****

**HALF-PINT**

**Heart and Lung Failure – Pediatric Insulin Titration Trial**

**Study Protocol Document**

Version 13-Feb-2012

**National Institutes of Health**

**National Heart Lung and Blood Institute**

**U01 HL107681 (CCC) and U01 HL108028 (DCC)**

Michael Agus, MD

Vinay Nadkarni, MD

**CCC Principal Investigators**

David Wypij, PhD

**DCC Principal Investigator**

Table of Contents

[A. Introduction 3](#_Toc303732356)

[A1. Abstract 3](#_Toc303732357)

[A2. Specific Aims and Objectives 3](#_Toc303732358)

[B. Background and Significance 5](#_Toc303732364)

[B1. Mechanism of Harm of Hyperglycemia 5](#_Toc303732365)

[B2. Mechanism of Benefit of TGC 6](#_Toc303732366)

[B3. Adult TGC Data 6](#_Toc303732367)

[B4. Pediatric TGC Data 7](#_Toc303732368)

[B5. Risk of Hypoglycemia 7](#_Toc303732369)

[B6. Algorithms for Titrating Insulin to Maintain Glucose within the Target Range 8](#_Toc303732370)

[C. Investigators 8](#_Toc303732371)

[C1. Principal Investigators and Coinvestigators 9](#_Toc303732372)

[C2. Clinical Coordination Center (CCC) 9](#_Toc303732373)

[C3. Data Coordination Center (DCC) 10](#_Toc303732374)

[C4. Sergievsky Center at Columbia University Medical Center (SC-CUMC) 10](#_Toc303732375)

[C5. Collaborating Clinical Sites 10](#_Toc303732376)

[D. Design and Methods 11](#_Toc303732377)

[D1. Study Overview 11](#_Toc303732378)

[D2. Patient Selection and Inclusion/Exclusion Criteria 11](#_Toc303732379)

[D3. Recruitment Methods 12](#_Toc303732380)

[D4. Informed Consent Process 12](#_Toc303732381)

[D5. Description of Study Treatments and Procedures 13](#_Toc303732382)

[D6. Study Outcomes 16](#_Toc303732386)

[D7. Measurement of Study Variables 19](#_Toc303732400)

[D8. Study Safety 20](#_Toc303732401)

[D9. Study Coordination 21](#_Toc303732402)

[D10. Data Management and Quality Control 23](#_Toc303732403)

[D11. Statistical Considerations 26](#_Toc303732404)

[D12. Anticipated Problems and Solutions 30](#_Toc303732405)

[E. Specimen Handling 31](#_Toc303732406)

[F. Study Drugs or Devices 31](#_Toc303732407)

[G. Follow-up Study Instruments 32](#_Toc303732411)

[H. Privacy Protections 33](#_Toc303732414)

[I. Potential Risks 33](#_Toc303732415)

[J. Data and Safety Monitoring 34](#_Toc303732416)

[K. Potential Benefits 35](#_Toc303732417)

[L. Alternatives 35](#_Toc303732418)

[M. References 35](#_Toc303732419)

A. Introduction

A1. Abstract

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 (13) but has come under intense scrutiny due to conflicting results in 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 (17). The **H**eart **A**nd **L**ung **F**ailure – **P**ediatric **IN**sulin **T**itration (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.

The purpose of the study is to determine the comparative effectiveness of tight glycemic control (TGC) to 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, 8.3-10.0 mmol/L) on hospital mortality and intensive care unit (ICU) length of stay (LOS) in hyperglycemic critically ill children with cardiovascular and/or respiratory failure. This will be accomplished using an explicit insulin titration algorithm and continuous glucose monitoring to safely achieve these glucose targets. Both groups will receive identical standardized intravenous glucose at an age-appropriate rate in order to provide basal calories and mitigate hypoglycemia. Insulin infusions will be titrated with an explicit algorithm combined with continuous glucose monitoring using a protocol that has been safely implemented in >800 critically ill infants and children.

**A2. Specific Aims and Objectives**

Specific Aim 1

To determine the comparative effectiveness of tight glycemic control (TGC) using an explicit insulin titration algorithm and continuous glucose monitoring to 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, 8.3-10.0 mmol/L) on hospital mortality and ICU LOS in hyperglycemic critically ill children with cardiovascular and/or respiratory failure, while minimizing hypoglycemia and its potential acute adverse metabolic and neurologic consequences.

Primary Hypothesis

Hyperglycemic pediatric patients with cardiovascular and/or respiratory failure managed with TGC-1 will experience lower hospital mortality and shorter ICU LOS than those managed with TGC-2.

Primary Outcome Measure

ICU-free days (equivalent to 28-day hospital mortality-adjusted ICU LOS).

Secondary Outcome Measures

90-day hospital mortality, 28-day accumulation of multiple organ dysfunction syndrome (MODS) (25), ventilator-free days, and incidence of nosocomial infections (bloodstream, pulmonary, urinary tract, and wound hospital-acquired infections). Algorithm safety as measured by severe hypoglycemia (blood glucose <40 mg/dL) incidence and duration, lipid activation (serum triglycerides, free fatty acids, and lipoprotein profile), lactate, and byproducts of metabolic stress related to hypoglycemia. Algorithm performance as measured by time to glucose target range, percent of time in target range, time-weighted glucose average, 24-hour insulin sensitivity index, and 72-hour variability index.

Specific Aim 2

To compare the effectiveness of TGC-1 vs. TGC-2 treatment strategy to improve neurodevelopmental outcomes in critically ill children with cardiovascular and/or respiratory failure.

Primary Hypothesis

Hyperglycemic patients with cardiovascular and/or respiratory failure managed with TGC-1 will have better developmental neurobehavioral status at one year post-ICU discharge than those managed with TGC-2.

Primary Outcome Measure

Developmental neurobehavioral outcomes measured at one year post-ICU discharge by Vineland Adaptive Behavioral Scales, Second Edition (Vineland-II) score (26).

Secondary Outcome Measures

Child Behavior Checklist (CBCL) (27, 192) and Pediatric Quality of Life Inventory (PedsQL) (28) at baseline and at one year post-ICU.



**Figure 1. HALF-PINT Design Summary**

**B. Background and Significance**

Stress hyperglycemia, a state of abnormal metabolism with supra-normal blood glucose levels, is often seen in critically ill patients. Tight glycemic control (TGC) to 80-110 mg/dL was originally shown to reduce morbidity and mortality in a landmark randomized clinical trial (RCT) of adult critically ill surgical patients (13) but has come under intense scrutiny with the recent adult multi-center Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study (14), which showed a small but statistically significant increase in mortality with TGC to 81-108 vs. <180 mg/dL (27.5% vs. 24.9%, p=0.02). Additionally, three other large similarly designed trials were halted due to concerns about hypoglycemia (29-31). Nonetheless, some of the benefits shown in the original adult trial of TGC (13) were reproduced by the same group in the adult medical intensive care unit (ICU) (15; 80-110 vs. 180-200 mg/dL) and pediatric ICU (PICU) (17; 50-80 in age <1 and 70-100 in age 1-16 vs. <200 mg/dL), with the PICU study showing a 55% decrease in 30-day ICU mortality (2.3% vs. 5.1%, p=0.047) and a 10% reduction in ICU length of stay (LOS) (5.51 vs. 6.15 days, p=0.017) despite an extremely high rate of severe hypoglycemia (SH; defined hereafter as blood glucose <40 mg/dL).

The benefits of TGC were also shown in several additional subsequent adult cohort studies comparing 80-110 mg/dL to standard care (11, 32-37), albeit largely in specific subpopulations including cardiac, surgical, trauma, and burn patients. Benefit was not confirmed, however, in multiple RCTs in mixed medical and surgical patients (30, 31, 38-40). Thus, TGC recommendations in adults are increasingly focused on specific populations driven by specific RCTs, which have been predominantly surgical (41-43). No such specific recommendations currently exist in pediatrics due to the lack of RCTs performed to date in this population.

The two study populations that have derived the most benefit from TGC protocols treating to the 80-110 mg/dL range are postoperative cardiac surgery patients and those with multi-organ failure who receive prolonged duration of therapy. The cardiac surgical population in pediatrics is already being studied in an ongoing 980-subject, NHLBI-supported trial conducted by our study group (R01 HL08848, Safe Pediatric Trial of Euglycemia in Cardiac Surgery, "SPECS"). Importantly, the SPECS trial employs continuous glucose monitoring (CGM) and has demonstrated the lowest hypoglycemia risk of any RCT ever published, at 3.2% in the TGC group (2.3% across both groups) after 755 subjects enrolled, which is comparable or lower than the "usual care" rate of hypoglycemia in critically ill children. The current proposal will study TGC within "usual care" ranges typical of pediatric ICUs, with the identical glycemic control and CGM protocols to ensure safety, in pediatric ICU patients with heart and/or lung failure since these are the patients with the highest mortality and longest ICU LOS (44, 45).

**B1. Mechanism of Harm of Hyperglycemia**

Hyperglycemia is associated with the formation of non-enzymatically glycated proteins also known as advanced glycation end-products (AGEs) (47, 48). AGEs, now known to form even with short-term exposure to hyperglycemia, are implicated in neutrophil and macrophage dysfunction, oxidant stress, and microvascular leakage (49-52).

The more recent and abundant clinical association of short-duration hyperglycemia with negative outcomes in both critically ill adults (53-57) and children (7, 35) has stimulated further study. Despite a significant body of evidence, the exact modalities by which hyperglycemia impairs organ function have yet to be fully elucidated. Hyperglycemia directly and indirectly affects cellular function by impairing immune cell function (chemotaxis, phagocytosis, and the formation of reactive oxygen species); increasing interactions between leukocytes and endothelium (via activation of nuclear factor-κβ and protein kinase-C, with elevated plasma concentrations of intercellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin); increasing inflammatory cytokines and C-reactive protein; impairing myocardial contractility (due to myocardial apoptosis); altering vascular smooth muscle tone (due to dysregulation of endothelial nitric oxide production and release); and influencing coagulation pathways (via inhibition of Protein C and activation of plasminogen activation inhibitor-1) (58-75). Multiple potential mechanisms exist by which hyperglycemia interferes with normal immune responses to infection, both pro- and anti-inflammatory.

Hyperglycemia has pro-inflammatory effects, including up-regulation of IL8 and nuclear factor-κβ (8). Hyperglycemia also impairs immune function through glycosylation of immunoglobulin, complement inactivation, impaired leukocyte phagocytosis, chemotaxis, and oxidative burst (8). High glucose concentrations also impair wound healing by protein glycosylation and stimulation of collagenase activity (76). In critical illness, more specific pathology has been linked to cardiac myocyte toxicity (77-79), renal toxicity (80), and hepatotoxicity at the level of the hepatic mitochondria (81).

Thus, there is evidence and biologic plausibility that even a short duration of hyperglycemia in vulnerable critically ill children with heart and/or lung failure could trigger harmful pathways exacerbating organ failure and infection. Further, it is unknown whether rapid control of hyperglycemia to a normal range will reverse the mechanisms of harm and improve clinical outcomes.

**B2. Mechanism of Benefit of TGC**

Insulin is a potent anabolic hormone and has been shown to decrease protein breakdown, a process associated with significant morbidity and mortality in critically ill pediatric patients with limited protein stores (82). The exact mechanisms of the beneficial effects of euglycemia remain unclear. Post-hoc analyses of clinical trials suggest that it is control of the blood glucose (BG) concentration primarily, in combination with insulin effect, that is associated with the reduction in sepsis and multi-organ system failure (54, 83). Insulin also has multiple effects that may contribute to improved clinical outcomes, including inhibition of pro-inflammatory cytokines and inflammatory growth factors and enhancement of nitric oxide synthase (84-87). With evidence from adult clinical trials that TGC reduces postsurgical infections, the immune modulatory effects of mitigating hyperglycemia appear to be very important clinically (12, 13, 88).

TGC benefit to the cardiac myocyte also appears to be an important mechanism, as evidenced by historical benefit of glucose-insulin-potassium (GIK) infusions in postoperative cardiac surgical patients to improve cardiac contractile function, reduce need for inotropic support, reduce arrhythmia incidence, and reduce free fatty acid concentrations (89-93). GIK infusions without TGC algorithms, however, may lead to poorly controlled hyperglycemia thereby mitigating the independent benefits of insulin infusion. Taken together, clinical data from TGC and GIK trials as well as in vitro data on cellular insulin effects are promising. There is, therefore, evidence and biologic plausibility that control of BG in vulnerable critically ill children with heart and/or lung failure could mitigate the pro-inflammatory state of critical illness, improve immune function, and bolster cardiac function leading to improved clinical outcomes.

**B3. Adult TGC Data**

Hyperglycemia is common, and the timing, intensity, duration, and variability of serum glucose are associated with morbidity and mortality in adults (53-57). Two issues confound the interpretation of prior TGC trials. TGC with a lower BG target range of 80-110 mg/dL is difficult to achieve safely when a glucose source infusion and CGM are not employed. Additionally, significant heterogeneity between the comparison treatment groups exists among the published studies (41-43).

Second are the substantial differences in the incidence of hypoglycemia both between treatment groups and across different studies. Reported rates of hypoglycemia in prior prospective adult TGC trials vary between 5% and 20% (13, 15, 30, 94), with the NICE-SUGAR study (14) reporting a 14.7-fold increase in the odds of becoming severely hypoglycemic (BG <40 mg/dL, p<0.001) with their protocol which compared 80-110 vs. 144-180 mg/dL. Hypoglycemia is in-and-of-itself a risk factor for increased mortality (37, 95-97) and while it is unclear if the association is causal, its acute metabolic and long-term neurobehavioral consequences could be significant.

**B4. Pediatric TGC Data**

Hyperglycemia is common, and its timing, intensity, and duration, as well as the variability of serum glucose are associated with morbidity and mortality in critically ill children (110). The single prospective pediatric RCT that was conducted in the PICU at Leuven, Belgium (17) had significant limitations. Results demonstrated significant survival and ICU length of stay benefit, but was plagued by an extraordinarily high rate of SH (BG <40 mg/dL) at 25% overall and 44% of those less than one year of age. Hypoglycemia was likely so common because of the trial's uniquely low target ranges of 50-80 mg/dL in children less than one year, and 70-100 mg/dL in the remainder, without CGM. In addition, there was no explicit methodology to ensure adequate glucose source infusion. This design, therefore, does not represent a viable TGC strategy that would be adopted by US practitioners. Nonetheless, given the number of studies showing a substantial benefit of TGC to 80-110 mg/dL in various adult populations (10, 13, 15, 17, 46), and notwithstanding a similar number of RCTs showing no benefit (30, 31, 38, 39), many pediatric centers have now implemented TGC protocols at the adult target of 80-110 mg/dL despite the lack of validation of the safety or efficacy of such a regimen in the PICU (19). Furthermore, centers are reluctant to modify their approach without prospective data generated by a well-designed, safe, replicable protocol in which sufficient separation of glycemic level between treatment groups is achieved without substantial increase in the incidence of hypoglycemia (98). Such a trial, with a sufficiently explicit algorithm, continuous glucose source infusion and CGM, has not been published to date and is not currently underway anywhere in the world.

Conflicting results in different populations and study designs will remain puzzling (99) until well-designed studies which minimize hypoglycemia risk and maximize replicability can be conducted in cohorts most likely to derive benefit. The most effective method of achieving good control with the desired separation in glucose levels (>45 mg/dL (17)) and minimal increase in hypoglycemia is to monitor BG more frequently. However, monitoring more frequently adds burden to nursing staff (100) and in the absence of an explicit methodology for titrating insulin is likely to generate results that cannot be replicated. Alternatively, CGM devices have been demonstrated to be reliable in PICU patients (20) and are being actively and successfully utilized by our study group in a 980-subject clinical trial of TGC in the pediatric cardiac ICU (SPECS, R01 HL08848). After the accrual of 755 subjects, the trial had the lowest reported rate of SH in any prospective trial in adults or children to date, at 3.2% in the TGC group (unpublished preliminary data). Continuous monitoring represents a viable technology which may substantially reduce the incidence of hypoglycemia in future trials.

