PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Mohamed El-Dib

PROTOCOL TITLE
Transcutaneous carbon dioxide monitoring in neonates receiving therapeutic hypothermia for neonatal encephalopathy

FUNDING
Not funded

VERSION DATE
9/8/2020

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Optimization of intensive care of neonates with Neonatal Encephalopathy (NE) has the potential to prevent injury progression and further improve neurodevelopmental outcomes. Several studies have shown the association between hypocarbia and the increased risk of adverse neurodevelopmental outcome in infants with NE. The consistent findings of an association between hypocarbia and adverse outcomes suggest that the close monitoring of carbon dioxide exchange and the avoidance of hypocarbia is highly important in this vulnerable patient population. Arterial blood gas analysis, the gold standard for monitoring the respiratory components of acid-base homeostasis, has obvious limitations that preclude its continuous use to follow the dynamically changing level of PCO_2. Alternative, non-invasive monitoring techniques have been developed to measure PCO_2 trends continuously. Transcutaneous measurement of CO_2 tension ($tcPCO_2$) has never been tested in infants undergoing therapeutic hypothermia (TH).

The first aim of the present study is to evaluate the feasibility of application of transcutaneous CO_2 monitoring in neonates receiving therapeutic hypothermia for Neonatal Encephalopathy and to evaluate the agreement between $tcPCO_2$ and PCO_2 in this population. The second aim of the study is to assess the association between cerebral oxygen saturation ($CrSO_2$) as a marker of cerebral perfusion and $tcPCO_2$ trends as a marker of PCO_2 in blood. The monitoring of cerebral

oxygenation by using Near Infrared Spectroscopy (NIRS) together with $tcPCO_2$ measurements can be beneficial for infants with NE and can help to understand the pathophysiology of autoregulation in this specific patient population.

1) To evaluate the feasibility of applying transcutaneous CO_2 monitoring in neonates receiving therapeutic hypothermia and to quantify the agreement between $tcPCO_2$ and PCO_2 in this population with or without respiratory support.

We hypothesize that $tcPCO_2$ will be feasible and its trend will correlate with trends of PCO_2 measurements

Although continuous CO2 monitoring would be desirable in this patient population, to date $tcPCO_2$ technique has not been evaluated systematically or used routinely in the intensive care of infants with neonatal encephalopathy receiving TH. Continuous monitoring may allow to avoid the extreme levels and the fluctuation of PCO_2 and may improve the intensive care and the long-term outcomes of infants with NE

2**) To assess the correlation between cerebral oxygen saturation as a marker for cerebral perfusion and $tcPCO_2$, as a marker of PCO_2 in neonates receiving therapeutic hypothermia.**

We hypothesize that an acute decrease in $tcPCO_2$ will reduce cerebral oxygenation as a marker of decreased cerebral perfusion.

Decreased cerebral perfusion could be deleterious to the previously injured brain if oxygen transport and extraction are diminished, and the removal of potentially toxic metabolites is reduced.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Neonatal encephalopathy affects 3 infants per 1000 live birth every year and can lead to death or permanent neurological deficit. Therapeutic hypothermia (33.5 ^{o}C) has been clearly proven to reduce mortality and adverse neurodevelopmental outcome in patients with moderate to severe NE. However, even with hypothermia, nearly half of the infants with NE are at risk of

death or severe disability. Optimization of intensive care of these neonates might have the potential to prevent injury progression and further improve neurodevelopmental outcomes.

Multiple analyses noted a high rate of incidence of hypocarbia during the first hours of postnatal life possibly due to the strong respiratory effort secondary to metabolic acidosis and the hypothermia treatment which causes a 20-30% reduction in metabolic rate. Furthermore, several studies have shown the association between hypocarbia and the increased risk of adverse neurodevelopmental outcome in infants with NE. Hypocarbia has the potential to exacerbate brain injury via multiple mechanisms. Hypocarbia was associated with nuclear DNA fragmentation in the cerebral cortex, membrane lipid peroxidation and increased neuronal excitability in animal models.

