RESEARCH PROTOCOL OUTLINE

Title of Project:

Preventing hypothermia in moderate and late preterm neonates – a pilot randomized controlled trial

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Abstract
Preterm births make up 10% of all births in the United States and the cost to care for these infants is approximately 10 times higher than term infants. One of the complications that is common in preterm infants is hypothermia. Hypothermia which has been linked to an increased risk of mortality, leads to low glucose, apnea and respiratory distress in preterm infants amongst other complications. Currently, after preterm babies are born we keep them connected to the mother via the umbilical cord for at least 60 seconds because it reduces the risk of complications for the neonate, however, this allows for a significant period of time during which hypothermia may develop. We are proposing a pilot randomized controlled trial evaluating the benefit of immediately warming preterm babies using a warming mattress and a plastic wrap, while we delay clamping the umbilical cord at the time of c-section in babies born between 32 and 36 weeks to determine if it reduces the risk of hypothermia

A. Specific Aims

We *hypothesize* that neonates delivered preterm and wrapped with a sterile polyethylene wrap while being warmed with a standard neonatal transport warming mattress immediately after birth and awaiting delayed cord clamping will be less likely to be hypothermic at arrival to the neonatal warmer. Since this is not currently a method that is employed, we have insufficient preliminary data to determine a sufficient sample size needed for a randomized controlled trial. **The aim of this grant is to perform a pilot trial investigating the effect size of immediate neonatal warming and wrapping of preterm infants on neonatal temperature.** Our team is well positioned to address these questions as there is tremendous synergy between the maternal fetal medicine and neonatology groups at OU, and our large referral base for preterm deliveries—we accept 600 maternal transfers yearly.

We propose a pragmatic randomized pilot trial evaluating the effect size of this strategy employed for moderate and late preterm infants (32 weeks 0 days to 36 weeks 6 days) who are being delivered by non-emergent cesarean. We plan on enrolling 74 patients and allocating patients to the intervention and control groups 1:1 using a block randomization scheme stratified by gestational age. Patients and clinicians cannot be practically blinded to the interventions given the physical nature of the interventions; however, statisticians will be blinded to the group assignments. Primary outcome will be the difference in temperature of the neonate at time of arrival to the warmer for neonatal evaluation between groups. Secondary outcomes will include temperature at completion of resuscitation, need for NICU admission, temperature upon leaving the delivery room, temperature upon admission to the NICU (if required), hypoglycemia (less than 30mg/dL in the first 24 hours), highest bilirubin level, respiratory support in the form of intubation or continuous positive airway pressure, pulmonary hemorrhage, hyperthermia (>37.5

degrees C), days in the NICU, and composite neonatal morbidity and mortality outcome of death or intraventricular hemorrhage (all grades), sepsis (determined by treating neonatologist). Data obtained from this pilot trial will be used to apply for a NIH K08 grant in order to perform an adequately powered multi-center randomized controlled trial in order to investigate the efficacy of this approach and associated outcomes.

B. Background and Significance

Preterm delivery is a significant public health issue, with approximately 10% of births in the United States occurring prior to 37 weeks of gestation, and is a leading cause of perinatal mortality and childhood morbidity. In Oklahoma, 144 babies are born preterm on a weekly basis, representing an average of 11.1% of births in 2017. Although infants born less than 28 weeks are at highest risk for morbidity and mortality, approximately 80% of infants born preterm are born between 32-36-weeks gestation representing the largest proportion of affected neonates. Apart from mortality, these children are at risk for complications that impact multiple organ systems including sepsis, intraventricular hemorrhage, retinopathy of prematurity and respiratory distress[1]. An initial step in improving outcomes according to neonatal resuscitation algorithms includes drying infants and maintaining euthermia, as hypothermia has been associated with an increase in mortality of 28% for each 1C below 36.5 degree C[1,2]. Such measures are significant as the current rate of mortality ranges from 70% in those born at 23 weeks to less than 1% at 37 weeks, with an even higher proportion suffering from long term morbidity[3].

Recent recommendations from the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) recommend delayed clamping of the umbilical cord by 30-60 seconds to minimize severe complications such as intraventricular hemorrhage, necrotizing enterocolitis, and anemia in preterm infants. During this period, the infant remains at risk of hypothermia as heat loss starts immediately after delivery. The infant moves from an environment of the 37°C womb to the temperature in the delivery room, with decreases in temperature between 0.2-1 degree every minute[4]. With the above recommended interventions, the neonate typically does not arrive at the radiant warmer for assessment by the neonatology team until 2-3 minutes of life. Prior studies have investigated warming the neonate using transport mattresses and polyethylene wraps after evaluation by the neonatology team and demonstrated efficacy in minimizing hypothermia at admission to the NICU5. There are no contemporary studies evaluating strategies to maintain infant euthermia during delayed cord clamping. As such, there remains a critical gap during which hypothermia may develop and adversely affect the neonatal transition to extrauterine life.