**B5. Risk of Hypoglycemia**

Despite the adverse effects of hyperglycemia, there is a reluctance to aggressively maintain euglycemia in children because of the significant risk of unrecognized SH (101). In a single center review (Children's Hospital Boston, unpublished data) of all BG concentrations measured over one year in a PICU, 11% of patients had at least one BG concentration <60 mg/dL (mild hypoglycemia) and 2.7% had SH, despite rare insulin use. Similar results were recently published in a 5-year experience at a second PICU with an incidence of 7.5% and 2.2%, respectively, for all PICU patients and 15.3% and 6.1%, respectively, for patients with cardiovascular and/or respiratory failure. The odds ratio (OR) and 95% confidence interval (CI) for SH in this group compared to their less sick counterparts was 7.21 (2.74-18.98) (16).

RCTs of TGC to 80-110 mg/dL have consistently resulted in SH rates that substantially exceed PICU "usual care" rates cited above. In the Leuven adult TGC trial, the risk of SH increased six-fold in tight glycemic control patients compared to the standard care cohort (13), and in their subsequent PICU study, 25% of all subjects and 44% of those less than one year of age had SH (17), likely attributable to the low target glucose ranges detailed above. Another adult RCT documented SH in 34% of subjects receiving insulin (102).

Hypoglycemia is of even more concern in children, as the developing brain is particularly sensitive to low BG concentrations (103). The OR for mortality among PICU patients for a single episode of SH was 3.71 (1.12-12.34, p<0.01) (16). This is similar to findings in two even larger adult studies that similarly noted increased mortality with hypoglycemia exposure (37, 104). In a study of intraoperative BG concentration and neurodevelopmental outcomes in pediatric cardiac surgery patients, there was an increase in electroencephalographic seizures in patients without hyperglycemia, possibly related to transient, unrecognized episodes of hypoglycemia (105). Onset of hypoglycemia is often not clinically apparent in critically ill children due to the common use of sedatives and analgesics in the ICU, yet is associated with acute clinical effects such as lethargy, coma, and seizures and long-term effects on the central nervous system with an unquantified risk of brain damage (103). As a result, there is a reluctance to use insulin infusions to lower BG in critically ill children, particularly in light of the high baseline incidence of hypoglycemia.

Thus, in order to safely conduct the proposed trial of tight glycemic control in this population, it is imperative to incorporate both a continuous glucose source infusion and a CGM technique that is both accurate and readily available. The proposed system allows for immediate recognition of both high and low BGs and the administration of tight glycemic control in children, while minimizing the risks.

**B6. Algorithms for Titrating Insulin to Maintain Glucose within the Target Range**

Choosing an appropriate insulin titration algorithm is a difficult task. We have recently reviewed many of the available written instructions and computer-based programs (23) but acknowledge that such reviews can, at best, provide guidelines. For the SPECS study, the target was achieved using the Proportional Integral Derivative (PID) algorithm developed by Coinvestigator Dr. Steil and first implemented in the PICU at Stanford Medical Center in 2007 (127). The algorithm was adapted from Dr. Steil's earlier work on the automation of subcutaneous insulin delivery based on subcutaneous glucose sensing (128-130). The algorithm itself is based on the P-, I-, and D-components of a classical Proportional Integral Derivative control law but with modifications to limit occurrences and/or duration of hypoglycemia and to reduce the frequency of blood draws. Our experiences with this algorithm as part of the SPECS trial have largely been positive both in terms of achieving and maintaining target glucose and staff acceptance. We believe staff acceptance is an important component of such an algorithm with virtually all algorithm recommendations being routinely accepted by bedside nurses following minor modifications. The insulin titration algorithm for HALF-PINT will be employed in a similar fashion as the ongoing SPECS trial, making recommendations for insulin dosing, dextrose rescue doses, as well as time for next BG determination, ranging from 30 minutes (after hypoglycemia and rescue) to 4 hours (during periods of BG stability in the target range, off insulin). The protocol is named **CH**ildren’s **E**ugly**C**emia for **K**ids **S**preadsheet (CHECKS). CHECKS is further detailed below (Section D5).

**C. Investigators**

The investigative team for this study includes the two Principal Investigators and seven Coinvestigators who bring expertise in tight glycemic control and continuous glucose monitoring, clinical trial design in critical care settings, and the long-term follow-up of complex patients. The investigative team also includes a Clinical Coordination Center, a Data Coordination Center, and one Site Director at each of approximately 20 clinical sites.

**C1. Principal Investigators and Coinvestigators**

**Michael S.D. Agus, MD,** Principal Investigator (PI) and Contact PI, is a pediatric endocrinologist and intensivist and an Assistant Professor of Pediatrics at Harvard Medical School, Director of Medicine Critical Care Program at Children’s Hospital Boston, and an NHLBI-funded R01 investigator with an ongoing large trial of TGC in the postoperative pediatric cardiac surgery population (SPECS).

**Vinay M. Nadkarni, MD,** Principal Investigator, is an Endowed Chair and Associate Professor of Anesthesia, Critical Care and Pediatrics at the University of Pennsylvania School of Medicine, Medical Director of the Center for Simulation, Advanced Education and Innovation at Children's Hospital of Philadelphia, and a member of the Scientific Steering Committee of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI).

**Martha A.Q. Curley, RN, PhD,** Coinvestigator, is Professor of Nursing at University of Pennsylvania School of Nursing. She is an expert in the nursing care of critically ill infants and children and their families. She has extensive experience in managing change in complex organizations and in the conduct of clinical research studies. Dr. Curley was the principal investigator for a multisite randomized controlled clinical trial of prone positioning in pediatric patients with acute lung injury (ALI) (187). She is the principal investigator of the ongoing multi-center RESTORE trial (U01 HL086622) of sedation management in pediatric patients intubated and mechanically ventilated for acute respiratory failure.

**Edward Vincent S. Faustino, MD,** Coinvestigator from Yale University, has published about the prevalence and risks of abnormal glucose concentrations in critically ill children. He will serve as Site Director at his institution and will focus on investigations of ICU technology to assist in achieving safe tight glycemic control.

**Ellie L. Hirshberg, MD,** Coinvestigator from University of Utah, has extensive experience in the development and piloting of glucose control protocols and of explicit algorithms in general. She will serve as Site Director at her institution and play a leading role in honing the CHECKS spreadsheet for use in HALF-PINT.

**Peter M. Luckett, MD,** Coinvestigator from University of Texas Southwestern and Dallas Children’s Hospital, is a founding member of the PALISI research network and will provide senior oversight at the committee level.

**Vijay Srinivasan, MD,** Coinvestigator from University of Pennsylvania, has published about the prevalence and risks of abnormal glucose concentrations in critically ill children. He will serve as Site Director at his institution and will focus on investigations of the mechanism of harm of poor glycemic control.

**Gary M. Steil, PhD,** Coinvestigator from Children’s Hospital Boston, is a research scientist at Harvard Medical School who has extensive experience developing and implementing the glucose control and monitoring algorithms used both in the ongoing SPECS trial as well as outpatient diabetes research. He is the creator of CHECKS and will be responsible to facilitate the interactions between the glucose sensor and insulin algorithm and to adjust these over the course of the study in order to continue to achieve a high level of safety.

**C2. Clinical Coordination Center (CCC)**

The Clinical Coordination Center (CCC) is based primarily out of the Medicine Critical Care Program (MCCP) in the Department of Medicine at Children’s Hospital Boston (CHB). The CCC staff for the HALF-PINT trial includes PI Dr. Agus, Coinvestigator Dr. Steil, as well as a Research Manager, Grants and Subcontracts Administrator, Lead Study Nurse, and Programmer. An additional arm of the CCC, under the direction of PI Dr. Nadkarni, is operated in full collaboration out of the Division of Critical Care Medicine at Children's Hospital of Philadelphia (CHOP). CCC staff at CHOP includes the manager of Institutional Review Board (IRB) operations for HALF-PINT.

**C3. Data Coordination Center (DCC)**

The Biostatistics and Data Coordinating Center in the Department of Cardiology at CHB will function as the independent HALF-PINT Data Coordination Center (DCC). This group also serves as the DCC for the SPECS and RESTORE trials. The DCC staff for the HALF-PINT trial includes PI Dr. Wypij, as well as a Biostatistician, Project Manager, Applications Developer, Data Manager, and Study Coordinator.

**David Wypij, PhD,** Principal Investigator/Senior Biostatistician of the DCC, is a Senior Biostatistician at Children’s Hospital Boston, Associate Professor of Pediatrics at Harvard Medical School, and Senior Lecturer on Biostatistics at Harvard School of Public Health. Dr. Wypij has considerable experience in the leadership of DCC efforts for single- and multi-center studies, with special expertise in ICU management, surgical follow-up studies, and pediatric cardiology. Dr. Wypij will direct all DCC efforts for the HALF-PINT trial.

The DCC will:

(1) Provide overall study coordination, including development of case report forms and manual of operations, data entry training of study personnel, participation in committees, and coordination of Data and Safety Monitoring Board meetings.

(2) Support study monitoring and create data reports for the Data and Safety Monitoring Board.

(3) Provide data management and data quality services, including database development, database checks and updates, quality control and quality assurance, site monitoring visits, maintenance of patient confidentiality, and firewalls.

(4) Perform all data analyses for the main study, support publication and abstract preparation, assist with the rapid dissemination of findings, and create final data sets for archiving.

(5) Coordinate with the Sergievsky Center at Columbia University Medical Center for the follow-up study.

**C4. Sergievsky Center at Columbia University Medical Center (SC-CUMC)**

The Sergievsky Center at Columbia University Medical Center (SC-CUMC) will mail questionnaires to and conduct telephone interviews with parents/guardians at one year post-discharge to measure neurodevelopmental status. Emotional health, and quality of life outcomes in HALF-PINT subjects will be assessed by survey instrument at baseline (CBCL, PedsQL) and at one year after ICU hospitalization (Vineland-II, CBCL, PedsQL). The goal of baseline data collection is to assess pre-ICU health and quality of life. SC-CUMC staff includes trained Spanish-speaking interviewers who can complete translation and back translation of interview instruments (to and from Spanish) as needed.

**Katherine Biagas, MD,** Coinvestigator from Columbia University and Morgan Stanley Children’s Hospital of New York-Presbyterian, has expertise in the neurologic assessment of children and will champion the assessment and follow-up aspect of the study.

**Veronica Hinton, PhD,** Associate Professor of Clinical Neuropsychology at the Sergievsky Center at Columbia University Medical Center, is an experienced researcher in the neurodevelopmental evaluation of children. She will conduct and/or directly supervise the individuals who will conduct the parent/guardian interviews to measure neurodevelopmental, emotional health, and quality of life outcomes in HALF-PINT subjects.

**C5. Collaborating Clinical Sites**

Approximately 20 pediatric ICUs will collaborate in this research. Each participating clinical site includes a Site Director and lead Study Nurse who will champion the protocol and maintain responsibility for proper protocol execution and data collection. All ICUs are required to complete study training of at least 80% of staff. The study cannot be implemented without delivery and installation of all study-related devices. These ICUs were selected because of their high patient volumes and their commitment to participation in clinical trials in the ICU.

**D. Design and Methods**

**D1. Study Overview**

HALF-PINT is a multi-center randomized clinical trial that tests the efficacy of two target blood glucose ranges using our innovative and safe TGC protocol to reduce mortality and ICU LOS in critically ill children. Study teams at approximately 20 ICUs will enroll patients who meet inclusion criteria and do not meet any exclusion criteria (Section D2). Upon developing hyperglycemia (BG ≥150 mg/dL), a consented subject will be randomized to either the TGC-1 group or the TGC-2 group. Randomized subjects in both groups will be followed from the time of consent to ICU discharge or Day 28 (whichever occurs first). For the purposes of this protocol, Day 28 is counted from Day 0, when the subject is randomized. A subject is considered to meet study-defined ICU discharge criteria when all of the following are true for at least 24 consecutive hours: subject is (a) extubated, (b) off non-invasive ventilation that provides ≥5 cm H2O or reached premorbid ventilatory settings, and (c) able to maintain age-appropriate mean arterial pressures without the use of vasopressors or inotropes. Additionally, a subject will no longer be followed if the family/team have decided to limit/redirect from aggressive ICU technological support, the parents/guardians withdraw consent, or the subject has a new cardiac surgery. At ICU discharge or on Day 28, daily data collection will cease but subjects will be followed for 90-day hospital mortality. We will administer a telephone-based follow-up interview one year after ICU discharge to the parents/guardians of a random sample of subjects to assess the subject’s neurodevelopmental status, emotional health, and long-term quality of life.

The PIs Drs. Agus and Nadkarni and the CCC will lead the clinical training of the sites. Training videos and other training materials will be developed both for initial site certification and, subsequently, for just-in-time refreshers upon recruitment and randomization of subjects. Prior to study enrollment, training videoconferences will be held. System nuances may impact site-specific protocol implementation and training and will require group discussion and team problem-solving. Each site will be required to complete training of at least 80% of nurses who care for patients in any ICU that the study is performed. Each ICU will identify multidisciplinary HALF-PINT “Champions” to facilitate the successful implementation of the insulin titration algorithm within each unit. This Champion team will allow staff access to local continuous glucose monitoring experts 24/7 and will also accommodate the monthly training schedules of new physicians-in-training and nurse orientees as per unit norm.

The primary hypothesis is that hyperglycemic pediatric patients with cardiovascular and/or respiratory failure managed by TGC-1 will experience lower mortality and shorter ICU LOS compared to those managed by TGC-2. The primary outcome measure is ICU-free days (equivalent to 28-day hospital mortality-adjusted ICU LOS) after randomization. Secondary outcome measures include 90-day hospital mortality, 28-day accumulation of multiple organ dysfunction syndrome (MODS) (25), ventilator-free days, and incidence of nosocomial infections (bloodstream, pulmonary, urinary tract, and wound hospital-acquired infections); algorithm safety as measured by severe hypoglycemia (blood glucose <40 mg/dL) incidence and duration, lipid activation (serum triglycerides, free fatty acids and lipoprotein profile), lactate, and byproducts of metabolic stress related to hypoglycemia; algorithm performance as measured by time to glucose target range, percent time in target range, time-weighted glucose average, 24-hour insulin sensitivity index, and 72-hour variability index; and neurodevelopmental outcomes as measured at baseline and at one year post-ICU by Vineland Adaptive Behavioral Scales-II (Vineland-II) score (26), Child Behavior Checklist (CBCL) (27), and Pediatric Quality of Life Inventory (PedsQL) (28).

**D2. 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 via tracheostomy overnight or during sleep 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

Of note, co-enrollment with other clinical studies will be allowed with observational studies, as long as parents/guardians consent to both HALF-PINT and the observational study. If a study proposed for co-enrollment is an interventional trial, then the Core Leadership Committee shall consider the various aspects of the trial using the document entitled “Competing trial comparison grid” and will make a determination about whether co-enrollment would compromise the conduct of HALF-PINT. The committee will present its findings to the Data and Safety Monitoring Board (DSMB) at the subsequent DSMB meeting, or sooner via e-mail if appropriate. No co-enrollment with another interventional trial shall take place without prior authorization from the DSMB.

**D3. Recruitment Methods**

All subjects will be cared for in the Pediatric ICU. All ICU admissions will be screened for potential eligibility for HALF-PINT daily. Research Coordinators or the Site Director will be responsible for conducting these screenings. The attending physician will be notified of any patient who meets eligibility criteria and she/he or a designee will be asked to make an introduction of study staff to the parents/guardians. If the patient in question is female, prior to introducing study staff to the parents/guardians, the attending physician or designee will be asked to attest to the pregnancy status of the patient in question. A tool has been developed which will be reviewed and signed by the physician, attesting to the fact the patient is not pregnant, and the basis upon which this determination was made. If upon review the patient is in fact pregnant, or the physician has any other objections to the patient being approached for potential enrollment in this study, the parents/guardians will not be approached.