It is well established, that carbon dioxide is one of the most potent regulator of cerebral blood flow (CBF), with hypercarbia causing cerebral vasodilation and increased cerebral blood flow by 1 to 2 ml/100g/minute per 1 mmHg in $PaCO_2$, whereas hypocarbia causes cerebral vasoconstriction. Reducing $PaCO_2$ to 20 to 25 mmHg decreases CBF by 40 to 50%. Hypocarbia may decrease oxygen supply further due to the cerebral vasoconstriction and the leftward shift of oxyhemoglobin curve.

It has been well known for decades that hypocarbia is associated with periventricular leukomalacia and, or, cerebral palsy in preterm neonates. In term, asphyxiated neonates the secondary analysis of the landmark CoolCap and NICHD hypothermia trials established that hypocarbia has a dose-dependent effect on long term neurodevelopmental outcomes. Both minimum and cumulative exposure to PCO_2 less than 35 mmHg within the first 12 hours of life increased the risk of death and adverse neurodevelopmental outcome in the secondary analysis of NICHD trial. Consistent with this, the post-hoc analysis of CoolCap study showed that the probability of unfavorable outcome was raised dose-dependently with decreasing PCO_2 in infants with moderate and severe HIE. Moreover, a recent retrospective study also reported an association between hypocarbia over the first 4 days of life and brain injury on MRI. The consistent findings of an association between hypocarbia and adverse outcomes suggest that the close monitoring of carbon dioxide exchange and the avoidance of hypocarbia is highly important in this vulnerable patient population.

Arterial blood gas analysis, the gold standard for monitoring the respiratory components of acid-base homeostasis, has obvious limitations that preclude its continuous use to follow the dynamically changing level of PCO_2. Moreover, repeated arterial samplings can lead to significant blood loss and an increased risk of bacteremia.

Alternative, non-invasive monitoring techniques have been developed to measure PCO_2 trends continuously. Transcutaneous measurement of CO2 tension is the most commonly used non-invasive CO_2 monitoring system in neonatal intensive care and several studies demonstrated a good agreement between the PCO_2 in blood samples and $tcPCO_2$ in premature infants. Transcutaneous CO_2 monitoring is recommended when there is a limited arterial blood gas access and/or the patient is on invasive mechanical ventilation. In the present study our aim is to measure PCO_2 continuously in infants undergoing TH regardless of the respiratory support in order to evaluate its feasibility in cooled infants.

As detailed above, changes in pCO_2 affect cerebral perfusion. Therefore, it is important to analyze the cerebral oxygenation and metabolism with the association of PCO_2 trends. Continuous cerebral regional oxygen saturation monitoring has been already used routinely in the intensive care of the infants with NE by using Near Infrared Spectroscopy (NIRS). NIRS is a non-invasive tool that can be used to measure changes in oxygenated, deoxygenated, and total hemoglobin of brain tissue from which cerebral regional oxygen saturation can be derived as a surrogate of cerebral oxygen consumption. A significant positive correlation was found between transcutaneous PCO_2 levels and tissue oxygenation index in preterm infants. In line with this, an acute increase in end tidal CO_2 ($etCO_2$) was associated with an increase in cerebral oxygenation, whereas an acute decrease was associated with reduced cerebral oxygenation. The $tcPCO_2$ and $etCO_2$ were used as a surrogate marker of PCO_2.

Although continuous CO_2 monitoring would be desirable in this patient population, to date $tcPCO_2$ technique has not been evaluated systematically or used routinely in the intensive care of infants with neonatal encephalopathy receiving TH. Continuous monitoring may allow to avoid the extreme levels and the fluctuation of PCO_2 and may improve the intensive care and the long-term outcomes of infants with NE The monitoring of cerebral oxygenation by using NIRS together with $tcPCO_2$ measurements can be beneficial for infants with NE and can help to clarify the pathophysiology of autoregulation in this specific patient population.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This will be a single center prospective study conducted in the Brigham and Women's Hospital, Department of Pediatric Newborn Medicine. All infants greater than or equal to 34 weeks gestation and eligible for therapeutic hypothermia will be enrolled regardless of their respiratory support.

