed at each site’s clinical laboratory or via unit-based blood gas analyzer. No new lines will be placed solely for the purposes of the study.

1. **Recruitment Methods**

All subjects will be cared for in the Pediatric ICU. All ICU admissions will be screened for potential eligibility in HALF-PINT twice daily. Research Coordinators or the Site Director will be responsible for conducting these screenings. The attending physician or a delegate will be notified of any patient who meets eligibility criteria and will be asked to make an introduction of study staff to the parents/guardians. Parents/guardians of eligible patients will be approached by a member of the study-trained staff who is not currently caring for the patient clinically and will explain the study and the essential elements of informed consent. Most patients will be intubated, mechanically ventilated and sedated so will be unable to provide assent while acutely ill. Patients will be asked to provide assent when they are cognitively capable. Clinical sites will be instructed to follow their local IRB recommendations for the age of assent.

More than 1,880 patients will be consented in order to study approximately 1,880 (940 per group) who have blood glucose greater than 150 mg/dL.

1. **Potential Risks**

The primary risk of the study is hypoglycemia. The methodology of HALF-PINT centers on minimizing the risk of hypoglycemia by using CGM as an added alarm system and an insulin titration algorithm to give nurses explicit guidance about frequency of BG checks and insulin infusion doses. This same infusion protocol resulted in a severe hypoglycemia rate of 3.1% in children randomly assigned to a BG target range of 80-110 mg/dL (unpublished data). This is the lowest severe hypoglycemia rate of any published prospective trial of TGC (adult or pediatric) and supports our methodology to limit this risk.

There is also a non-significant risk of hypokalemia with insulin therapy. Potassium is measured twice daily for study subjects on insulin. Hypokalemia is treated with parenteral or enteral administration of potassium per usual ICU practice. It should be noted that episodes of hypokalemia are relatively frequent in critically ill children, especially in children requiring the use of loop diuretics (e.g., furosemide, bumetanide). Potassium supplementation is a very frequent practice in the pediatric ICU.

There is no significant risk associated with the use of the CGM device. This device is composed of a platinum-plated sensor encased in a permeable membrane. The device measures glucose concentration in the interstitial fluid of the subcutaneous space every 10 seconds and reports an average of these measurements every 5 minutes. It is inserted with minimal discomfort, often into a sedated patient. There may be scant bleeding or bruising at the sensor insertion site with such devices, though no injuries, serious bleeding, or infections have been reported in the ongoing SPECS trial after >800 insertions in children less than 3 years of age.

1. **Potential Benefits**

Potential direct benefits of the intervention include shortened ICU and hospital lengths of stay, lower mortality rate, more ventilator-free days, and/or accumulation of fewer multiple organ dysfunctions with improved neurodevelopmental behavior. An indirect benefit to society is improved knowledge about the implementation and safety of tight glycemic control.