**D4. Informed Consent Process**

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. If the parents/guardians are interested, study personnel will ask them to read the consent and HIPAA forms. Study personnel will review the information on these forms with the parents/guardians and answer any questions. Most patients will be intubated, mechanically ventilated, and sedated so will be unable to provide assent while acutely ill. If a patient has reached the age of assent, he/she will be asked to provide assent when he/she is cognitively capable; specifically, when he/she has a baseline Pediatric Cerebral Performance Category of 1-3 (normal to moderate disability) and has not been on sedatives for the past 72 hours. Assent will be obtained up until hospital discharge or Day 28, whichever occurs first. Clinical sites will be instructed to follow their local IRB recommendations for the age of assent. Consented subjects who turn 18 years old while still receiving interventional insulin therapy and who are cognitively able to provide consent will be asked to provide consent using the study consent form.

Parents who are Spanish speaking will be approached using an interpreter. A Spanish version of the consent form will be filed with the IRBs as a subsequent modification and no Spanish-speaking parents/guardians will be approached until IRB approval is obtained for the translated form. Additional languages will be added by a similar process on an as needed basis. Enrollment into the study will be performed when consent is obtained.

Approximately 2,850 patients will be consented in order to randomize approximately 1,880 (940 per group).

**D5. Description of Study Treatments and Procedures**

We outline the study procedures briefly below. A detailed manual of operations provides additional details for HALF-PINT research staff.

Consented subjects will be tracked on a daily basis by the study team (Site Directors or Research Coordinators), though without study-related interventions. The team will evaluate on a continual basis to ensure that the subject remains eligible according to the study inclusion/exclusion criteria. BG will be measured every four hours or according to usual practice and frequency in the ICU (and at the discretion of the treating physician). If at any point during the subsequent 28 days of the subject's ICU stay the BG is ≥150 mg/dL, the sample will be repeated and, if confirmed within 24 hours of the first sample, the subject will then be randomized to a treatment group, TGC-1 or TGC-2. Randomization is conducted such that only confirmed hyperglycemic (i.e., ≥150 mg/dL) subjects will eligible for the intervention (N=1,880) and inclusion in the final analysis. Subjects consented but not randomized will not be included. Both randomized cohorts will receive the identical protocolized intervention, but with different BG ranges.

Randomization will be accomplished using a web-based, DCC guided randomization assignment process. Results of the randomization will be automatically communicated to the DCC. The computer will also conduct a just-in-time refresher tutorial to assist the clinical team in placing the CGM sensor and initiating the protocol. Staff members at the CCC will be available to provide additional assistance by page 24/7. Subjects will be randomly assigned, in a 1:1 ratio, to receive insulin to target glycemic range (TGC-1) 80-110 mg/dL or to target glycemic range (TGC-2) 150-180 mg/dL. Randomized subjects will have measurement of BG per the direction of CHECKS, the insulin titration algorithm.

Continuous Glucose Monitoring

Continuous glucose monitoring will be conducted in all subjects in both the TGC-1 and TGC-2 treatment groups. The initial step in the protocol after randomization will involve insertion of the Guardian REAL-Time® device by a study physician, Study Nurse, or other designated study personnel trained to insert the device.

a) The sensor portion of the device will be kept in its sterile packaging until insertion using standard sterile technique. The sensor will be inserted into the subcutaneous fat through a 27-gauge insertion needle into the lateral thigh, or, if determined to be an inconvenient location, into the anterior abdominal wall or upper extremity.

b) After insertion, the sensor will be connected to a wireless transmitter. The monitor that receives the signal will be activated and placed within transmission range on or near the subject’s bed.

c) After the manufacturer-specified warm up time of two hours, Guardian REAL-Time® will be calibrated using a blood glucose concentration measured with the study glucose meter.

d) Thereafter, calibration of the Guardian REAL-Time® will be done with the blood glucose level from the glucose meter at a minimum of every six hours. Calibration will be done more frequently if requested by the computer calibration algorithm or the insulin infusion protocol.

e) If at any time there is a problem or question with sensor insertion, the HALF-PINT CCC will be available 24/7 by page to assist. A local HALF-PINT champion will also “round” at least daily on any subject with an active Guardian REAL-Time® sensor to verify that the device has remained properly attached and secured to the subject and is functioning properly.

The alarm on the Guardian REAL-Time® devices will be set to alarm bedside clinicians of hypoglycemia (glucose level <70 mg/dL) in both study groups. Sensors will be replaced according to the protocol by a study physician, Study Nurse, or designated study personnel trained to insert the device using the same method described above. Topical anesthetic (e.g., EMLA cream, 0.5 gram on 3 cm2 for up to one hour) may be placed prior to insertion if the subject is not already receiving IV sedation.

Insulin Infusion Protocol

The CHildren’s EuglyCemia for Kids Spreadsheet (CHECKS) uses a combination of discrete blood glucose values, continuous glucose monitor values, and an algorithm for recommending insulin infusion rates and, if necessary, intravenous glucose. The algorithm is intended to establish and maintain glucose within a specified target range. CHECKS uses discrete blood glucose values entered by the user at time intervals recommended by the algorithm together with a continuous glucose monitor that reports sensor glucose (SG) values every 5 minutes. SG values are used only as general guides as to whether insulin dosing should be changed or glucose rescue should be administered; these interventions are never recommended solely based upon the SG value, rather only after confirmation with a blood glucose value from a bedside glucose meter or central laboratory device. Nurses are instructed to check the SG at a variable interval according to the algorithm, from 30 to 60 minutes, and type the value into the CHECKS spreadsheet. If, based upon the SG, CHECKS recommends an insulin dosing change or dextrose rescue, the nurse is instructed to draw a confirmatory BG, which is used by CHECKS for the final therapeutic recommendation to the clinical team caring for the subject.

The CHECKS algorithm is based on rules derived from PID control theory (see Section B6). These rules are used to inform the user when to check the SG or obtain a blood sample for BG, with time intervals ranging from 30 to 360 minutes. The user is required to enter appropriate data at these time points and thereafter follow instructions written on a user interface screen, programmed as a Microsoft Excel® dashboard. The dashboard allows instructions to be placed at the same location on the screen whenever the program is running and to accept values entered only in specific locations on the screen. This is done to prevent user errors that are common with spreadsheet applications. Values entered by the user are copied to their correct cell locations located on a Microsoft Excel® spreadsheet which performs all of the algorithm calculations.

Insulin therapy will begin once the CGM has completed warm-up and is ready for initial calibration. The nurses will start an intravenous insulin infusion according to the study algorithm spreadsheet if the derivative adjusted glucose concentration is greater than 110 mg/dL in TGC-1, or greater than 180 mg/dL in TGC-2, or at any time thereafter in the ICU when the CGM is in place. Blood glucose concentration will be monitored by the CGM, as well as the study glucose meter, with a frequency determined by the computer algorithm, as indicated clinically. Glucose meter checks will be at least as frequent as every two hours during insulin infusion and every six hours when insulin is not being infused. The meter will also be checked 30 minutes after any dextrose bolus is recommended by the infusion algorithm to confirm that the bolus was successful. The Site Director and/or a Study Nurse trained in using and teaching the insulin infusion protocol will also “round” twice daily to troubleshoot with the ICU nurses using the insulin infusion, answering questions, and addressing any concerns with the insulin infusion protocol and its implementation. The insulin infusion will continue until it appears the subject will imminently (in the next 3-6 hours) meet study-defined ICU discharge criteria, at which point the insulin infusion will be discontinued.

In order to ensure a continuous supply of dextrose, avoid metabolic starvation, and minimize the risk of hypoglycemia, subjects <6 years of age will have a continuous dextrose infusion of at least 5 mg/kg/min and subjects ≥6 years of age will have a continuous dextrose infusion of at least 2.5 mg/kg/min (193). Weight will be calculated based on ideal body weight in obese subjects. The dextrose dose will be calculated using ideal body weight if the subject is obese. The dextrose rate can be delivered via a dedicated dextrose intravenous infusion, as a result of dextrose content in other medication or nutrition intravenous infusions, or enterally via feeds.

Endpoints for Continuous Glucose Monitoring and Insulin Infusion

Tight glycemic control will continue in the ICU for up to 28 days after randomization, as long as the subject has an available intravenous line to infuse insulin and is able to provide sufficiently frequent arterial, venous, or capillary blood samples for glucose measurement. Continuous glucose monitoring will performed for at least the life of the original glucose sensor (6 days). A new sensor will be inserted every 6 days if any of the following conditions are met:

a) The subject has received insulin within the previous 12 hours

b) The subject has had a glucose meter or laboratory blood glucose measurement >110 mg/dL within the previous 12 hours

c) A planned change in the subject’s treatment is expected to cause hyperglycemia (BG >110 mg/dL) within the next 12 hours (e.g., administration of steroids, increase in nutritional intake, etc.)

If the subject did not meet any of the above criteria at the time of sensor removal, blood glucose will be monitored for hyperglycemia at least every six hours. A new sensor will be inserted if either of the following conditions is met:

a) The subject has 2 subsequent glucose meter or laboratory blood glucose measurements >110 mg/dL

b) A planned change in the subject’s treatment is expected to cause hyperglycemia (BG >110 mg/dL) within the next 12 hours

In general, insulin will only be infused while continuous glucose monitoring is being performed. An exception may be made during times of transition between sensors (i.e., between the time of removal of an expiring sensor and initialization of a replacement sensor) and in cases that the continuous glucose monitor is temporarily unable to display a sensor glucose (e.g., if the monitor is out of radio signal range of the transmitter). In these instances insulin may be given according to the study infusion algorithm, but blood glucose must be checked at least every hour during insulin infusion.

Insulin infusion and continuous glucose monitoring will stop if one of the following occurs:

a) Transfer of the subject out of the ICU

b) 28 days have elapsed since randomization

c) Initiation of ad lib feeds by mouth

d) The family/team have decided to limit/redirect from aggressive ICU technological support

e) The parent(s)/guardian(s) withdraw consent or the subject withdraws assent to participate in the study

f) The subject has a new cardiac surgery

g) If three concurrently inserted sensors fail and the Site Director believes that the failure is likely due to the subject’s clinical condition (e.g., significant body wall edema, poorly perfused extremities).

**D6. Study Outcomes**

Specific Aim 1

Primary Outcome Measure

***ICU-Free Days (28-Day Hospital Mortality-Adjusted ICU LOS)***

The primary outcome variable in this trial is ICU-free days, which is equivalent to 28-day hospital mortality-adjusted ICU LOS. Although many trials in pediatric critical care have measured surrogate markers, including notably the Leuven group which powered their pediatric trial based upon C-reactive protein concentrations (17), we believe that the costs and risks of TGC-1 intervention are best weighed against the potential improvements in clinical outcomes. The 28-day mortality outcome has been recognized as the standard in several adult TGC and other ICU trials (14, 30, 31, 38, 39). ICU LOS has also been a primary target in several important studies (5, 6).

ICU LOS will be calculated based upon the following site-independent discharge criteria that must be true for at least 24 consecutive hours: subject is (a) extubated, (b) off non-invasive ventilation that provides ≥ 5 cm H2O pressure or has reached premorbid ventilator settings, and (c) able to maintain age appropriate mean arterial pressures without the use of vasopressors or inotropes.

Secondary Outcome Measures

***90-day Hospital Mortality***

In order to enable direct comparisons between data gathered in HALF-PINT and the prior adult NICE-SUGAR trial (14), we will collect data on 90-day hospital mortality.

***Accumulation of Multiple Organ Dysfunction Syndrome (MODS)***

Accumulation of MODS (25) during the 28 days following randomization will be measured. MODS is defined as the concurrent dysfunction of two or more organ systems (e.g., acute lung injury and renal failure). The clinical relevance of MODS as a surrogate outcome measure is well recognized in the intensive care community, and there is a clear relationship between the number of dysfunctional organ systems and the risk of death in critically ill children (164-166). In a recently completed study of blood transfusion requirements in critically ill children (the TRIPICU study (167)), accumulation of MODS was chosen as the primary outcome variable with successful ability to compare two transfusion strategies.

***Ventilator-Free Days***

Ventilator-free days during the 28 days following randomization is a productive endpoint for clinical trial design because the measure encompasses both reduction in the duration of ventilation and improvement in mortality (168). The end of the subject's duration of ventilation is defined as the date/time of extubation for subjects who are intubated or the date/time of the discontinuation of mechanical ventilation for subjects with tracheostomy. Removal of the endotracheal tube will be calculated from the first time the tube is continuously absent for at least 24 consecutive hours. For subjects with tracheostomy, the discontinuation of mechanical ventilation will be calculated from the first time that the subject is off mechanical ventilation for at least 24 consecutive hours. Subjects, when spontaneously breathing and with an oxygenation index ≤6, are expected to have a daily extubation readiness test performed until they are extubated (137). Although there has been no direct association between TGC and resolution of pulmonary disease specifically, numerous studies have shown benefits in critically ill populations and most of these patients are ventilated during their ICU course. Improving mortality and shortening the ICU course, therefore, should be associated with an increase in ventilator-free days. Only subjects who are ventilated during their ICU course will be included in this analysis.

***Incidence of Nosocomial Infections***

There have been numerous publications supporting the benefit of TGC to immune function (8, 75, 169-171). Prior surgery-based trials have used measures of hospital-acquired infections among their primary outcome measures (12), as well as SPECS, which is currently underway. In non-surgical ICU patients, however, infections are commonly the instigator of the critical illness and, therefore, prevention is not temporally possible. This may be a component of the lack of benefit demonstrated in the large adult medical ICU trials, while benefit seems to be more easily observed in postoperative patients. In the Leuven PICU trial, however, there was a 21% relative reduction in incidence of nosocomial infections in the intervention (50-80 or 70-100 mg/dL) cohorts (17).

For the purposes of this study, we will use Centers for Disease Control’s most recently published definitions (172) for the following nosocomial infections attributable to the ICU stay: total bloodstream infections including Central Venous Line (CVL)-associated bloodstream infections (BSI), respiratory tract infections including ventilator-associated pneumonias, urinary tract infections, and wound infections that occur in the ICU or within 48 hours of discharge to the non-ICU inpatient unit. Device-related infections will be counted per 1,000 device days, and non-device-related infections will be counted per 1,000 ICU days.

***Insulin Algorithm Safety***

Hypoglycemia will be tracked and reported according to three ranges: severe (SH; <40 mg/dL), moderate (40-49 mg/dL), and mild (50-59 mg/dL) per subject and per subject per insulin day. Duration of hypoglycemic episodes will be tracked with the use of the CGM device. Lipid activation and metabolic stress during SH will be measured by urgently drawing and sending blood to the local central laboratory for determination of serum glucose, serum triglycerides, free fatty acids, lipoprotein profile, and lactate. All episodes of SH will be reported to the DSMB Chair within 24 hours of notification of one of the PIs. As insulin infusion can cause slight changes to serum potassium concentration, hypokalemia <2.5 mmol/L will also be tracked. All adverse events will be judged by local study staff as to the likelihood the event was attributable to the protocol. Clear guidelines on this reporting will be laid out in the manual of operations.

***Insulin Algorithm Performance***

Although safety is the top priority, performance of the algorithm across diverse ages, weights, and disease processes will be critical to measure and compare to other published algorithm performance. Ideally, the algorithm will minimize time to glucose target range and maximize time spent in the glucose target range. We will track the overall glycemic profile using time-weighted glucose average because it is uniquely unaffected by the increased frequency of BG determinations that occur when glucose is abnormally low or high. Based upon insulin requirements, we will calculate insulin sensitivity index (ISI) in the first 24 hours of the protocol, as well as glucose variability (GV) index in the first 72 hours.