Inclusion criteria

Any neonates with neonatal encephalopathy admitted to receive therapeutic hypothermia will be a candidate for this study.

Current criteria for therapeutic hypothermia at BWH include the following:

1. ≥34 weeks' gestation
2. Any one of the followings
    a. Sentinel event prior to delivery
    b. Apgar score ≤ 5 at 10 min
    c. Requires PPV, Intubation or CPR at 10 min
    d. pH ≤ 7.1 (from cord or blood gas within 60 min of birth)
    e. Abnormal Base Excess ≤ - 10 mEq/L (from cord or blood gas within 60 min of birth)
3. Any one of the followings:
    a. Neonatal Encephalopathy Scale Exam Score ≥4
    b. Seizure or clinical concern for seizure

Exclusion criteria

1. Infants with major birth defect, genetic or metabolic syndrome

2. Neonates in extremis with possibility of redirection to palliative care

We will enroll up to 100 patients.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Once an infant is identified as being eligible for TH treatment and hypothermia was initiated according to the department clinical practice guidelines, and written informed consent was obtained from one of the parents, $tcPCO_2$ monitoring can be started. Transcutaneous CO_2 will be measured by SenTec Digital Monitor (software version SW-V07.00; MPB SW-V05.00.12) with

V-Sign™ Sensor (SenTec AG, Thervil, Switzerland). This study will follow the BWH Newborn respiratory care guideline titled *"Transcutaneous CO2 Monitoring"*. This guideline will be followed point by point to precisely calibrate and applicate the sensor to the skin. After accurate calibration a trained health care professional will be applied the attachment ring and electrode to the skin of abdomen, and/or inner or outer thighs (see respiratory protocol for details). Electrode temperature of 41 ^{o}C was chosen following the instructions of the manufacturer. Ten minutes are allowed to achieve stable measuring conditions. Special attention must be given to skin injuries. Changing sensor site and recalibrating the device as often as every 8 hours is necessary in order to avoid skin injury and improve correlation. Calibration should be done prior to with each site change.

Neonates on ventilatory support, will be already receiving $tcPCO_2$ monitoring as well as repeated blood gases for clinical purpose. In these cases, we will just collect clinical data in the research record. For patients who have fewer than 4 clinical blood gases ordered during the monitoring period, we may use a small blood sample (0.2 ml) from the routine daily clinical blood draw to measure blood gas for research purposes. There will be up to four blood gases including the ones that are clinically ordered.

For those on no respiratory support, we will also obtain up to four blood gases from the routine daily clinical blood draws, in addition to applying $tcPCO_2$ monitoring.

Although the results of the research blood gas will not be blinded to the clinicians, this blood gas will not be charged to the patient billing and will not be included in medical record. Further blood sample collections will be based on the decisions of attending physicians.

Moreover, the attending clinicians will be not blinded to the $tcPCO_2$ values. The $tcPCO_2$ values will be documented in the patient records as per the Department protocol.

Continuous cerebral regional oxygen saturation monitoring has been already used routinely in the intensive care of the infants with NE by using Near Infrared Spectroscopy. The clinical practice guideline of NIRS (INVOS™ 5100C Cerebral/Somatic Oximeter), titled *"Clinical NIRS (Near Infra-Red Spectroscopy) in the NICU"* will be followed in the present study.

