

Protocol Title:

**Efficacy of Continuous Glucose Monitoring in  
Neonatal Hypoglycemia**

NCT: 02300285

Protocol Date: July 24, 2017

**EFFICACY OF CONTINUOUS GLUCOSE MONITORING IN NEONATAL HYPOGLYCEMIA*****Project Summary:***

*We aim to evaluate the utility of continuous glucose monitors (CGMs) in improving the diagnosis and management of neonatal hypoglycemia in infants admitted to the neonatal intensive care unit (NICU). Specifically, we hope to assess whether the use of CGMs in this population reduces the number of hypoglycemic events, reduces the time to diagnosis of the etiology of hypoglycemia and/or reduces the time taken to achieve stable euglycemia on a sustainable feeding regimen. We plan to perform a prospective randomized controlled pilot study comparing the clinical course and outcomes of newborns with hypoglycemia admitted to the NICU who are actively monitored with CGMs versus those who receive routine care.*

**1. Specific Aims and Objectives**

We seek to improve the management and outcome of neonates diagnosed with hypoglycemia. We hope to accomplish this by using continuous glucose monitors (CGMs) in at-risk infants admitted to the neonatal intensive care unit (NICU). Current management of neonatal hypoglycemia involves intermittent blood sampling, which, unlike CGMs, does not offer real-time blood glucose trends and therefore leaves infants at risk for unrecognized hypoglycemia. Unrecognized hypoglycemia may not only lengthen time to diagnosis and appropriate treatment, but may also lead to poor neurodevelopmental outcomes. Our long-term goal is to assess whether use of CGMs can improve clinical course and outcomes in this population. This pilot study will allow us to test whether it is feasible to perform in larger-scale the proposed randomized, controlled trial comparing a “CGM Protocol” group and a “Standard of Care” group to assess whether use of CGMs in neonates can:

**a) Reduce the number and severity of hypoglycemic events**

*Hypothesis: Use of CGMs will provide real-time blood glucose trends, allowing hypoglycemia to be predicted and prevented, or detected and treated before becoming severe or symptomatic.*

**b) Reduce the time to diagnosis of the etiology of hypoglycemia**

*Hypothesis: Earlier recognition of hypoglycemia with CGMs will prompt earlier testing to evaluate the etiology of the hypoglycemia and therefore lead to earlier ascertainment of the underlying etiology.*

**c) Reduce the time taken to achieve stable euglycemia on a sustainable feeding regimen.**

*Hypothesis: CGMs will shorten time to achieving a stable, normal blood glucose concentration on a sustainable feeding regimen.*

By performing a pilot study we hope to test the feasibility of our study design. We plan to use the results to assess the validity of our chosen outcome measures, inform power and sample size considerations and test the practicality of our study timeline for larger-scale study on the same topic. The results of this study could potentially alter the way neonatal hypoglycemia is routinely managed and thereby improve neurodevelopmental outcomes in this population.

**2. Background and Significance**

Neonatal hypoglycemia affects approximately 10% of all newborns, and up to 50% of infants with risk factors such as maternal diabetes, small for gestational age (SGA; <2500g), large for gestational age

(>4000g), birth at <37 weeks gestational age, and maternal beta blocker or terbutaline therapy 48 hours prior to delivery (1,2). Timely detection and treatment of neonatal hypoglycemia are critical, as failure to do so is associated with poor long-term neurodevelopmental outcomes (3,4). Neonates with symptomatic hypoglycemia are at risk for learning disabilities, seizure disorders, mental retardation and cerebral palsy (5). SGA infants with recurrent hypoglycemia, for example, have been reported to have smaller head circumference at 18 months and lower scores on psychometric tests at 5 years (4). Infants of diabetic mothers with resultant neonatal hypoglycemia have been found to have higher incidence of attention deficits, motor control dysfunction and perception deficiencies (6). Persistent hypoglycemia, often associated with serious metabolic conditions such as hyperinsulinism and fatty acid oxidation defects, is also associated with worse neurological outcomes (7).

Part of the challenge in managing neonatal hypoglycemia is that signs and symptoms can be nonspecific or absent. Clinical signs of hypoglycemia include irritability, poor feeding, tremulousness, and somnolence, all of which can be subtle or mistaken for normal neonatal behavior. The more severe signs, such as seizure, hypothermia, respiratory depression, and coma usually do not present until hypoglycemia has been severe or prolonged (5).