ISI will be approximated via an analysis derived from minimal model analysis of changes in blood glucose in response to insulin delivery, IV glucose, and meal carbohydrates by assuming the change in blood glucose is primarily in response to the exogenous insulin, glucose, and carbohydrate (i.e., assuming the change is not due to a change in insulin secretion). The analysis will be performed using original minimal-model equations (182-185) with an added equation characterizing the concentration of plasma insulin in response to insulin delivery and rate of glucose appearance following meals. We have previously used a similar model-based approach to characterize insulin sensitivity and other metabolic indices (glucose effectiveness, insulin clearance) in individuals with type 1 diabetes undergoing closed-loop insulin delivery (186). GV is calculated by dividing the absolute difference of sequential glucose values by the difference in collection time (in hours +0.01). The mean of the ratios for each subject forms the variability index (138). Finally, in order to assess reproducibility of the results in the future, we will track clinical compliance with the recommendations of CHECKS.

***Nursing Workload***

TGC protocols are typically managed by bedside nurses. In practice, there has been substantial resistance to adherence with TGC by nursing staff, due both to the increased workload stemming from frequent glucose monitoring and changes in infusion rate and to concerns about the risk of hypoglycemia (188-189). While critical care nurses continuously multi-task and prioritize care based on patient safety and treatment efficacy, little is known about how best to implement and sustain TGC practices. We will describe protocol implementation and the cognitive burden placed on bedside nurses when managing a patient on TGC. Bedside nurses will be randomly selected to complete an anonymous survey describing their perceptions of workload burden associated with managing a patient on TGC (190). We will describe nurses' perceptions of their capacity to complete both TGC-related and non TGC-related nursing activities over several intervals of the study period. De-identified data (by nurse and site) will be reported using both qualitative and summary statistics.

Specific Aim 2

Outcome Measures

***Developmental Neurobehavioral Outcomes at Baseline and One Year after ICU Course***

Reliable, reproducible measures of adaptive functioning, behavior, and quality of life will be used to determine outcomes at baseline (CBCL, PedsQL) and at one year after ICU hospitalization (Vineland-II, CBCL, PedsQL). The goal of baseline data collection is to assess pre-ICU health and quality of life. These are described in greater detail in the Follow-up Study Instruments section (Section G). It should be noted that one of these measures, the Vineland-II, is also currently being used in children as a primary developmental neurobehavioral outcome measure in the NHLBI-funded pediatric multi-center clinical trial of Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA, U01 HL094345).

SC-CUMC, under the direction of Coinvestigator Dr. Biagas in collaboration with Dr. Hinton, will serve as the central site for administration and evaluation of these measures. Dr. Hinton and testing group personnel will be blinded as to treatment assignment.

D7. Measurement of Study Variables

Methods of Data Collection

Site personnel will be trained in data collection methods by the DCC Project and Data Managers prior to enrolling patients (see Section D10).

Data Collection Schedule

The following table summarizes the data collection schedule:

|  |  |  |  |
| --- | --- | --- | --- |
| **Measurement** | **At Randomization** | **Daily** | **End of Study Period** |
| Demographic data | X |  |  |
| Medical history | X |  |  |
| PIM2 score | X (score at admission) |  |  |
| PRISM III-12 score | X (score at admission) |  |  |
| PCPC score | X (score at admission) |  | X |
| POPC score | X (score at admission) |  | X |
| PELOD score |  | X |  |
| Intubation and ventilation status | X | X | X |
| Non-invasive ventilation status | X | X | X |
| Vasopressors/inotropes | X | X | X |
| Adverse events |  | X |  |
| Nutrition |  | X |  |
| Subject summary |  |  | X |

While Drs. Agus and Nadkarni and their research staff will receive summary reports (as appropriate) from the study database collated by the DCC. They cannot view or change any study data except from their own site.

D8. Study Safety

Please see standard operating procedures document entitled “HALF-PINT Adverse Event and Unanticipated Problem Monitoring and Reporting” for detailed description of study safety procedures. A summary is provided below.

Subjects will be monitored daily for the occurrence of adverse events defined as any untoward or unfavorable occurrence. A description of all events will be recorded in the study database. Anticipated adverse events (AE), or “HALF-PINT Specified Events” include:

* Hypoglycemia <60 mg/dL
* Hyperglycemia >250 mg/dL (>6 hours after initiation of insulin infusion)
* Hypokalemia <2.5 mmol/L
* New seizure (in subject without a known seizure disorder)
* Catheter-associated bloodstream infection (CA-BSI)
* Catheter-associated urinary tract infection (CA-UTI)
* Surgical site infection (SSI)
* Ventilator-associated pneumonia (VAP)
* Other hospital-acquired infection
* Continuous Glucose Monitor (CGM) related adverse event, bleeding or other (that did not involve hypoglycemia, hyperglycemia, or infection)
* Bedside glucose meter related adverse event (that did not involve hypoglycemia, hyperglycemia, or infection)
* VAMP Jr. related adverse event
* Computerized insulin dosing protocol related adverse event (that did not result in a hypoglycemia or hyperglycemia event)
* Insulin dosing error (that did not result in a hypoglycemia or hyperglycemia event)

The relationship of each event to the protocol will be classified according to severity, expectedness and relatedness by the bedside clinicians and recorded on eCRF Form 7.

Unanticipated problems (UP) involving risk to subjects or others will also be tracked. UP includes any incident, experience, or outcome that is unexpected, related or possibly related to HALF-PINT, AND suggests that research places subjects or others at greater risk for harm.

An AE is a reportable Serious Adverse Event (SAE) if it is serious, unexpected and related or possibly related to HALF-PINT. Any episode of severe hypoglycemia (BG <40 mg/dL) or any episode of hypoglycemia (BG <60 mg/dL) accompanied by seizure or mental status change is also considered to be an SAE. Any SAE or UP is to be reported to the DCC using the expedited reporting timeline.

**Expedited** reporting timeline for all SAE and unanticipated problems related to HALF-PINT or from protocol violations:

1. Site Directors will notify their local IRB and DCC within 24 hours of the event. The DCC will acknowledge receipt of the notification and will notify the PI within 48 hours of the event.
2. Site Directors will submit to the DCC the electronic case report form (eCRF Form 7) within 24 hours followed by a full narrative report describing the event within 7 calendar days. Such reports will include a detailed description of the SAE/UP, an explanation of the basis for determining that the event represents a SAE/UP, and a description of any corrective actions that are proposed in response to the SAE/UP.
3. The DCC will send the full narrative report to the HALF-PINT CCC PIs, NHLBI project officer, and Chair of the DSMB. HALF-PINT CCC PIs will forward the full narrative report to the Director of Human Research Protections at Children's Hospital Boston (Coordinating Center IRB).
4. DSMB recommendations will be reported to the DCC for submission to the local IRB and HALF-PINT PI. All DSMB recommendations will be discussed by the Steering Committee and reported to external IRBs as indicated.

The DCC will summarize and communicate all reported events to the PI in a Monthly Event Report. This Monthly Event Report will be a standing agenda item during Steering Committee meetings/calls. The PI and Steering Committee will monitor the frequency of HALF-PINT Specified Events. If HALF-PINT Specified Events rates occur more frequently than predicted across all participating centers their occurrence may represent an unanticipated problem. The DCC will provide an annual summary of all reported AE across all participating centers for submission to local IRBs, the NHLBI, and the DSMB. In this summary, hypoglycemia data will be stratified by age categories. The full narrative of individual AEs will be reported to all Site Directors and all local IRBs when the determination has been made that an event meets criteria for an UP.

In addition, we will assess psychological sequelae in subjects for post-ICU discharge adverse events with a follow-up assessment at one year post-ICU discharge.

D9. Study Coordination

The HALF-PINT DCC will coordinate interactions between clinical sites, SC-CUMC, study committees, and the DSMB. The DCC will work with each clinical site to ensure that database training and certification is obtained by all new staff and that data forms are submitted, data queries are resolved, and forms-related questions are answered in a timely manner. The HALF-PINT CCC will work with each clinical site to ensure that IRB approvals, renewals, and consent/assent forms are current and that protocol-related questions are answered in a timely manner.

Development of Case Report Forms and Manuals of Operations

The HALF-PINT DCC has extensive experience in the design of Case Report Forms (CRFs) and preparation of the manual of operations. DCC staff will assist Drs. Agus and Nadkarni and the CCC in CRF and manual of operations development and refinement to ensure the highest possible data quality. Forms design features include the selection of valid, reliable measurements that are least burdensome, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open-ended questions), and smooth flow in question patterns to reduce missing data. The detailed manual of operations ensures efficient and accurate data collection and ease of communication and allows for manual of operations updating, as needed, including dated footers. Members of the Core Leadership and Steering Committees will have signed off on CRFs and the manual of operations before implementation. The CRFs and manual of operations for this study are based on those used successfully in the SPECS and RESTORE trials.

Methods of Data Collection

Prior to enrolling patients, the Site Directors and other designated site personnel will be trained by the DCC Project and Data Managers to collect data using the CRFs. The manual of operations describing Standard Operating Procedures for data collection will ensure consistent decision-making across clinical sites. These procedures will be evaluated during study site visits.

Study Committees

Five study committees will be formed: the Core Leadership, Manuscript, Steering, Operations, and Ancillary Studies Committees.

The Core Leadership Committee, composed of PIs Drs. Agus and Nadkarni, Dr. Wypij, and the seven Coinvestigators, will have ultimate authority on study conduct, support of ancillary studies, and addition or elimination of participating sites. It will act as an advisory body for issues related to communications with IRBs, the NIH, and the DSMB. It will also make determinations about whether an interventional ICU trial will be considered a competing trial, and thereby not allow for co-enrollment with HALF-PINT. This determination will be made using the document entitled “Competing trial comparison grid.” The Core Leadership Committee meets by conference call on at least a quarterly basis.

The Manuscript Committee will be composed of three members to be appointed by the Core Leadership Committee. It will oversee authorship of all publications generated by the study.

The Steering Committee, composed of the Core Leadership Committee members and the Site Directors, will be responsible for execution of the study design and for its accurate conduct at each site, as well as dissemination of study-related decisions, clarification, or refinements to the protocol. This committee will meet by conference call every other month and discuss performance issues as well as troubleshoot issues in protocol implementation. The standing agenda will include enrollment review, operational issues, protocol issues including protocol deviations, quality monitoring, safety and adverse event data, and DCC update.

The Operations Committee, composed of PIs Drs. Agus and Nadkarni, the CCC, Dr. Wypij, and the DCC will review problems and issues related to day-to-day management of the study. Initial meetings will focus on the development of CRFs, the manual of operations, teaching/training materials, and the study website. The Operations Committee will meet by conference call at least monthly and the standing agenda will include review of the timeline, screening/enrollment reports, site performance reports, and overall performance. The DCC will prepare reports as needed for the Operations Committee.

The Ancillary Studies Committee is composed of several Coinvestigators, as well as leading researchers in the critical care field who are not participants in HALF-PINT. This committee will review all proposed ancillary studies and make recommendations to the Steering Committee about whether to support an ancillary proposal. Submission to the NIH for consideration for funding cannot proceed without the support of the Ancillary Studies Committee. Detailed guidelines regarding the review process have been developed and will be included as part of the manual of operations.

Coordination of Data and Safety Monitoring Board Meetings

An independent Data and Safety Monitoring Board (DSMB) has been appointed by the NHLBI Director and is responsible for protocol sign-off and monitoring of subject safety, data quality, implementation of the protocol, and potential early stopping. The DCC schedules and sets up all DSMB meetings in the format of conference calls, prepares and distributes, prior to the meetings, a written report that provides updates on overall status of the study and summarizes adverse events and key outcome variables, and supports other requests from the DSMB. (For more details, see Section J).

Coordination with the Sergievsky Center at Columbia University Medical Center for Neurodevelopmental Follow-up

Coinvestigator Dr. Katherine Biagas at the SC-CUMC will oversee all aspects of the follow-up data collection and monitoring as well as coordination with the DCC and clinical sites. Dr. Biagas’ team at the SC-CUMC will hold regular monthly project meetings to ensure that all aspects of the project are progressing optimally. The DCC maintains a second database (Section D10) for use by the SC-CUMC team and performs all data analyses for the neurodevelopmental follow-up component of the study.

D10. Data Management and Quality Control

Data Management System

The DCC has developed a web-based data management system (DMS) for HALF-PINT using the InFormTM electronic data capture (EDC) system (Version 4.6, Phase Forward, Waltham, MA) with access via a secure website built at http://www.halfpintstudy.org. According to programmed workflow logic, the DMS generates electronic Case Report Forms (eCRFs) as needed for each patient (e.g., daily forms, study discharge form). The DMS allows for the data to be viewed in real time by the DCC staff and certified data entry personnel at the clinical sites. Many logic and range checks and cross-form validations are programmed to ensure data quality. Automated queries are generated as data are entered, and the DCC Data Manager and Biostatistician also generate queries as they review data. The system supports source data verification and maintains a complete audit trail of transactions to ensure data integrity and regulatory compliance. Furthermore, the DMS provides staff with a variety of reports to assist project management and study data, which may be readily exported for use in Microsoft Excel®, SAS®, or other software. The Clinical Research Information Technology (CRIT) group at CHB helps the DCC with database releases, upgrades, and troubleshooting.

Data Coordination

The InFormTM DMS includes standard reports about enrollment and queries and custom reports can be easily programmed. The DCC provides weekly reports to the PIs about enrollment, consent rates, and adverse events. The DCC also provides monthly reports to Coinvestigators and Site Directors regarding data entry accuracy and timeliness and query resolution. The DCC has a full-time Data Manager available to assist site personnel on all DMS-related issues during data collection phases.

Data Entry, Editing, and Audit Trails

All clinical data are entered into the web-based DMS by certified clinical site personnel to ensure accurate record keeping. The DMS data capture screens closely resemble the appearance of a paper CRF. The DMS allows data entry personnel to easily view which eCRFs are complete, incomplete, or incomplete with open queries and highlights missing required fields. Context-specific help and logic and range checks reduce the number of errors and assist the data entry process. As data are being entered, the DMS generates queries about out of range or illogical values. The query may give the range of valid responses or reference responses to other related questions that make the current entry invalid. At this point, the system user may confirm an out of range value, correct a data entry error, or temporarily bypass the error and continue with data entry. The DMS contains a complete audit trail of all original values and all edits.

Data Quality Control/Assurance

The DMS can be used to assist the source data verification process. Certain fields can be preselected to require source verification. Once a data value entered into the DMS has been checked against the source documentation, the field can be marked as source verified. The DMS can generate reports about which data have been source verified or changed, the user, and the date of verification.

In addition, routine monthly and ad-hoc reports are run from the DMS as part of quality control and assurance. The reports track patient accrual, patient status, protocol deviations, and completeness of data. The DCC Director, Project Manager, and Data Manager review all reports monthly with a view to improving or maintaining high performance.

Data Confidentiality, Security, and Back-up

To ensure data safety and reliability, server back-up procedures are executed daily to back up all electronic study-related materials, which include the database, Word® documents, statistical programs, and files. Access to the DMS requires user authentication. Authorized users include the DCC staff and certified data entry personnel at each clinical site. Identifiable subject data, such as contact information and medical record numbers, are not tracked in the DMS. For the main study, a Patient Study ID paper log containing the Patient Study ID Number, subject initials, and the last 3 digits of the Medical Record Number (MRN), will be stored separately and securely at the clinical sites, away from the DCC. Signed consents and assents will be kept in a locked file cabinet in a locked research office, separate from other study documents. All study documents stored at DCC, CCC and individual sites will be stored for three years after publication of the central study manuscript, in accordance with NIH regulations.

Firewalls

All DCC application software and data are hosted securely on the CHB network. The network is protected by several firewalls and security is monitored and audited regularly by the CRIT group at CHB. All application and database software enforce access rules through user authentication and authorization schemes established by the DCC and CRIT group. The DCC ensures that no data are compromised or shared inappropriately by maintaining strict security procedures between personnel, data, and all other study investigators. For example, Drs. Agus and Nadkarni and their research staffs have limited access to status reports within the database and they are unable to view or change any of the study participant data, except at their own study sites.