As part of the study we will collect data from clinical monitors (amplitude integrated electroencephalography, NIRS, cardiovascular monitor) connected to the neonates for clinical reasons. In addition, we will collect data from the medical record including demographic, clinical, laboratory and imaging data. Demographic, clinical, monitoring and imaging data will be

extracted from medical charts and electronic hospital medical records accessed through the participating hospital's network, then entered into our encrypted, password-protected redcap database accessible only to the PI and study staff members.

A Moberg CNS Monitor will be used to consolidate the recording process for NIRS and clinical monitor data. If the Moberg Monitor is unavailable, then an external auxiliary box will be used to record and co-register clinical parameters from the patient's bedside monitor up to 16 channels. Most data from the patient's bedside monitors will be extracted and stored in our computer with the $tcPCO_2$ data. Specifically, outputs of the cardiovascular and other bedside monitors will be either attached directly to our device for data collection. When not possible the data will be recovered from Epic. The extracted data will be time locked with the $tcPCO_2$ data for synchronization.

If the external auxiliary box is used instead of the Moberg CNS Monitor, then an additional research pulse oximeter (Masimo Radical 7) will be used. The current bedside pulse oximeter monitors data in the BWH NICU currently cannot be recorded or saved at sufficient temporal resolution. In Epic data are saved once per minute, which is too slow for our purposes. Hence, using an extra research pulse oximeter, when Moberg Monitor will be unavailable, will allow us to acquire digital output with sufficient temporal resolution. The FDA- approved device will be used in the same way as the clinical pulse oximeter during the study period.

Study period will end when rewarming is completed.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

This research protocol will not interfere with standard of care. Standard of care at BWH includes assessment for therapeutic hypothermia based upon a clinical practice guideline.

Transcutaneous CO_2 monitoring is recommended to all patients undergoing therapeutic hypothermia if the patient receives respiratory support. In the present study our aim is to measure PCO_2 continuously in infants undergoing TH with or without respiratory support in order to evaluate its feasibility in cooled infants. Neonates on ventilatory support, will be already receiving $tcPCO_2$ monitoring as well as repeated blood gases for clinical purpose. In these cases, we will just collect these clinical data in the research record. For patients who have fewer than 4 clinical

blood gases ordered during the monitoring period, we may use a small blood sample (0.2 ml) from the routine daily clinical blood draw to measure blood gas for research purposes. There will be up to four blood gases including the ones that are clinically ordered.

For those on no respiratory support, we will also obtain up to four blood gases from the routine daily clinical blood draws, in addition to applying $tcPCO_2$ monitoring. Although the results of the blood gas will not be blinded to the clinicians, this blood gas will not be charged to the patient billing and will not be included in medical record. Further blood sample collections will be based on the decisions of attending physicians. Moreover, the attending clinicians will be not blinded to the $tcPCO_2$ values. The $tcPCO_2$ values will be documented in the patient records as per the Department protocol.

If the external auxiliary box is used instead of the Moberg CNS Monitor, then an additional research pulse oximeter (Masimo Radical 7) will be used. The current bedside pulse oximeter monitors data in the BWH NICU currently cannot be recorded or saved at sufficient temporal resolution. In Epic data are saved once per minute, which is too slow for our purposes. Hence, using an extra research pulse oximeter, when Moberg Monitor will be unavailable, will allow us to acquire digital output with sufficient temporal resolution. The FDA- approved device will be used in the same way as the clinical pulse oximeter during the study period.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Transcutaneous measurement of CO_2 tension is the most commonly used non-invasive CO_2 monitoring system in neonatal intensive care. At our Department $tcPCO_2$ monitoring is strongly recommended during TH while infants receiving invasive mechanical ventilation and/or there is a limited arterial blood gas access. This study will follow the BWH Newborn respiratory care guideline titled *"Transcutaneous CO2 Monitoring"*. This guideline will be followed point by point to precisely calibrate and applicate the sensor to the skin.

To estimate the CO_2 level in the skin surface, the sensor of the device heated up to 41 ^oC to improve carbon-dioxide solubility in capillary vessels. We will change the sensor site as often as every 8 hours at the time of the routine nursing care in order to minimize the risk for skin irritation.