NICU practice guidelines for hypoglycemia monitoring vary from institution to institution. Often, blood glucose testing is done only prior to feeds, which leaves these infants vulnerable to undetected hypoglycemia. Even with frequent blood sampling using bedside glucometers there can be a delay in recognition and treatment of hypoglycemia. CGMs measure glucose concentration in the interstitial fluid of the subcutaneous space every few seconds and report average blood glucose levels approximately every 5 minutes. CGMs have 3 components: a glucose sensor, a transmitter, and a receiver. The glucose sensor is inserted subcutaneously with a 26-gauge introducer needle and remains in place under the surface of the skin for up to 7 days. The sensor's platinum tip is embedded with glucose oxidase enzyme, which catalyzed a reaction whereby electrical current is generated which is proportional to ambient glucose concentration. The current is then measured and translated into a glucose reading once it is wirelessly sent by the transmitter to the small hand-held receiver. The receiver then displays the glucose level in mg/dL and can alert at specified glucose levels. CGMs are inserted with minimal discomfort and no significant complications have been reported when they are used in children less than 3 years of age (8). CGMs are considered by IRBs to be non-significant-risk devices because they are not considered implants, they are placed only subcutaneously, they are completely removed within 7 days, and they do not offer treatment for or diagnosis of a medical condition. In our study, no clinical decision or intervention will be made based on the CGM readings. Instead, the CGMs will function as monitoring systems that will prompt FDA-approved glucose meter measurements, and only on these blood-based results will clinical care be based.

Although CGMs are increasingly being used in the diabetic population, their efficacy has not been investigated in the management of neonatal hypoglycemia. However, their use in the neonatal population, including in very-low-birth-weight infants, has been validated. Studies report that the sensor is well tolerated and provides readings comparable to those of whole blood results (9). It has also been shown that currently in a typical NICU, there are often prolonged periods (up to 12 hours) between blood glucose measurements, and that with CGMs, hypoglycemia is detected up to 3 hours prior to the scheduled blood glucose test (9).

We plan to explore the utility of CGMs in a new clinical context with the hope that they will improve the diagnosis and management of neonatal hypoglycemia. We will compare in a systematic way the clinical course and outcomes of newborns with hypoglycemia admitted to the NICU who are actively monitored with CGMs versus those who receive routine care. As of today, this comparison has yet to be made. The results of this study could potentially alter the way neonatal hypoglycemia is routinely managed and thereby improve outcomes in this population.

### 3. Preliminary Studies

The Safe Pediatric Euglycemia in Cardiac Surgery (SPECS) trial was performed by members of this research team at Boston Children's Hospital. In that study critically ill children undergoing heart surgery were randomized to a control group or a treatment group in which insulin was used to treat maintain euglycemia. All patients in this study were monitored with CGMs. Close to 1,000 children less than 36 months old had CGMs inserted and no injuries, serious bleeding, or infections were reported (10). Moreover, use of CGMs allowed reduction of severe hypoglycemia for patients undergoing tight glycemic control (11).

### 4. Design and Methods

#### a. Study Design

We aim to carry out a prospective, randomized clinical study examining the efficacy of continuous glucose monitoring in neonates with hypoglycemia. Eligible infants will be late preterm and term infants admitted to the Boston Children's Hospital NICU, who have had two documented hypoglycemic episodes during their admission. Hypoglycemia will be defined depending on age: <50 mg/dL prior to 48 hours of life and <70 mg/dL after 48 hours of life.

The research team will review the glucose levels for patients admitted to the NICU daily in order to identify those with hypoglycemia. Screening will be conducted by study staff through the electronic medical record system; supplemental screening will be provided daily through BCH360. After obtaining permission and an introduction from the patient's NICU staff, a member of the research team will contact the family to obtain consent. The goal will be for patients to be recruited within 24 hours after criteria for hypoglycemia have been met.

All enrolled infants will be placed on a CGM monitor (Dexcom G4 Platinum Pediatric Continuous Glucose Monitoring System). The CGM sensor will be inserted subcutaneously in the lateral thigh by a trained study team member. Prior to study commencement, as well as actively throughout the study duration, the research team will review the proper use of CGMs with the NICU staff (most importantly, how to calibrate the sensor with glucose levels from blood sampling). The NICU staff will also be trained to avoid using sensor values to guide treatment directly, as it is only a monitoring device. All concerning CGM glucose readings must be confirmed by blood glucose sampling.