Site Monitoring Visits

The DCC coordinates site monitoring visits. A study monitor (pediatric critical care nurse with research experience) conducts site visits at the approximately 20 ICUs once per year in year 2 (after at least ten subjects are randomized) through year 5. The monitoring visits include a review of the location, security, and completeness of all regulatory documents, an examination of all study procedures and procedures to resolve queries, and verification of data entered into InFormTM against source documents. The following safety and efficacy data are 100% source verified by the monitor on all randomized subjects: Human Subjects Protection, Informed Consent, inclusion/exclusion criteria, primary outcome measure, selected secondary outcomes measures, and adverse events. A random selection of data elements on a subset of subjects is also source verified.

A site-specific visit checklist is used and a report generated after completion of the visit. The checklist includes study protocol and Informed Consent Form version and approval dates, study documents (e.g., Patient Study ID Log, Staff Log), and subject-specific data downloaded from the InFormTM database (inclusion/exclusion criteria, selected demographic data, primary outcome measures, selected secondary outcome measures, adverse events, protocol deviations, discharge data). The site visit report covers staff and facilities, site evaluation, study conduct, subject data review, and problems encountered and resolutions. Members of the Steering Committee and DSMB review these reports. The Site Directors are responsible for correcting deficiencies, if any, to the satisfaction of the Steering Committee and DSMB members (majority vote).

Data Management for the Follow-up Study

While their child is in the ICU, all parents/guardians fill out the caregiver baseline questionnaires for the CBCL and PedsQL. At ICU discharge, site personnel complete a Follow-up Contact and Demographic Information Form via an interview with the parents/guardians. Site personnel send completed baseline questionnaires, coded only with subject study number and not any protected health information (PHI), to the CCC via secure fax. The Follow-up Contact and Demographic Information Forms, which contains PHI, are kept locked in a secure file cabinet in a locked research office at the individual study sites, and are only accessed when it is time to conduct the follow-up phone interview. At that time, a random sampling of subjects eligible for one-year follow-up will be defined by the DCC, and the follow-up contact information will be accessed for that select group and faxed via secure fax to SC-CUMC who will use the contact information to conduct follow-up interviews by mail and by phone. The CCC will work with SC-CUMC to code the baseline CBCL and PedsQL baseline questionnaires.

All follow-up interviews, including Vineland-II, CBCL, and PedsQL assessments, are administered centrally by a trained Research Associate at the SC-CUMC under the direction of Dr. Hinton one year after ICU discharge through a combination of mailed surveys and phone follow-up. A two-month time window (one month before and one month after the one-year time point) is allowed. Families identified for follow-up will be contacted once at approximately three months after their ICU stay to remind them that they will contacted again at one year to complete the follow-up instruments. A family may be contacted three times by telephone before being considered lost to follow-up. Lost families will be replaced with another subject chosen randomly from the randomized pool of 1,880.

Staff at the SC-CUMC completing follow-up phone interviews are blinded to subject treatment assignment and patient course. They record the data obtained during the interview on paper CRFs, developed by Dr. Biagas, the SC-CUMC Data Manager, and the DCC, which will serve as the source documentation. Completed follow-up questionnaires are kept in a locked file cabinet in a locked research office. Within one week of the phone interview, the data are entered into the follow-up study database.

The DCC has developed a second web-based DMS using InFormTM for the follow-up study. All follow-up data are entered into the DMS by certified members of the SC-CUMC study team who have completed the data entry certification process and have their own unique logins and passwords. Context-specific help and logic and range checks reduce the number of errors and assist the data entry process. The follow-up study database does not contain subject identifiers or any of the data collected in the main HALF-PINT study. It contains only Patient Study ID numbers and the follow-up data entered by the SC-CUMC study team.

At no time will the SC-CUMC reveal subject identities in any description or publication of the research for scientific purposes. All data obtained with subject identifiers are kept in locked file cabinets to ensure confidentiality, and all paper file contents are shredded before disposal. A site monitor visits the SC-CUMC to review the location, security, and completeness of all regulatory documents and other documents containing identifiable data and to verify data entered into the DMS against source documents.

The SC-CUMC monitors subject enrollment and follow-up rates. The SC-CUMC Data Manager generates monthly reports, which include number of contacts and number enrolled. Also on a monthly basis, the DCC reviews data in the follow-up database and issue queries to the SC-CUMC study team. The DCC Biostatistician will generate appropriate datasets in response to the specific needs of the proposed analysis and merges data from the follow-up database and data from the main study database as needed in order to perform analyses.

D11. Statistical Considerations

The primary aim of the study is to determine the comparative effectiveness of tight glycemic control (TGC) using an explicit algorithm and continuous glucose monitoring to 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) on mortality and ICU LOS in hyperglycemic critically ill children with cardiovascular and/or respiratory failure. The study design is a multi-center randomized clinical trial. The clinical outcome measures for Specific Aim 1 are designed to be as objective as possible since it is not possible to blind the clinical teams to treatment assignment. The primary outcome measure for Specific Aim 1 is ICU-free days (equivalent to 28-day hospital mortality-adjusted ICU LOS). The primary neurodevelopmental outcome measure for Specific Aim 2 is the one-year post-ICU Vineland-II Adaptive Behavior composite score (26). The follow-up team at the SC-CUMC is blinded to treatment assignment and patient course. The DCC PI and Biostatistician are responsible for all statistical analyses for the main study and the follow-up study.

Sample Size and Power Considerations

We assume that hyperglycemic pediatric patients with cardiovascular and/or respiratory failure managed with TGC-1 will experience lower mortality and shorter ICU LOS than those managed with TGC-2. Pilot data was provided by the Paediatric Intensive Care Audit Network (PICANet), a British national audit coordinated by the Universities of Leeds and Leicester that collects data on all children admitted to PICUs across the United Kingdom. Patients in the PICANet database are similar to US PICU patients in terms of diagnoses, severity of illness scores, and mortality. The PICANet database contains data on 61,512 PICU admissions from 2004 to 2008 that were not status post cardiac surgery. Of these admissions, 29,172 patients had cardiovascular failure (on intravenous vasopressors or inotropes) and/or respiratory failure (acute mechanical ventilation for >24 hours), were <18 years old, and remained in the ICU >24 hours. Among these 29,172 patients, the hospital mortality rate was 10.1%, approximately double that of the entire PICANet cohort (5%), and the mean PICU LOS among the 26,234 survivors was 8.5 days.

In our power calculations, for the TGC-2 group we conservatively hypothesized an 8% 28-day hospital mortality rate and, among survivors, used the same ICU LOS distribution as the PICANet survivors (mean 8.5 days). A survey of PALISI Investigators, a US collaborative of 79 Pediatric ICUs, indicated a willingness to change practice based upon results of a clinical trial which demonstrated a 20% mortality reduction combined with a one-day reduction in ICU LOS. Thus, for the TGC-1 group we assumed a 6.4% mortality rate and, among survivors, an ICU LOS distribution with mean 7.5 days (an 11.8% decrease from 8.5 days). The TGC-1 group ICU LOS distribution among survivors was derived from a proportional odds model, effectively shifting the distribution of ICU LOS among survivors in the TGC-2 group to yield a new distribution with mean ICU LOS of one fewer day. This clinically important reduction in mortality and ICU LOS appears to be plausible based on the results achieved in the Leuven PICU trial (17). The Leuven PICU trial, conducted in a predominantly pediatric cardiac surgical population (N=700), used extremely low blood glucose (BG) targets and was complicated by 44% severe hypoglycemia in children <1 year of age. Nonetheless, the Leuven trial achieved a 55% decrease in 30-day PICU mortality (2.3% vs. 5.1%, p=0.047) and a 10% reduction in PICU LOS (5.51 vs. 6.15 days, p=0.017). Power calculations were based on the above assumptions for our primary outcome measure, PICU-free days, using a Wilcoxon rank sum test. In our proposed cohort, we conservatively hypothesized a significantly smaller mortality reduction of 20% from a baseline of 8% combined with a similar LOS reduction of one day from a conservative baseline estimate of 8.5 days. Using PROC POWER (SAS Version 9.2, SAS Institute, Inc., Cary, NC), to detect a 20% reduction in 28-day hospital mortality and a one-day reduction in ICU LOS requires a sample size of 1,708 randomized subjects (854 per group) for 90% power with a two-sided alpha level of 0.05.

These sample size calculations needed some adjustment to allow for interim analyses and potential early stopping for efficacy or futility. Based on East Version 5.4, Cytel Statistical Software, Cambridge, MA), allowing looks after 50%, 67%, 83%, and 100% of the data have accrued and assuming general endpoints based on treatment effects estimated through generalized linear regression models, requires a sample size of 1848 subjects (924 per group). To allow for interim analyses and attrition (withdrawals, expected to be <1%), we select the total sample size to be 1,880 randomized subjects (940 per group).

Adequacy of the Study Population

The incidence of blood glucose concentration ≥150 mg/dL (≥8.3 mmol/L) in critically ill children ranges from 61% (in all PICU patients) (7) to 74% (in patients with one or more organ failures) (8). We therefore predicted that 66% of consented children will develop blood glucose concentrations ≥150 mg/dL during ICU admission and thereby trigger either TGC-1 or TGC-2 intervention. In light of the predicted 66% incidence of hyperglycemia among this cohort, we predicted the need to consent and enroll 2,850 subjects, of which 1,880 will ultimately become hyperglycemic and be randomized. Over a 48-month period, we require enrollment of 60 subjects per month and randomization of 40 subjects per month (2 completed subjects/site/month at approximately 20 sites) to meet our sample size needs.

Follow-up Study

The primary developmental outcome measure is the VABS-II Adaptive Behavior Composite score (26) measured at one year post-ICU. The Vineland-II Adaptive Behavior Composite score is normally distributed with a mean of 100 and a standard deviation (SD) of 15. The sample size required to detect a 5-point difference (“effect size” = 5/15 = 1/3 SD difference) in means between the TGC-1 and TGC-2 groups with 90% power is 378 subjects (189 per group). With an enrollment of 1,880 randomized subjects, we need to follow approximately 20% of our study cohort at one year post-ICU. The SC-CUMC team randomly selects sufficient subjects to follow from those in the main study. If our loss to follow-up rate is unexpectedly high, the team will randomly select additional subjects from the pool of survivors to follow to ensure that the follow-up sample size will be adequate. We will also compare demographic and clinical characteristics of contacted subjects with those who were lost to follow-up (and with subjects whom we did not attempt to contact) to ensure that the follow-up cohort is representative of the trial as a whole. Overall, the study is adequately powered to determine the safety of tight glycemic control in terms of post-discharge outcomes.

Randomization Scheme and Process

Randomization is orchestrated via bedside computer using a web-based, DCC guided randomization assignment process. A permuted blocks randomization scheme stratified by site will be used to populate the database. Randomization occurs once a study participant develops hyperglycemia. A BG reading of ≥150 mg/dL triggers a second reading. If the second BG reading is also ≥150 mg/dL, the subject is randomized. Results of the randomization are automatically communicated to the DCC. The computer also conducts a just-in-time refresher tutorial to assist the bedside nurse in placing the CGM sensor and initiating the protocol. Staff members at the CCC are available to provide additional assistance by page 24/7. Subjects are randomly assigned, in a 1:1 ratio, to receive insulin to target a normal glycemic range (TGC-1) 80-110 mg/dL or to target a higher glycemic range (TGC-2) in which glucose will be reduced into the 150-180 mg/dL range. Randomized subjects have measurement of BG per the direction of CHECKS, the insulin titration algorithm using explicit methodology.

Preparation of the Analysis Data Set

Datasets for analyses consist only of data for which all queries have been resolved. In addition to the data management steps described in Section D10 to reduce errors in data acquisition and entry, biostatistical cleaning focuses on inconsistencies, missing data, and outliers in variables related to the derivation of outcome measures and on documenting heterogeneity across sites. These activities are ongoing throughout the study and involve both the data management team and the biostatistics team. Preplanned construction of new variables is conducted in accordance with the study hypotheses and analysis plans. Variable transformation may be required for interpretive and statistical purposes.

Statistical Analysis Plans

The primary outcome measure for this study is ICU-free days (equivalent to 28-day hospital mortality-adjusted ICU LOS). Secondary outcome measures include 90-day hospital mortality, 28-day accumulation of multiple organ dysfunction syndrome (MODS) (25), ventilator-free days, and incidence of nosocomial infections (bloodstream, pulmonary, urinary tract, and wound hospital-acquired infections); algorithm safety as measured by severe hypoglycemia (blood glucose <40 mg/dL) incidence and duration, lipid activation (serum triglycerides, free fatty acids and lipoprotein profile), lactate, and byproducts of metabolic stress related to hypoglycemia; algorithm performance as measured by time to glucose target range, percent time in target range, time-weighted glucose average, 24-hour insulin sensitivity index, and 72-hour variability index; and neurodevelopmental outcomes as measured at baseline (CBCL, PedsQL) and at one year post-ICU (Vineland-II, CBCL, PedsQL).

Descriptive statistics will be calculated, including means, standard deviations, medians, interquartile ranges, and ranges for continuous variables and frequency counts and percentages for categorical variables. Data will be examined for skewness, outliers, and systematic missing data. Transformations will be undertaken as needed.

Specific Aim 1

Our primary analysis will compare ICU-free days in TGC-1 vs. TGC-2 subjects using Kaplan-Meier survival curves and proportional hazards regression adjusting for age (<2 years, 2-6 years, >6 years) and severity of illness (PRISM III-12 score (156)). The outcome ICU-free days is defined as 28 – ICU LOS. For the purposes of this protocol, Day 28 is counted from Day 0 when the subject is randomized. For primary analyses, subjects who die during the 28-day study period whether in the ICU or a non-ICU inpatient unit, who have not yet met ICU-discharge criteria by Day 28, or who are transferred to a non-participating ICU will be censored at 28 days and assigned zero ICU-free days. Withdrawals will also be assigned the worst outcome of zero ICU-free days. This outcome is a continuous variable that is effectively equivalent to using hospital mortality-adjusted ICU LOS as the primary outcome. This method for handling deaths, transfers, and withdrawals is a conservative approach in that these subjects are equated with the longest duration of ICU LOS values. An alternative analysis approach for the primary outcome variable will be based on a permutation test of the median duration of mortality-adjusted length of ICU stay across the sites.

For analyses of secondary outcomes, we will use proportional hazards regression for time to event outcomes, linear regression for continuous outcomes, and logistic regression for binary outcomes to compare TGC-1 vs. TGC-2 subjects and to control for variables that are likely to be associated with outcomes, including age (<2 years, 2-6 years, >6 years) and severity of illness (PRISM III-12 score (156)). For non-normal continuous outcomes, we will consider data transformations or nonparametric methods, as appropriate.

Interim Analysis Plans

An independent DSMB monitors this clinical trial for adverse events, adherence to study protocol, and potential early stopping. The trial may be stopped if any of the following occur:

1. The intervention is associated with an increased length of ICU stay, increased mortality, or increased adverse events
2. A highly significant benefit of one group (efficacy) or extreme lack of difference (futility) emerges before the planned end of the study
3. Adherence or compliance to study protocol and/or recruitment is well below acceptable goals and the ability of the study to achieve its goals is seriously compromised
4. Evidence external to the study renders it unethical to continue the study

Group sequential monitoring based on East software (Version 5.4 or higher, Cytel Statistical Software, Cambridge, MA) will be used to stop the study if large treatment differences appear before the end of the study (efficacy) or if there is little chance of finding a significant difference between groups (futility). Formal interim analyses will occur after 50%, 67%, 83%, and 100% of the data have accrued. Lan and DeMets (194) developed flexible α-spending rules (for Type 1 error) for consideration of stopping due to efficacy. Subsequently, Pampallona, Tsiatis, and Kim (195, 196) developed flexible β-spending rules (for Type II error) for consideration of stopping due to futility. Using East software, we will develop stopping boundaries for test statistics or p-values based on O’Brien-Fleming (197) rules for both efficacy and futility. The study sample size has been adjusted to accommodate these interim looks at the primary outcome. Monitoring of study data and recommendations for possible changes to the study are the prerogative of the DSMB.