We consider that, there are no specific risks or discomforts related to the additional blood gases (up to four) for research purposes as we are obtaining 0.2ml from the routine clinical blood draws. Additionally, we consider that there are no specific risks or discomforts for the potential application of an additional pulse oximetry probe.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

In general, any safety concerns will be addressed immediately with PI Dr. Mohamed El-Dib. The PI will attend monthly meetings with the study team where any safety issues are further discussed and then presented to the Partners IRB if required. Severe or urgent safety concerns will be communicated immediately to the PI by cell phone. The PI will report immediately to the Partners IRB.

Physical Safety during $tcPCO_2$ monitoring

Sensor of the $tcPCO_2$ monitor is operated at a constant sensor temperature of typically 41 °C in neonatal patients. Special attention will be given to skin integrity at the sensor site. Changing the sensor site will be mandatory every 8 hours. The measurement will be stopped immediately if skin injury is noted or if the parents request it for any reason.

Safeguarding Patient Privacy

To ensure subject confidentiality and limit unauthorized access, all data will be transferred and stored using anonymized subject identifiers, identifiable only by randomly assigned alphanumeric identifiers. All protected health information (PHI) will be maintained in the strictest confidence. PHI data will be held in secure format in a password-protected redcap database behind Partner's Firewall. PHI records can be identified only by study number. A log of study number and identifying data and hard copy will be kept in a locked file cabinet.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Sensor is operated at a constant sensor temperature of typically 41 °C in neonates. Because of the increased local skin temperature thermal injury may occur. Special attention must be given to patients under hypothermia because of the poor skin tissue perfusion due to vasoconstriction, that may increase the risk of skin damage. However, $tcPCO_2$ monitoring was tested before on very preterm infants with more fragile skin and skin complications were reported in the minority of the cases. The skin integrity under the sensor will be assessed at a minimum of every 8 hours throughout the monitoring period to change site and recalibrate the device per manufacturer recommendation. If there is any concern for development of skin complications the electrode will be removed from this site immediately. This monitoring technique is considered to present minimal risk–that is, no more risk than the subject would encounter in everyday life.

Risks Related to Privacy and Confidentiality

Demographic, clinical, monitoring and neuroimaging data will be extracted from medical charts and electronic hospital medical records accessed through the participating hospital's network, then entered into our encrypted, password-protected redcap database accessible only to the PI and study staff members. Information will be extracted from medical charts and electronic hospital medical records accessed through the participating hospital's network. Confidentiality will be ensured by alphanumeric identifiers to each subject. The original consent forms will be stored in a secure locked cabinet at BWH. Medical Records Numbers will be stored electronically, separate from patients' data that will be stored in a password protected database.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

While there is no direct benefit to the infants enrolled in this study, the results from this observational study could improve the supportive care of infants with NE and may have an impact on long term outcome. The continuous non-invasive monitoring of CO_2 levels may help to avoid the extreme levels in PCO_2 and prevent further brain damage. Results of these monitor will be

displayed on the bedside. Any severe alteration would alert the clinician to correlate with clinical condition of the baby.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Our inclusion/exclusion criteria are based on clinical information that are proven diagnostic measures for encephalopathy, and have not been shown to systematically vary between individuals of differing sociodemographic qualities.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

We will not exclude non- English speaking participants.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Non-English-Speaking-Subjects.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruitment of study infants will be undertaken in accordance with our departmental standard operating procedure (see SOP and letter of introduction for parents attached) for participant recruitment in the NICU.

In this study, it is important to enroll patients in the first hours after birth. This is the time where babies get most of the blood gases routinely done for clinical care. In addition, this the most critical time to monitor these babies since hypocarbia in the first hours of life was associated with abnormal outcome. According to the SOP, and since enrollment is time sensitive, PI or IRB approved study designate will approach families after having permission from the attending overseeing the care of the potential subject.