Infants will be randomized to a "CGM Protocol" or a "Standard of Care" group. We aim to enroll ten patients in each study arm. Those on the CGM Protocol will have a fully accessible CGM that will be analyzed in real-time for blood glucose trends and will alarm for any blood glucose level approaching hypoglycemic threshold. The CGM alarm will sound if blood glucose is less than 60 mg/dL for all patients. The CGM will also alarm if the rate of drop in blood glucose is greater than 20 mg/dL/minute and thus concerning for impending hypoglycemia. These thresholds are programmed into the CGM by a study team member and will not be modifiable by the medical team. Those in the "Standard of Care" group will have a CGM in place but live readings will not be available to the clinical team. However, the research team will review CGM data from the "Standard of Care" group daily and if a subject in the "Standard of Care" group has three episodes of unrecognized severe hypoglycemia (eg. BG <40 mg/dL), the study team will alert the NICU providers. Notification will occur immediately following identification of the third unrecognized severe episode of hypoglycemia, which will at most be 24 hours after the event occurred.

For subjects in the "CGM Protocol" group, whenever the CGM alarms or there is a concerning blood glucose trend according to the CGM, the nurse will be asked to check a blood glucose value. All clinical

management decisions will be made by the clinical team based on laboratory or bedside monitor-confirmed blood glucose values. The CGMs will be calibrated, at a minimum, every 12 hours with a blood glucose value measured by bedside glucometer. Additional calibrations will be performed if more frequent blood glucose monitoring is deemed necessary by the NICU team. In the “Standard of Care” group, the only change to current management is the potential performance of additional blood glucose checks that may be prompted if repeated unrecognized severe hypoglycemia is detected by the research team. The CGM will remain in place until the infant is no longer being monitored for glycemic stability or until the infant is discharged. If hypoglycemia work-up and management lasts longer than a week, the CGM sensor will be replaced on the seventh day after initial insertion. In the case of a sensor dislodgement or malfunction, it would also be replaced. Lastly, if a patient continues to have unstable hypoglycemia for longer than 28 days (eg. four 7-day cycles of CGM) then their study participation will also end at that time.

#### ***b. Patient Selection and Inclusion/Exclusion Criteria***

Study-trained staff will screen and recruit eligible patients. All NICU admissions will be screened for potential eligibility. The NICU attending physician will be informed of any patient who meets eligibility criteria and he/she or a designee will be asked to make an introduction of study staff to the parents/guardians. The goal will be for patients to be recruited within 24 hours after criteria for hypoglycemia has been met.

##### **Inclusion Criteria:**

- Age: 0-60 days old
- Gestational Age: > 33 6/7 weeks gestational age (late-preterm and term)
- Hypoglycemia: two episodes of hypoglycemia >1 hour apart (hypoglycemia will be defined by age: <48 hours of life <50mg/dL and >48 hours of life <70mg/dL)

##### **Exclusion Criteria:**

- Diffuse skin disease such that placement of a CGM sensor would be difficult to secure
- Infants colonized or infected with multi-drug resistant organisms (i.e. MRSA, VRE, ESBL producing bacteria)
- Patients on hypothermic protocols
- Expected to remain in NICU <24 hours
- Enrolled in a competing clinical trial
- Family/team have decided to limit or redirect from aggressive NICU technological support
- Ward of the state

#### ***Description of Study Treatments or Exposures/Predictors***

Continuous Glucose Monitors (CGMs) will be placed in all enrolled patients. CGMs measure glucose concentration in the interstitial fluid of the subcutaneous space every few seconds and report average blood glucose levels approximately every 5 minutes. CGMs have 3 components: a glucose sensor, a transmitter, and a receiver. The glucose sensor is inserted subcutaneously with a 26-gauge introducer needle and remains in place under the surface of the skin for up to 7 days. The sensor’s platinum tip is embedded with glucose oxidase enzyme, which catalyzed a reaction whereby electrical current is generated which is proportional to ambient glucose concentration. The current is then measured and translated into a glucose reading once it is wirelessly sent by the transmitter to the small hand-held receiver. The receiver then displays the glucose level in mg/dL and can alert at specified glucose levels.