Specific Aim 2

Our primary analysis will compare Vineland-II Adaptive Behavior Composite scores in TGC-1 vs. TGC-2 subjects using *t*-tests and linear regression adjusting for age (<2 years, 2-6 years, >6 years) and severity of illness (PRISM III-12 score (156)). As for Specific Aim 1, analysis of secondary outcome variables for Specific Aim 2 will use appropriate regression methods, data transformations, and nonparametric statistics, as appropriate. Due to the randomized clinical trial design, we anticipate that the CBCL and PedsQL scores at baseline will be similar between the TGC-1 and TGC-2 groups. However, in secondary analyses we will compare treatment groups via the use of differences or change scores (between one-year post-ICU and baseline values for CBCL and PedsQL), which may offer some additional power to the analyses.

Additional Analyses

We do not expect secular or time trends on outcome measures or treatment group effects (due to seasonal variation or learning effects) for primary or secondary outcome measures, but we will carefully examine for them. If necessary, we will adjust for time in regression models. We do not expect effects of sex/gender or racial/ethnic group on outcome variables or treatment group differences, but we will carefully examine for them. We will perform stratified analyses in subgroups and assess statistical interactions in the total sample. If necessary, we will present sex- and/or race-specific results. We will assess whether adjustment for site affects study inferences through the use of mixed effects and generalized estimating equations models. We will also assess whether varying levels of protocol compliance result in varying levels of intervention effects using regression methods. Finally, we will explore other medical and hospital course variables to assess their prognostic significance in exploratory analyses. For example, we will assess whether hypoglycemia is a risk factor for increased mortality, longer ICU LOS, or worse neurodevelopmental outcomes. We will also assess nutritional intake and compare the success of achieving nutritional targets between the TGC-1 and TGC-2 groups, as well as explore the relationship between nutritional intake and incidence of hypoglycemia, hyperglycemia, and associated morbidities. Additionally, we will characterize the nursing workload and explore how it relates to the success of each TGC regimen and to the achievement of all primary and secondary outcome variables.

Throughout, residual analyses and model fit assessments will be performed to assess the appropriateness of modeling assumptions and check for outlying or overly influential observations.

Overall, the primary goal of the HALF-PINT trial is to compare the number of ICU-free days in the TGC-1 and TGC-2 groups. Differences between treatment groups will be considered statistically significant if the two-tailed p-value is <0.05. Careful assessment of the results from secondary analyses will be made, though no formal multiple comparisons procedures are planned. Data analyses will be performed using SAS® (Version 9.2, SAS Institute, Inc., Cary, NC) or similar statistical packages.

D12. Anticipated Problems and Solutions

Enrollment Lower than Predicted

Each ICU is expected to screen their ICU daily and enter their screening data into the HALF-PINTdatabase each week. The PIs monitor eligibility, enrollment, and refusal rates and problem-solve lower than expected enrollment rates with the Coinvestigators and Site Directors. The Steering Committee reviews enrollment data as a standing conference call agenda item.

More than the target of 20 ICUs have formally expressed a commitment to participate in the trial. This provides additional back-up sites which we could add to the participating ICU cohort in order to increase recruitment.

Non-compliance with the Study Protocol

This protocol is designed to provide clinicians with a straightforward system of glucose measurement and insulin titration in hyperglycemic critically ill infants and children with cardiovascular and/or respiratory failure. The protocol is not intended to establish a protocol for all critically ill patients. It is understood that some clinicians will deviate from the dosing recommendations given their perception of the unique clinical situation. The algorithm is built to track those unique decisions and modify its own instructions based upon the dose the patient is receiving as opposed to what had been recommended. The algorithm tracks these deviations and allows for clinicians to comment explaining the rationale for the protocol deviation (PD). The PIs will monitor monthly PD reports for trends and will contact Coinvestigators and Site Directors when increases in trackable deviations are noted. The Steering Committee also reviews quarterly PD reports as a standing conference call agenda item.

Protocol Failure

Some subjects may develop more than one episode of hypoglycemia, and parents/guardians and/or clinicians may opt to withdraw such a subject from the protocol. The rationale for all subject withdrawals is tracked and discussed by the Steering Committee. Withdrawn subjects will be included in an intention-to-treat analysis.

Development of New Glucose Sensors

The science and marketplace of continuous glucose monitoring continue to evolve, and it is possible that over the course of the trial a new device will outperform the Guardian REAL-Time® current sensor to a significant degree. If this occurs, the Steering Committee will evaluate the new technology, and if it is judged to enhance the ability of the protocol to control blood glucose and avoid hypoglycemia to a significant degree, propose adoption of the new device to the DSMB.

Unblinded Assessment

Inclusion and exclusion criteria and outcome measures are designed to be as objective as possible since it is not possible to blind the clinical teams to treatment assignment. However, SC-CUMC research staff completing post-discharge quality of life and emotional health assessments are blinded to treatment assignment during their evaluation.

Impact of Changes in Pediatric Critical Care Management Over Time on Outcome Measures

The impact of changes in pediatric critical care management is expected to affect both groups equally so should not bias treatment group comparisons. Including approximately 20 ICUs will decrease the duration of the study to the shortest time possible that would still allow a change in practice to be evaluated.

**E. Specimen Handling**

In an attempt to avoid CVL-associated bloodstream infections, BGs for purposes of the trial will not be drawn from the central venous line unless the line is being entered for other reasons, such as replacement of IV fluids. Blood samples will be drawn from pre-existing vascular access 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.

Blood compartment or sample site (arterial, venous, or capillary) will be recorded at the time of patient entry and at the time of any reported adverse event. Subjects with an arterial line in use or planned for use in clinical care will have all glucose measurements drawn from the arterial line. If no arterial line is in place, blood will be drawn from a capillary blood compartment from a peripheral stick. No new lines will be placed solely for the purposes of the study.

**F. Study Drugs or 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 manufacturers’ guidelines prior to using devices in the study. Each institution’s IRB, either directly or indirectly (if responsibility is ceded to CHB IRB), addresses all local administrative and regulatory requirements, using common tools and language distributed by the CCC.

In all cases, there exist multiple FDA-approved products available in the class of devices noted. The specific devices were chosen based upon careful review by the CCC but are subject to change if a new and improved product becomes available. In several cases, after having been chosen, the product’s manufacturer has agreed to donate devices and training to the study.

***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 monitoring system 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. All therapy adjustments are based on measurements obtained using either the local hospital laboratory or the official glucose meter for the HALF-PINT study, the NOVA StatStrip® glucose meter. The Guardian REAL-Time® CGM System represents only an added layer for safety in order to prevent severe hypoglycemia. It is for these reasons that the CGM system has been considered a non-significant risk (NSR) device in a nearly identical study in 980 cardiac ICU patients below the age of 3 years led by Dr. Agus. More complete discussion of the NSR status of the CGM system is available as a guidance document for sites as part of the manual of operations.

***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). (<http://www.accessdata.fda.gov/cdrh_docs/reviews/K060345.pdf>). It uses glucose oxidase technology and an electrochemical biosensor to provide a plasma equivalent blood glucose concentration in 1.3 uL of whole blood within 6 seconds over a glucose measurement range of 20-600 mg/dL (0.9-33.3 mmol/L). The StatStrip® device measures and eliminates hematocrit interferences and is accurate over a hematocrit range of 30-60 percent.

***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 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=81342>).

**G. Follow-up Study Instruments**

Neurobehavioral, adaptive functioning, and quality of life are assessed at baseline (CBCL, PedsQL) and one year after ICU hospitalization (Vineland-II, CBCL, PedsQL). Baseline measures are assessed by having the family complete paper questionnaires during the ICU stay. The goal of baseline data collection is to assess pre-ICU health and quality of life. One-year follow-up measures are administered by mail and telephone interview to the parent/guardian by a central testing group from the SC-CUMC. The measures are as follows:

***The composite score of the Vineland Adaptive Behavior Scales-II (Vineland-II)***

Vineland-II represents a valid and reliable test to measure a child's adaptive level of functioning. Vineland-II forms are the most accepted evaluation of developmental neurobehavioral outcomes (26, 173). As with the original VABS, the content and scales of Vineland-II are organized within three domains (Communication, Daily Living, and Socialization), and there is a composite score. This structure corresponds to the three broad domains of adaptive functioning recognized by the American Association of Mental Retardation (174). In addition, the Vineland-II offers a Motor Skills Domain and a Maladaptive Behavior Index to provide more in-depth information on behavior. The Vineland-II has high validity (r = 0.90 to 0.99 for all domains and the composite score) with high test-retest reliability (r = 0.81 to 0.88). Normative data are available on children from birth through adulthood with one version for all ages. Overall, the Vineland-II is useful in assessing an individual's daily functioning and has been validated in relevant groups of impaired children. It has been found to be a sensitive measure of adaptive difficulties experienced after traumatic brain injury (175, 176), circulatory arrest (177, 178), and surgical repair of congenital heart defects (179).

***The Child Behavior Checklist (CBCL)***

The Child Behavior Checklist (CBCL) is an empirically based set of measures for normative behavior using caregiver reports of children; there are two versions, one assesses children aged 2 to 3 years (27) and the other aged 4-18 years (192). Domains of measurement include: Social Withdrawal, Somatic Complaints, Anxiety/Depression, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior. In addition, the CBCL examines the areas of Internalizing and Externalizing Problems. The CBCL is valid (r= 0.59 to 0.86) with high test-retest reliability (r = 0.87 to 0.89). Use of the CBCL adds to the Vineland-II data in that the CBCL reports on more normative behaviors.

***The Pediatric Quality of Life Inventory (PedsQL)***

The Pediatric Quality of Life Inventory (PedsQL) for children and adolescents ages 2 to 18 years uses caregiver reports. The PedsQL is organized within four domains (Physical, Emotional, Social, and School), and there is a total score (28). The test is reliable (Crohnbach's alpha = 0.88 to 0.90 for the Total Score) with high validity (r = 0.83). The PedsQL has been used in healthy school and community populations (28), as well as pediatric populations with acute and chronic health conditions including cardiac and respiratory disease (180, 181).

**H. Privacy Protections**

Identifying data will not be published. Identifying data are kept in separate, locked storage as described. Such protection will cover all screening, recruitment, enrollment, operations, and follow-up activities.

**I. Potential Risks**

The predominant risk of the study is the induction of hypoglycemia. As described elsewhere, RCTs of TGC in adults have consistently resulted in high SH rates, more than 20-30% of subjects in some studies (13, 102). Published data from the Yale pediatric ICU demonstrate the rate of spontaneous mild hypoglycemia (<60 mg/dL) to be 7.5% and severe hypoglycemia (<40 mg/dL) to be 2.2% (16). Experience at Columbia University Medical Center has demonstrated a spontaneous mild hypoglycemia rate of 11.7% and a spontaneous rate of SH of 3.2% in a selected population of patients with 48 hours or greater ICU LOS (191). The methodology of HALF-PINT centers on minimizing the risk of hypoglycemia by using CGM as an added alarm system and an explicit insulin titration algorithm to give nurses specific guidance about frequency of BG checks and insulin infusion doses. Using these methods in the ongoing SPECS trial of TGC at CHB, the rate of SH was 3.2% in the TGC group after the accrual of 755 subjects in the trial (unpublished data). Though this trial involves a population (children with congenital heart disease undergoing corrective procedures using cardiopulmonary bypass) with greater severity of illness than the average ICU population, the SH rate is below that 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 insertions in 755 children less than 3 years of age.

**J. Data and Safety Monitoring**

The DCC presents to the Data and Safety Monitoring Board (DSMB), an independent board recruited and coordinated by NHLBI. After approving the protocol, the DSMB meets after the first 50 randomized subjects have been studied and then approximately every 6 months until the end of the study (see Figure 2), or as requested by the DSMB.

The DCC schedules and sets up all DSMB meetings, in the format of conference calls. Before each DSMB meeting, the DCC Biostatistician prepares a written report. The report includes the following topics (plus any other topics requested by DSMB):

1. Update on overall status of the study, recruitment, and accrual
2. Summary of baseline demographic and clinical characteristics
3. Information on data completeness, data quality, protocol compliance, site monitoring, and other quality-control measures
4. Statistical summary of adverse events
5. Statistical summary of primary and key secondary outcome variables

**Figure 2.** Five Year Study Plan. DSMB = Data Safety and Monitoring Board; CRF = Case Report Form; E&AER = Enrollment and adverse event review



These topics are grouped into an open section containing information to which the CCC PIs are not blinded (items up to adverse events and summary of outcome variables in the combined treatment groups) and a closed section containing information to which the investigators are blinded (outcome variables and events broken down by treatment). The full report is distributed to the DSMB and the open section of the report to the CCC PIs one week in advance of the meeting and then reviewed during the meeting. The CCC PIs participate in the first part of DSMB meetings to present the open section of the report and answer questions from the DSMB and then are excused for the closed session. The DCC PI and Biostatistician present data in the closed section. After each meeting, the DSMB makes a statement regarding the quality of the study and safety of participants and writes a brief recommendation either to continue the study without changes, modify the study in specific ways, or discontinue the study. This recommendation is submitted by the Site Directors to the IRBs at or prior to the next annual IRB review of the study. Final decisions regarding interim analysis plans are made in consultation with the DSMB, but we anticipate that the first interim look for potential early stopping for efficacy or futility occurs after half of the study subjects have outcome variables.

**K. Potential Benefits**

Potential direct benefits of the intervention (TGC-1) 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 TGC.

**L. Alternatives**

The alternative to participation in this study is non-participation. Usual ICU care for children with hyperglycemia and cardiac and/or respiratory failure will be provided to those children whose parents/guardians elect to not give consent for their child's participation. Such care may involve the use of insulin infusion and will be administered at the direction of the treating attending physician.

M. References

1. Heron M, Sutton PD, Xu J, Ventura SJ, Strobino DM, Guyer B. Annual summary of vital statistics: 2007. Pediatrics. 2010;125(1):4-15.

2. Vernon DD, Dean JM, Timmons OD, Banner W, Jr., Allen-Webb EM. Modes of death in the pediatric intensive care unit: withdrawal and limitation of supportive care. Crit Care Med. 1993;21(11):1798-802.

3. Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC. Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med. 2005;6(4):470-2.

4. Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. Journal of Pediatrics. 2005;146(1):304.

5. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med. 2008;9(4):361-6.

6. Polito A, Thiagarajan RR, Laussen PC, Gauvreau K, Agus MS, Scheurer MA, Pigula FA, Costello JM. Association between intraoperative and early postoperative glucose levels and adverse outcomes after complex congenital heart surgery. Circulation. 2008;118(22):2235-42.

7. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatr Crit Care Med. 2004;5(4):329.

8. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med.2004;30(5):748-56.

9. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med. 2005;33(12):2772-7.

10. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. Endocrine Practice. 2004;10 Suppl 2:21-33.

11. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. Journal of Thoracic & Cardiovascular Surgery. 2003;125(5):1007-21.

12. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedure. Annals of Thoracic Surgery. 1999;67(2):352-60; discussion 60-2.

13. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-67.

14. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.

15. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.

16. Faustino EV, Bogue CW. Relationship between hypoglycemia and mortality in critically ill children. Pediatr Crit Care Med. 2010;11(6):690-8.

17. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547-56.

18. Agus MSD, Javid PJ, Piper HG, Modi BP, Duggan CP, Ryan DP, Jaksic T. The Effect of Insulin Infusion Upon Protein Metabolism in Neonates on Extracorporeal Life Support. Annals of Surgery. 2006;244(4):536-44.