Study aims, and procedure will be reviewed with all interested parents. Ample opportunity for questions and consideration of discomforts will be provided. Subjects will be provided with a copy of the consent form (and if applicable, the short form) they signed. The original signed consent form will be kept in a secured storage file

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Non applicable

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Research investigators will be the only persons obtaining consent from each study infant's parent/s. These persons will be responsible for ensuring that informed consent is given freely, without coercion, and based on a clear understanding of what participation involves. Mothers and fathers/partners will be approached in the Neonatal Intensive Care Unit. Study aims and procedure will be reviewed with all interested parents. We also have a simply written brochure specifically designed for parents that explains what would be involved for their infant and their rights as a research participant. Ample opportunity for questions and consideration of discomforts will be provided. Subjects will always be made aware that they may speak with the PI or any of the other co-investigators if they so wish. Subjects will be provided with a copy of the consent form (and if applicable, the short form) they signed. The original signed consent form will be kept in a secured storage file.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aicipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

(1) The safety and/or efficacy data that will be reviewed include:

- Study accrual rate (how many subjects are consented to participate)
- Compliance with eligibility criteria
- Adherence to study methods
- Adverse events and other problems or trends that may indicate safety concern for participants

(2) Planned frequency of review:

- The team will be continuously updated on recruitment and study staff will meet regularly to review progress and safety with Dr. El-Dib, as well as to discuss challenges in recruitment, implementation, and data analysis.
- These regular meetings will help to ensure that additional risks to subjects are identified in a timely manner, and that research data are validly capturing all appropriate information that can be used to answer the study questions.

(3) Quality control input will also be provided by the study staff.

- Principal Investigator, Mohamed El-Dib will be responsible for reviewing both study implementation and data collected to ensure the safety and efficacy of this study.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

If a study subject experiences an adverse event, it will be reported by the researcher who identified the event to the PI, then subsequently to the Partners IRB. The AE will be reported within 24 hours of occurrence via fax or e-mail. A full report will be submitted to the IRB within seven days of initial receipt for life-threatening severe adverse events, and within 15 days for non-life-threatening adverse events. The PI will submit any and all reports regarding the event to the IRB once available.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

All co-investigators, collaborators, and research staff are certified to conduct their assigned responsibilities in this study. The PI, Mohamed El-Dib, will be responsible for monitoring the implementation of the research and analysis of study data. All investigators and study staff will be responsible for maintaining the integrity of this project and for monitoring the components of the study in which they have expertise. Study staff will meet regularly to review adherence to the IRB-approved protocol, report on conduct of assigned responsibilities, and discuss monitoring the integrity of the data.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-in-Human-Subjects-Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Patient information is always confidential and only accessed by approved study personnel. Documents are stored in locked filing cabinets and on password-protected servers. Subjects will be assigned a unique study ID number and no names, medical record numbers, or characteristic data that could identify patients will appear in publications or presentations of the data collected.

Research team members will undergo all confidentially and HIPAA training before being granted access.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No specimens or data will be sent to research collaborators outside Partners.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

There will be no specimens or data stored at collaborating sites outside Partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

There will be no specimens or data collected by research collaborators outside Partners.

References

1. Kurinczuk, J.J., M. White-Koning, and N. Badawi, *Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy.* Early Hum Dev, 2010. **86**(6): p. 329-38.

2. Edwards, A.D., et al., *Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data.* BMJ, 2010. **340**: p. c363.

3. Jacobs, S.E., et al., *Cooling for newborns with hypoxic ischaemic encephalopathy.* Cochrane Database Syst Rev, 2013(1): p. CD003311.

4. Nadeem, M., et al., *Blood carbon dioxide levels and adverse outcome in neonatal hypoxic-ischemic encephalopathy.* Am J Perinatol, 2010. **27**(5): p. 361-5.

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