*c. Definition of Primary and Secondary Outcomes*

This is a pilot study to determine the feasibility of using CGMs to improve short term outcomes of neonates with hypoglycemia. Planned comparisons for a larger study will be powered from the data obtained. The primary endpoint will be a reduction in incidence and severity of hypoglycemia in infants on the CGM Protocol. Secondary outcomes will include reduction in in time-to-diagnosis, time-to-treatment initiation and time-to-euglycemia on a sustainable feeding regimen.

*d. Data Collection Methods, Assessments and Interventions*

- *Data collection:*

When a subject is first enrolled we will collect demographic Information (age at diagnosis of hypoglycemia, gestational age at birth, sex) as well as physical characteristics (weight and body surface area). Once a subject is on a CGM, the CGM glucose data will be downloaded onto a research team computer and reviewed daily. Laboratory results (including blood glucose levels and critical sample results (ketones, insulin, cortisol, growth hormone, fatty acids, total and free carnitine, plasma amino acids, urine organic acids, lactic acid, pyruvate), brain imaging and EEG readings, all intravenous and enteral sources of glucose, other sources of nutrition, hypoglycemia therapeutic interventions (eg. glucagon, diazoxide, octreotide, corticosteroids and carnitine replacement) as well as underlying etiology of hypoglycemia and other associated diagnoses will be reviewed and collected every 2-3 days.

- *Assessments:*

The CGM site will be evaluated daily to assess for any signs of bleeding or infection. CGM readings will be downloaded to a study team computer once a day. The CGM data will be reviewed daily to ensure the CGM monitor is functioning properly, being calibrated appropriately and to assess whether any episodes of severe unrecognized hypoglycemia have occurred.

- *Interventions:*

Subjects in the study will have a continuous glucose monitor (CGM) placed in one of their thighs. A numbing cream will be used before the CGM is inserted to reduce pain. The CGM has a small plastic catheter with a needle in it. It comes with an insertion device which pushes the catheter under the skin. The needle is then removed, so only the catheter stays under the skin with the device on top of it. After the CGM is placed, two blood glucose levels will be obtained (usually by heel prick) so that the device can be calibrated. Afterwards at least two blood sugar levels need to be obtained every day so that the CGM can continue to work properly. Infants with hypoglycemia need to have their blood glucose monitored routinely, so on most days no extra blood glucose sampling will be required as we will use the values obtained by the NICU team. Additional blood glucose levels may need to be obtained if the CGM reports current or impending hypoglycemia. All non-CGM monitoring and management decisions will be at the discretion of the NICU team. The CGM may need to be replaced in case of a sensor dislodgement or malfunction, or if it has been in place for more than 7 days. Live CGM glucose values will be available to the medical team in the “CGM protocol” group. Additionally the medical team will be provided print outs of the CGM data on a daily basis for the “CGM protocol” group. CGM data from patients in the “Standard of Care” group will also be reviewed daily. Notification will occur immediately following identification of three unrecognized severe episodes of hypoglycemia. Given that the CGM data will be analyzed daily, this will at most be 24 hours (although most likely less than 24 hours) after the event occurred.

### *e. Study Timeline*

Subjects will be enrolled ideally within 24 hours of diagnosis of hypoglycemia. The CGM will remain in place until the subject is on a sustainable feeding regimen and no longer having hypoglycemia. The CGM will be removed 24-48 hours after the NICU team has deemed the hypoglycemia resolved or stable enough for its continued management at home. We expect most patients to be in the study for at least a week but duration can vary significantly depending on the etiology of the hypoglycemia and how challenging it is to control. In the event that a patient continues to have unstable hypoglycemia 28 days after randomization into the study, then study participation will conclude on the 28<sup>th</sup> day and the CGM will be removed at that time. We expect to carry on the study for approximately 18 months.

## **5. Adverse Event Criteria and Reporting Procedures**

This is a small clinical study and so the acting primary investigator will perform continuous monitoring of events. The CGM site and individual patient data will be monitored daily for any patient who is on a CGM monitor. Any protocol deviations and subject withdrawals will be reviewed within 24 hours of occurrence. Aggregate data and enrollment data will be reviewed monthly.