19. Hirshberg E, Lacroix J, Sward K, Willson D, Morris AH. Blood glucose control in critically ill adults and children: a survey on stated practice. Chest. 2008;133(6):1328-35.

20. Piper HG, Alexander JA, Shukla A, Pigula F, Costello J, Laussen PC, Jaksic T, Agus MS. Real-time continuous glucose monitoring in pediatric cardiac surgery patients. Pediatrics. 2006;118(3):1176-84.

21. Srinivasan V, Drott H, Hutchins L, Roth C, Helfaer M, Nadkarni V. Hypoglycemia in critically ill children has increased in association with the practice of glycemic control in the ICU. Pediatr Crit Care Med. 2006;7(5):516.

22. Steil GM, Agus MS. Critical illness hyperglycemia: is failure of the beta-cell to meet extreme insulin demand indicative of dysfunction? Crit Care. 2009;13(2):129. PMCID: 2689480.

23. Steil GM, Deiss D, Shih J, Buckingham B, Weinzimer S, Agus MS. Intensive Care Unit Insulin Delivery Algorithms: Why So Many? How to Choose? J Diabetes Sci Technol. 2009;3(1):125-40. PMCID: 2768418.

24. Faraon-Pogaceanu C, Banasiak KJ, Hirshberg EL, Faustino EV. Comparison of the effectiveness and safety of two insulin infusion protocols in the management of hyperglycemia in critically ill children. Pediatr Crit Care Med. 2010;11(6):741-9.

25. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple Organ Dysfunction Score: A reliable descriptor of a complex clinical outcome. Critical Care Medicine. 1995;23(10):1638-52.

26. Sparrow SS, Cicchetti DV. Diagnostic uses of the Vineland Adaptive Behavior Scales. Journal of Pediatric Psychology. 1985;10(2):215-25.

27. Achenbach TM. Manual for Child Behavior Checklist/ 4-18 and 1991 Profile. Burlington, VT: University of Vermont, Dept. of Psychiatry; 1999.

28. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39(8):800-12.

29. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Ahluwalia JS, Vanhole C, Palmer C, Midgley P, Thompson M, Cornette L, Weissenbruch M, Thio M, de Zegher F, Dunger D. A randomised controlled trial of early insulin therapy in very low birth weight infants, "NIRTURE" (neonatal insulin replacement therapy in Europe). BMC Pediatr. 2007;7:29. PMCID: 1994677.

30. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125-39.

31. Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chiolero R. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35(10):1738-48.

32. Furnary AP, Wu Y. Eliminating the diabetic disadvantage: the Portland Diabetic Project. Semin Thorac Cardiovasc Surg. 2006;18(4):302-8.

33. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992-1000.

34. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg. 2006;18(4):317-25.

35. Scalea TM, Bochicchio GV, Bochicchio KM, Johnson SB, Joshi M, Pyle A. Tight glycemic control in critically injured trauma patients. Ann Surg. 2007;246(4):605-10; discussion 102.

36. Treggiari MM, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. Crit Care. 2008;12(1):R29. PMCID: 2374630.

37. Bagshaw SM, Egi M, George C, Bellomo R. Early blood glucose control and mortality in critically ill patients in Australia. Crit Care Med. 2009;37(2):463-70.

38. Arabi YM, Dabbagh OC, Tamim HM, Al-ShimemeriAA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36(12):3190-7.

39. De La Rosa Gdel C, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, Bedoya M, Toro JM, Velasquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomized clinical trial. Crit Care. 2008;12(5):R120. PMCID: 2592751.

40. Farah R, Samokhvalov A, Zviebel F, Makhoul N. Insulin therapy of hyperglycemia in intensive care. Isr Med Assoc J. 2007;9(3):140-2.

41. Gandhi GY, Murad MH, Flynn DN, Erwin PJ, Cavalcante AB, Bay Nielsen H, Capes SE, Thorlund K, Montori VM, Devereaux PJ. Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and Meta-analysis of randomized trials.Mayo Clin Proc. 2008;83(4):418-30.

42. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821-7. PMCID: 2665940.

43. Pittas AG, Siegel RD, Lau J. Insulin therapy and in-hospital mortality in critically ill patients: systematic review and meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr. 2006;30(2):164-72.

44. Ruttimann UE, Pollack MM. Variability in duration of stay in pediatric intensive care units: a multi-institutional study. J Pediatr. 1996;128(1):35-44.

45. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med.2003;29(2):278-85.

46. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L. Randomized trial of Insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year [see comments]. J Am Coll Cardiol. 1995;26(1):57-65.

47. Jakus V, Rietbrock N. Advanced glycation end-products and the progress of diabetic vascular complications. Physiol Res. 2004;53(2):131-42.

48. Makita Z, Yanagisawa K, Kuwajima S, Yoshioka N, Atsumi T, Hasunuma Y, Koike T. Advanced glycation endproducts and diabetic nephropathy. Journal of diabetes and its complications. 1995;9(4):265-8.

49. Bonnardel-Phu E, Wautier JL, Schmidt AM, Avila C, Vicaut E. Acute modulation of albumin microvascular leakage by advanced glycation end products in microcirculation of diabetic rats in vivo. Diabetes. 1999;48(10):2052-8.

50. Bonnefont-Rousselot D. Glucose and reactive oxygen species. Current opinion in clinical nutrition and metabolic care. 2002;5(5):561-8.

51. Wautier JL, Wautier MP, Schmidt AM, Anderson GM, Hori O, Zoukourian C, Capron L, Chappey O, Yan SD, Brett J, et al. Advanced glycation end products (AGEs) on the surface of diabetic erythrocytes bind to the vessel wall via a specific receptor inducing oxidant stress in the vasculature: a link between surface-associated AGEs and diabetic complications. Proceedings of the National Academy of Sciences of the United States of America. 1994;91 (16):7742-6.

52. Yan SD, Schmidt AM, Anderson GM, Zhang J, Brett J, Zou YS, Pinsky D, Stern D. Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. The Journal of biological chemistry. 1994;269(13):9889-97.

53. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37(12):3001-9.

54. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. Jama. 2003;290 (15):2041-7.

55. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE. Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest. 2005;128(5):3109-16.

56. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78(12):1471-8.

57. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978-82.

58. Altannavch TS, Roubalova K, Kucera P, Andel M. Effect of high glucose concentrations on expression of ELAM-1, VCAM-1and ICAM-1in HUVEC with and without cytokine activation. Physiol Res. 2004;53(1):77-82.

59. Cai L, Li W, Wang G, Guo L, Jiang Y, Kang YJ. Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. Diabetes. 2002;51(6):1938-48.

60. Dhindsa S, Tripathy D, Mohanty P, Ghanim H, Syed T, Aljada A, Dandona P. Differential effects of glucose and alcohol on reactive oxygen species generation and intranuclear nuclear factor-kappaB in mononuclear cells. Metabolism. 2004;53(3):330-4.

61. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation. 2002;106(16):2067-72.

62. Gallacher SJ, Thomson G, Fraser WD, Fisher BM, Gemmell CG, MacCuish AC. Neutrophil bactericidal function in diabetes mellitus: evidence for association with blood glucose control. Diabet Med. 1995;12(10):916-20.

63. Kado S, Wakatsuki T, Yamamoto M, Nagata N. Expression of intercellular adhesion molecule-1 induced by high glucose concentrations in human aortic endothelial cells. Life Sci. 2001;68(7):727-37.

64. Krogh-Madsen R, Moller K, Dela F, Kronborg G, Jauffred S, Pedersen BK. Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF-alpha and FFAs to low-dose endotoxemia in humans. Am J Physiol Endocrinol Metab. 2004;286(5):E766-72.

65. Liu BF, Miyata S, Kojima H, Uriuhara A, Kusunoki H, Suzuki K, Kasuga M. Low phagocytic activity of resident peritoneal macrophages in diabetic mice: relevance to the formation of advanced glycation end products. Diabetes. 1999;48(10):2074-82.

66. Marfella R, Esposito K, Giunta R, Coppola G, De Angelis L, Farzati B, Paolisso G, Giugliano D. Circulating adhesion molecules in humans: role of hyperglycemia and hyperinsulinemia. Circulation. 2000;101(19):2247-51.

67. Marfella R, Siniscalchi M, Esposito K, Sellitto A, De Fanis U, Romano C, Portoghese M, Siciliano S, Nappo F, Sasso FC, Mininni N, Cacciapuoti F, Lucivero G, Giunta R, Verza M, Giugliano D. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. Diabetes Care. 2003;26(11):3129-35.

68. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes Care. 1992;15(2):256-60.

69. Nielson CP, Hindson DA. Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentrations in vitro. Diabetes. 1989;38(8):1031-5.

70. Rao AK, Chouhan V, Chen X, Sun L, Boden G. Activation of the tissue factor pathway of blood coagulation during prolonged hyperglycemia in young healthy men. Diabetes. 1999;48(5):1156-61.

71. Santilli F, Cipollone F, Mezzetti A, Chiarelli F. The role of nitric oxide in the development of diabetic angiopathy. Horm Metab Res. 2004;36(5):319-35.

72. Schiekofer S, Balletshofer B, Andrassy M, Bierhaus A, Nawroth PP. Endothelial dysfunction in diabetes mellitus. Seminars in thrombosis and hemostasis. 2000;26(5):503-11.

73. Wasmuth HE, Kunz D, Graf J, Stanzel S, Purucker EA, Koch A, Gartung C, Heintz B, Gressner AM, Matern S, Lammert F. Hyperglycemia at admission to the intensive care unit is associated with elevated serum concentrations of interleukin-6 and reduced ex vivo secretion of tumor necrosis factor-alpha. Crit Care Med. 2004;32(5):1109-14.

74. Wierusz-Wysocka B, Wysocki H, Wykretowicz A, Klimas R. The influence of increasing glucose concentrations on selected functions of polymorphonuclear neutrophils. Acta Diabetol Lat. 1988;25(4):283-8.

75. Weekers F, Giulietti AP, Michalaki M, Coopmans W, Van Herck E, Mathieu C, Van den Berghe G. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. Endocrinology. 2003;144(12):5329-38.

76. Hennessey PJ, Ford EG, Black CT, Andrassy RJ. Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats. J Pediatr Surg. 1990;25(1):75-8.

77. Hreiche R, Plante I, David LP, Simard C, Turgeon J, Drolet B. Impact of glucose concentration on cardiac ventricular repolarization under I Kr/I Ks blocking agents. J Mol Cell Cardiol. 2009;47(2):210-20.

78. Joyner NT, Smoak IW. In vivo hyperglycemia and its effect on Glut-1 expression in the embryonic heart. Birth Defects Res A Clin Mol Teratol. 2004;70(7):438-48.

79. Vanhorebeek I, Ingels C, Van den Berghe G. Intensive insulin therapy in high-risk cardiac surgery patients: evidence from the Leuven randomized study. Semin Thorac Cardiovasc Surg. 2006;18(4):309-16.

80. Vanhorebeek I, Gunst J, Ellger B, Boussemaere M, Lerut E, Debaveye Y, Rabbani N, Thornalley PJ, Schetz M, Van den Berghe G. Hyperglycemic kidney damage in an animal model of prolonged critical illness. Kidney Int. 2009;76 (5):512-20.

81. Mesotten D, Delhanty PJ, Vanderhoydonc F, Hardman KV, Weekers F, Baxter RC, Van Den Berghe G. Regulation of insulin-like growth factor binding protein-1 during protracted critical illness. Journal of Clinical Endocrinology & Metabolism. 2002;87(12):5516-23.

82. Agus MS, Javid PJ, Ryan DP, Jaksic T. Intravenous insulin decreases protein breakdown in infants on extracorporeal membrane oxygenation. J Pediatr Surg. 2004;39(6):839-44; discussion -44.

83. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003;31(2):359-66.

84. Hirsch IB. Effect of insulin therapy on nonglycemic variables during acute illness. Endocr Pract. 2004;10 Suppl 2:63-70.

85. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Insulin as an anti-inflammatory and antiatherogenic modulator. J Am Coll Cardiol. 2009;53(5 Suppl):S14-20.

86. Ghanim H, Aljada A, Daoud N, Deopurkar R, Chaudhuri A, Dandona P. Role of inflammatory mediators in the suppression of insulin receptor phosphorylation in circulating mononuclear cells of obese subjects. Diabetologia. 2007;50(2):278-85.

87. Ghanim H, Korzeniewski K, Sia CL, Abuaysheh S, Lohano T, Chaudhuri A, Dandona P. Suppressive effect of insulin infusion on chemokines and chemokine receptors. Diabetes Care. 2010;33(5):1103-8. PMCID: 2858184.

88. Dandona P, Mohanty P, Chaudhuri A, Garg R, Aljada A. Insulin infusion in acute illness. J Clin Invest. 2005;115(8):2069-72. PMCID: 1180564.

89. Koskenkari JK, Kaukoranta PK, Kiviluoma KT, Raatikainen MJ, Ohtonen PP, Ala-Kokko TI. Metabolic and hemodynamic effects of high-dose insulin treatment in aortic valve and coronary surgery. Ann Thorac Surg. 2005;80 (2):511-7.

90. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation. 2004;109(12):1497-502.

91. Quinn DW, Pagano D, Bonser RS. Glucose and insulin influences on heart and brain in cardiac surgery. Semin Cardiothorac Vasc Anesth. 2005;9(2):173-8.

92. Quinn DW, Pagano D, Bonser RS, Rooney SJ, Graham TR, Wilson IC, Keogh BE, Townend JN, Lewis ME, Nightingale P. Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: a randomized controlled trial. J Thorac Cardiovasc Surg. 2006;131(1):34-42.

93. Bothe W, Olschewski M, Beyersdorf F, Doenst T. Glucose-insulin-potassium in cardiac surgery: a meta-analysis. Ann Thorac Surg. 2004;78(5):1650-7.

94. Preiser JC, Devos P. Clinical experience with tight glucose control by intensive insulin therapy. Crit Care Med. 2007;35(9 Suppl):S503-7.

95. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg. 1999;89(5):1091-5.

96. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med. 2007;35(10):2262-7.

97. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008;300(8):933-44.

98. Agus MS, Hirshberg EL. Pediatrics: Intensive insulin therapy in critically ill children. Nat Rev Endocrinol. 2009;5(7):360-2.

99. Inzucchi SE, Siegel MD. Glucose control in the ICU—how tight is too tight? N Engl J Med. 2009;360(13):1346-9.

100. Vogelzang M, Ligtenberg JJ. Practical aspects of implementing tight glucose control in the ICU. Current opinion in clinical nutrition and metabolic care. 2007;10(2):178-80.

101. Nayak P, Lang H, Parslow R, Davies P, Morris K. Hyperglycemia and insulin therapy in the critically ill child. Pediatr Crit Care Med. 2009;10(3):303-5.

102. Grey NJ, Perdrizet GA. Reduction of nosocomial infections in the surgical intensive-care

unit by strict glycemic control. Endocr Pract. 2004;10 Suppl 2:46-52.

103. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics. 2000;105 (5):114-15.

104. Hermanides J, Bosman RJ, Vriesendorp TM, Dotsch R, Rosendaal FR, Zandstra DF, Hoekstra JBL, DeVries JH. Hypoglycemia is associated with intensive care unit mortality. Critical Care Medicine. 2010;38(6):1430-4.

105. de Ferranti S, Gauvreau K, Hickey PR, Jonas RA, Wypij D, du Plessis A, Bellinger DC, Kuban K, Newburger JW, Laussen PC. Intraoperative hyperglycemia during infant cardiac surgery is not associated with adverse neurodevelopmental outcomes at 1, 4, and 8 years. Anesthesiology. 2004;100(6):1345-52.

106. Cheyne EH, Cavan DA, Kerr D. Performance of a continuous glucose monitoring system during controlled hypoglycaemia in healthy volunteers. Diabetes Technol Ther. 2002;4(5):607-13.

107. Piper HG, Alexander JA, Shukla A, Costello J, Laussen PC, Pigula F, Jaksic T, Agus MS. Continuous glucose monitoring in pediatric cardiac surgery patients. Horm Res. 2005;64(Suppl. 1):160.

108. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9. PMCID: 2797383.

109. Rake AJ, Srinivasan V, Nadkarni V, Kaptan R, Newth CJ. Glucose variability and survival in critically ill children: allostasis or harm? Pediatr Crit Care Med. 2010;11(6):707-12.

110. Faustino EV, Apkon, M. Persistent hyperglycemia in critically ill children. J Pediatr. 2005;146(1):30-4.

111. Kanderian S, Steil GM, inventors; Medtronic Minimed, Inc, assignee. Apparatus and method for controlling insulin infusion with state variable feedback. US. 2007.

112. Steil GM, Kanderian S, Cantwell MT, Hoss U, inventors; Medtronic Minimed, Inc, assignee. Model predictive method for controlling and supervising insulin infusion. US. 2008.

113. Steil GM, Rebrin K, inventors; Medtronic Minimed, Inc, assignee. Closed-loop method for controlled insulin infusion. US. 2004.

114. Keenan DB, Mastrototaro JJ, Voskanyan G, Steil GM. Delays in minimally invasive continuous glucose monitoring devices: a review of current technology. J Diabetes Sci Technol. 2009;3(5):1207-14. PMCID: 2769894.

115. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PG, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. Intensive Care Med. 2009;35(8):1383-9.

116. Joseph JI, Hipszer B, Mraovic B, Chervoneva I, Joseph M, Grunwald Z. Clinical need for continuous glucose monitoring in the hospital. J Diabetes Sci Technol. 2009;3(6):1309-18. PMCID: 2787031.

117. Mraovic B. Analysis: Continuous glucose monitoring during intensive insulin therapy. J Diabetes Sci Technol. 2009;3(4):960-3. PMCID: 2769950.

118. Holzinger U, Warszawska J, Kitzberger R, Wewalka M, Miehsler W, Herkner H, Madl C. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. Diabetes Care. 2010;33(3):467-72. PMCID: 2827490.

119. Jacobs B, Bertheau L, Dogbey G, Schwartz F, Shubrook J. Continuous Glucose Monitoring System in a Rural Intensive Care Unit: A Pilot Study Evaluating Accuracy and Acceptance. J Diabetes Sci Technol. 2010;4(3):636-44.

120. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000;2(3):461-72.

121. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. Am J Physiol. 1999;277(3 Pt 1):E561-71.

122. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. Diabetologia. 2005;48(9):1833-40.

123. Steil GM, Rebrin K, Mastrototaro J, Bernaba B, Saad MF. Determination of plasma glucose during rapid glucose excursions with a subcutaneous glucose sensor. Diabetes Technol Ther. 2003;5(1):27-31.

124. Bequette BW. Continuous Glucose Monitoring: Real-Time Algorithms for Calibration, Filtering, and Alarms. J Diabetes Sci Technol. 2010;4(2):404-18.

125. Facchinetti A, Sparacino G, Cobelli C. Enhanced accuracy of continuous glucose monitoring by online extended kalman filtering. Diabetes Technol Ther. 2010;12(5):353-63.

126. Panteleon AE, Rebrin K, Steil GM. The role of the independent variable to glucose sensor calibration. Diabetes Technol Ther. 2003;5(3):401-10.

127. Wintergerst KA, Deiss D, Buckingham B, Cantwell M, Kache S, Agarwal S, Wilson DM, Steil G. Glucose control in pediatric intensive care unit patients using an insulin-glucose algorithm. Diabetes Technol Ther. 2007;9 (3):211-22.

128. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery-the path to physiological glucose control. Advanced Drug Delivery Reviews. 2004;56(2):125-44.

129. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes. 2006;55(12):3344-50.

130. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care. 2008;31(5):934-9.

131. Cohen E, Goldman RD, Ragone A, Uleryk E, Atenafu EG, Siddiqui U, Mahmoud N, Parkin PC. Child vs adult randomized controlled trials in specialist journals: a citation analysis of trends, 1985-2005. Arch Pediatr Adolesc Med. 2010;164(3):283-8.

132. Morris AH, Hirshberg E, Sward KA. Computer protocols: how to implement. Best Pract Res Clin Anaesthesiol. 2009;23(1):51-67.

133. Morris AH, Orme J, Rocha BH, Holmen J, Clemmer T, Nelson N, Allen J, Jephson A, Sorenson D, Sward K, Warner H. An electronic protocol for translation of research results to clinical practice: a preliminary report. J Diabetes Sci Technol. 2008;2(5):802-8. PMCID: 2769803.

134. Morris AH. Tools for rigorous experiments in the usual clinical environment. Crit Care Med. 2007;35(7):1776-7.

135. Thompson BT, Orme JF, Zheng H, Luckett PM, Truwit JD, Willson DF, Duncan Hite R, Brower RG, Bernard GR, Curley MA, Steingrub JS, Sorenson DK, Sward K, Hirshberg E, Morris AH. Multicenter validation of a Computer-based clinical decision support tool for glucose control in adult and pediatric intensive care units. J Diabetes Sci Technol. 2008;2(3):357-68. PMCID: 2769731.

136. Morris AH, Orme J, Jr., Truwit JD, Steingrub J, Grissom C, Lee KH, Li GL, Thompson BT, Brower R, Tidswell M, Bernard GR, Sorenson D, Sward K, Zheng H, Schoenfeld D, Warner H. A replicable method for blood glucose control in critically Ill patients. Crit Care Med. 2008;36(6):1787-95.

137. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, Luckett PM, Forbes P, Lilley M, Thompson J, Cheifetz IM, Hibberd P, Wetzel R, Cox PN, Arnold JH. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288(20):2561-8.

138. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics. 2006;118(1):173-9.

139. Yates AR, Dyke PC, 2nd, Taeed R, Hoffman TM, Hayes J, Feltes TF, Cua CL. Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. Pediatr Crit Care Med. 2006;7(4):351-5.

140. Chiaretti A, De Benedictis R, Langer A, Di Rocco C, Bizzarri C, Iannelli A, Polidori G. Prognostic implications of hyperglycaemia in paediatric head injury. Childs Nerv Syst. 1998;14(9):455-9.

141. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. Mayo Clin Proc. 1996;71(8):801-12.

142. Michaud LJ, Rivara FP, Longstreth WT, Jr., Grady MS. Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. J Trauma. 1991;31(10):1356-62.

143. Cochran A, Scaife ER, Hansen KW, Downey EC. Hyperglycemia and outcomes from pediatric traumatic brain injury. J Trauma. 2003;55(6):1035-8.

144. Paret G, Barzilai A, Lahat E, Feldman Z, Ohad G, Vardi A, Ben-Abraham R, Barzilay Z. Gunshot wounds in brains of children: prognostic variables in mortality, course, and outcome. J Neurotrauma. 1998;15(11):967-72.

145. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma. 2001;51(3):540-4.

146. Hall NJ, Peters M, Eaton S, Pierro A. Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis. Journal of Pediatric Surgery. 2004;39(6):898-901.

147. Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V, Kennedy KA. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol. 2006;26(12):730-6.

148. Blanco CL, Baillargeon JG, Morrison RL, Gong AK. Hyperglycemia in extremely low birth weight infants in a predominantly Hispanic population and related morbidities. J Perinatol. 2006;26(12):737-41.

149. Alaedeen DI, Walsh MC, Chwals WJ. Total parenteral nutrition-associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. J Pediatr Surg. 2006;41(1):239-44; discussion -44.

150. Ertl T, Gyarmati J, Gaal V, Szabo I. Relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Biol Neonate. 2006;89(1):56-9.

151. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birthweight infants. J Perinatol. 2003;23(3):186-94.

152. Jeschke MG, Kulp GA, Kraft R, Finnerty CC, Mlcak R, Lee JO, Herndon DN. Intensive Insulin Therapy in Severely Burned Pediatric Patients: A Prospective Randomized Trial. Am J Respir Crit Care Med. 2010.

153. Pearson GA, Stickley J, Shann F. Calibration of the paediatric index of mortality in UK paediatric intensive care units. Arch Dis Child. 2001;84(2):125-8. PMCID: 1718658.

154. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med. 1997;23(2):201-7.

155. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, Gottesman R, Joffe A, Pfenninger J, Hubert P, Lacroix J, Leclerc F. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet. 2003;362(9379):192-7.

156. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996;24(5):743-52.

157. Parslow RC, Tasker RC, Draper ES, Parry GJ, Jones S, Chater T, Thiru K, McKinney PA. Epidemiology of critically ill children in England and Wales: incidence, mortality, deprivation and ethnicity. Arch Dis Child. 2009;94 (3):210-5.

158. van Waardenburg DA, Jansen TC, Vos GD, Buurman WA. Hyperglycemia in children with meningococcal sepsis and septic shock: the relation between plasma levels of insulin and inflammatory mediators. J Clin Endocrinol Metab. 2006;91(10):3916-21.

159. Xu F, Yang X, Lu Z, Kuang F. Evaluation of glucose metabolic disorder: insulin resistance and insulin receptors in critically ill children. Chin Med J (Engl). 1996;109(10):807-9.

160. Gaster M, Handberg A, Beck-Nielsen H, Schroder HD. Glucose transporter expression in human skeletal muscle fibers. Am J Physiol Endocrinol Metab. 2000;279(3):E529-38.

161. Santalucia T, Camps M, Castello A, Munoz P, Nuel A, Testar X, Palacin M, Zorzano A. Developmental regulation of GLUT-1 (erythroid/Hep G2) and GLUT-4 (muscle/fat) glucose transporter expression in rat heart, skeletal muscle, and brown adipose tissue. Endocrinology. 1992;130(2):837-46.

162. Postic C, Leturque A, Printz RL, Maulard P, Loizeau M, Granner DK, Girard J. Development and regulation of glucose transporter and hexokinase expression in rat. Am J Physiol. 1994;266(4 Pt 1):E548-59.

163. Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. J Pediatr. 2004;144(6):792-8.

164. Lacroix J, Cotting J. Severity of illness and organ dysfunction scoring in children. Pediatr Crit Care Med. 2005;6(3 Suppl):S126-34.

165. Leclerc F, Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Martinot A, Gauvin F, Hubert P, Lacroix J. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. Am J Respir Crit Care Med. 2005;171(4):348-53.

166. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest. 1996;109(4):1033-7.

167. Desmet L, Lacroix J. Transfusion in pediatrics. Crit Care Clin. 2004;20(2):299-311.

168. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772-7.

169. Chandra RK. Nutrition and immune responses. Can J Physiol Pharmacol. 1983;61(3):290-4.

170. Daoud AK, Tayyar MA, Fouda IM, Harfeil NA. Effects of diabetes mellitus vs. in vitro hyperglycemia on select immune cell functions. J Immunotoxicol. 2009;6(1):36-41.

171. Turina M, Fry DE, Polk HC, Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. Critical Care Medicine. 2005;33(7):1624-33.

172. CDC. CDC Nosocomial Infection Definitions. 2005 [updated 2005; cited]; Available from: http://www.cdc.gov/ncidod/hip/NNIS/NosInfDefinitions.pdf.

173. Sparrow SS, Balla DA, Cicchetti DV. Vineland adaptive behavior scales: Circle Pines, MN: American Guidance Service; 1984.

174. AAMR. Conceptual, Practical, and Social: American Association on Mental Retardation; 2002 Contract No.: Document Number|.

175. Biagas K, DGoudreau, Dorman R, Gurland S, Sparrow S, editors. Long-term functional outcome in children with traumatic brain injury. Pediatric Critical Care Colloquium; 1996; Milwaukee.

176. Fletcher JM, Ewing-Cobbs L, Miner ME, Levin HS, Eisenberg HM. Behavioral changes after closed head injury in children. J Consult Clin Psychol. 1990;58(1):93-8.

177. Bloom AA, Wright JA, Morris RD, Campbell RM, Krawiecki NS. Additive impact of in-hospital cardiac arrest on the functioning of children with heart disease. Pediatrics. 1997;99(3):390-8.

178. Morris RD, Krawiecki NS, Wright JA, Walter LW. Neuropsychological, academic, and adaptive functioning in children who survive in-hospital cardiac arrest and resuscitation. J Learn Disabil. 1993;26(1):46-51.

179. Kern JH, Hinton VJ, Nereo NE, Hayes CJ, Gersony WM. Early developmental outcome after the Norwood procedure for hypoplastic left heart syndrome. Pediatrics. 1998;102(5):1148-52.

180. Seid M, Limbers CA, Driscoll KA, Opipari-Arrigan LA, Gelhard LR, Varni JW. Reliability, validity, and responsiveness of the pediatric quality of life inventory (PedsQL) generic core scales and asthma symptoms scale in vulnerable children with asthma. J Asthma. 2010;47(2):170-7.

181. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. Pediatrics. 2008;121(5):e1060-7.

182. Steil GM, Hwu CM, Janowski R, Hariri F, Jinagouda S, Darwin C, Tadros S, Rebrin K, Saad MF. Evaluation of insulin sensitivity and beta-cell function indexes obtained from minimal model analysis of a meal tolerance test. Diabetes. 2004 May;53(5):1201-7. PubMed PMID: 15111487.

183. Dalla Man C, Caumo A, Cobelli C. The oral glucose minimal model: estimation of insulin sensitivity from a meal test. IEEE Trans Biomed Eng. 2002 May;49(5):419-29. PubMed PMID: 12002173.

184. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. Diabetes. 2001 Jan;50(1):150-8. PubMed PMID: 11147781.

185. Caumo A, Bergman RN, Cobelli C. Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. J Clin Endocrinol Metab. 2000 Nov;85(11):4396-402. PubMed PMID: 11095485.

186. Kanderian SS, Weinzimer S, Voskanyan G, Steil GM. Identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. J Diabetes Sci Technol. 2009 Sep 1;3(5):1047-57. PubMed PMID: 20144418.

187. Curley MA, Hibberd PL, Fineman LD, Wypij D, Shih MC, Thompson JE, Grant MJ, Barr FE, Cvijanovich NZ, Sorce L, Luckett PM, Matthay MA, Arnold JH. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. JAMA. 2005;294(2):229-37. PMCID: 1237036.

188. Wiener RS; Wiener DC;. Larson R., Benefits and Risks of Tight Glucose Control in Critically Ill Adults, A Meta-analysis. JAMA. 2008;300(8):933-944.

189. Aragon, D., Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. Am J Crit Care, 2006. 15: p. 370-377.

190. Thompson, BT, Orme, JF, Zheng, H, Luckett, PM, Truwit, JD, Willson, DF, Hite, RD, Brower, RG, Bernard, GR, Curley, MAQ, Steingrub, JS, Sorenson, DF, Sward, K, Hirshberg, E, Morris, AH (2008). Multicenter validation of a computer-based clinical decision support tool for glucose control in adult and pediatric intensive care units. J Diabetes Sci and Technol, 2(3), 57-368. (PMID: 19885199)

191. Ognibene KL, Vawdrey DK, Biagas KV. The association of age, illness severity, and glycemic status in a pediatric intensive care unit. Pediatr Crit Care Med. 2011;12(6):e386-90.

192. Achenbach TM. Manual for the Child Behavior Checklist/2-3 and 1992 Profile. Burlington, VT: University of Vermont Department of Psychiatry; 1992.

193. Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. Diabetes. 1977;26(11):1016-23.

194. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.

195. Pampallona S, Tsiatis AA, Kim K. Spending functions for type I and type II error probabilities of group sequential trials. Boston: Dept. of Biostatistics, Harvard School of Public Health; 1995.

196. Pampallona S, Tsiatis AA, Kim K. Interim monitoring of group sequential trials using spending functions for the type I and type II error probabilities. Drug Information Journal. 2001;35:1113-21.

197. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35(3):549-56.