This study has minimal risks, however, in the event of an adverse event secondary to CGM use (such as any significant bleeding, bruising or infection) the acting principal investigator will promptly report the event to the IRB and the medical team. This is a Non-Significant-Risk (NSR) device study and therefore the *Unanticipated Adverse Device Effects* reporting guidelines as per the 21 CFR 812.46 will be followed. Specifically, the study sponsor will immediately conduct an evaluation of any unanticipated adverse device effect. If it is determined that an unanticipated adverse device effect presents an unreasonable risk to subjects all investigations or parts of the investigations presenting that risk will be terminated as soon as possible and no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect. An Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Because this is a small, pilot study with minimal risk no specific stopping rules will be developed and no interim analysis will be performed.

## **6. Data Management Methods**

We will keep and maintain documentation to verify the consent process, eligibility assessment, protocol compliance, problem/event reporting to the IRB, quality control as well as all data collection. This is a non-significant risk (NSR) study and the study PI, Dr. Michael Agus, will be the sponsor. Maintenance of records and reporting obligations by the sponsor and investigators as per Part 812 of the Investigational Device Exemption will be followed. These records will include name and intended use of the device, objectives of the investigation, explanation of why the device is not a significant risk device, name and address of investigators and IRB, description of good manufacturing practices followed, subject case history, device receipt, use or disposition history, all correspondence, the protocol and documentation of protocol deviations as well as any other records and reports required by the FDA. All hardcopies will be maintained in a locked office while electronic data will be saved on an access controlled network drive. 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 data requires user authentication. Authorized users include only research team members.

## 7. Quality Control Method

We will use checklists to verify that every subject has undergone appropriate consent, eligibility screening and safety monitoring during the study. Appropriate CGM placement and function will be performed daily on all enrolled subjects. Glucose data from CGM monitors will be compared to sampled blood glucose levels to assess for accuracy of the CGMs. We will also maintain a log of any protocol deviations and reportable events.

Criteria for early termination of study participation:

- Development of widespread skin disease such that placement of a CGM sensor would be difficult to secure
- Development of infection or colonization with multi-drug resistant organisms (i.e. MRSA, VRE, ESBL producing bacteria)
- Development of significant erythema, induration, infection or other adverse event at the CGM insertion site
- Study cancellation by the sponsor.
- Participant/family failure to follow the study requirements.
- The Principal Investigator judges it is in the best interest for the child to be taken off the study.
- Parent withdraws permission for the child to participate in the study.

## 8. Data Analysis Plan

Hypoglycemia will be defined as a laboratory or bedside monitor blood glucose value of <50 mg/dL prior to 48 hours of life and <70 mg/dL after 48 hours of life or CGM values below threshold for >30 minutes with no concomitant blood sugar reading. Hypoglycemic episodes within one hour of each other will be considered as one event. Severe hypoglycemia will be defined as less than 40mg/dL. Euglycemia will be defined as 48 hours with blood glucose equal or greater than 70mg/dL after 48 hours of life or equal or greater than 50mg/dL if before 48 hours of life.

We will record all blood glucose levels, laboratory data related to the investigation of the underlying cause of hypoglycemia, intravenous and enteral sources of glucose, and other related therapeutic interventions such as administration of diazoxide, octreotide, glucocorticoids, and carnitine. Data analysis will begin by comparing blood glucose data with information from the CGM monitors to assess for accuracy of the CGMs. This will be done by calculating the mean-absolute-relative-difference (MARD) between sensor-measured glucose levels and laboratory or bedside meter-measured blood glucose values. We will then compare the severity and frequency of hypoglycemia, as well as the time to diagnosis and time to euglycemia on a sustainable feeding regimen between the “CGM Protocol” and “Standard of Care” groups. Chi-squared analysis will be used to assess differences in the incidence of hypoglycemia while the Mann-Whitney U test will be used to analyze differences in time-to-diagnosis and time-to-euglycemia.

## 9. Statistical Power and Sample Considerations

This is a feasibility study and therefore is not powered; however, the choice of 10 subjects in each of two groups is generally considered acceptable for feasibility/pilot studies and should allow the variance in the primary outcome (decrease in frequency and severity of hypoglycemia with use of CGMs) to be formally assessed for use in a subsequent larger study.

## 10. Study Organization

This is a single center study to be performed at Boston Children's Hospital.

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