Preterm delivery and resuscitation in the late preterm period

As a result of the significant physiologic changes that occur postnatally and the risks of morbidity and mortality outlined earlier, strategies to optimize the neonate's transition to extrauterine life have been developed The first intervention for any preterm neonate consists of delivery at a hospital where neonatal needs are matched by available services. Previous studies indicating that post-natal transfer may increase the risk of neurological dysfunction and death. In addition to expedient maternal transfer, obstetricians administer betamethasone prior to delivery and delay cord clamping after delivery to minimize respiratory distress, intraventricular hemorrhage, minimize the risk of anemia and mortality[6]. Further, there may be an improvement in long term respiratory and neurodevelopmental outcomes, and short term cardiovascular function after delayed cord clamping[7-9]. Interestingly, the infant is not attended by a

neonatologist during this period of delayed cord clamping[6]. Prior to the recommendation for universal delayed cord clamping in 2017, this period had been acknowledged as the "golden minute" during which neonatologists assessed the infant's resuscitation needs starting with a maintenance of euthermia, followed by optimization of airway, breathing and circulation over the ensuing 'golden hour'. While obstetricians stimulate babies, attempt to clear the airway with bulb suction and dry the infant, these measures are executed with significant heterogeneity and variable efficacy. To this end, efforts are underway to investigate the utility of initiating positive pressure ventilation before cord clamping. Such efforts emphasize the perceived importance of the first minutes after birth, since these interventions can improve transition to post-natal life and reduce the risk of morbidity and mortality.

Hypothermia and Neonatal outcomes

An important component of care in the first few minutes of life, especially in the preterm neonate is ensuring euthermia. Neonates have decreases in their body temperature of 0.2-1 degrees per minute after birth[1]. Preterm neonates are at increased risk for hypothermia due to their increased body surface to weight ratios, thin skin and lower amounts of insulating subcutaneous fat[10,11], thus resulting in increased evaporative heat losses. Hypothermia results in increased metabolic and oxygen demands and impaired resuscitation1. From an outcome perspective, hypothermic neonates are at an increased risk for respiratory distress, chronic lung disease, metabolic derangements such as hypoglycemia, intraventricular hemorrhage, and late onset sepsis. Even moderate hypothermia (<36 degrees C) has been linked to mortality[1]. De Almeida et al noted that 44% of preterm neonates admitted to one of 12 university hospitals were hypothermic at 5 minutes of life, with 51% experiencing hypothermia at NICU admission. As such, various interventions have been studied during the golden hour and at the time of neonatal transport to the NICU[5]. These include using polyethylene wraps and caps, warming mattresses, warmed humidified gases and maintaining delivery room temperatures at 24 degrees C. Though such interventions may result in hyperthermia (>37.5 degrees C), no correlation between iatrogenic hyperthermia and adverse neonatal outcomes has been demonstrated[12]. However, strategies to avoid hypothermia reduce the need for respiratory support and lower the risk of pulmonary hemorrhage[1]. Thus, beginning to prevent hypothermia during delayed cord clamping presents itself as an opportunity for improvement in outcomes.

C. Preliminary Studies/Progress Report

This proposal includes two Co-PIs, both of whom currently work synergistically within the healthcare delivery system. The question to be addressed is at the transition of life which represents a strength for both PIs as we and our divisions currently collaborate in the care for these patients on a daily basis. The two divisions meet at least twice a month to discuss care related to fetuses and neonates with complex congenital anomalies that require a synergistic and longitudinal approach to care from the womb to the mother's arms. Individually, each PI will be responsible for ensuring that we lend both of our expertise to the design and execution of this proposal. Troubleshooting concerns and ensuring that stakeholders in each department are invited for and complete training in the study methodology will be an individual mandate for each PI. However, these training sessions, enrollment and data acquisition will be collaborative. Finally, it was via a collaborative effort that we were able to generate a grant application and obtain funding.

D. Research Design and Methods (What, When, How, Where)

Recruitment

The trial will be advertised and introduced to patients admitted to the OU Children's Hospital labor and delivery or antepartum units by research nurses. Interested participants will be consented. We are choosing to only include patients undergoing non-emergent cesarean in order to improve our ability to control parameters such as room temperature and labor-related clinical or subclinical maternal infection, which are known confounders. Further, we are limiting our investigation to fetuses 32-36 weeks gestation, since this population represents the largest preterm delivery population. Recruitment and randomization will be stratified by gestational age with an aim to enroll at least 44 pregnancies at 32- 34weeks and 6 days and 20 pregnancies between 35- 36weeks and 6days. Last, it is impossible to recruit patients outside of the inpatient setting for a study investigating preterm delivery, as such deliveries are rarely predictable in the outpatient setting. There will only be one site for this study, the OU Children's Hospital labor and delivery and antepartum units.

Protocol

The proposed study is a pragmatic randomized controlled pilot trial of neonatal warming techniques with participants allocated in a 1:1 ratio using a random block allocation table using blocks of size 4 and 6 that are stratified by gestational age ranges of 35-36 weeks and 6 days and 32-34 weeks and 6 days. Since there cannot be a placebo intervention, neither the patient nor the neonatal team will be blinded to the group assignment. The group assignments will be made and coded by a third party at the time of randomization. Patients will be randomized to their respective groups immediately prior to surgery.

We will aim for an operating room temperature of 65-70 degrees F. The surgical technician will be provided with the necessary neonatal wraps and mattresses in a sterile fashion, and they will ensure these are available on the surgical field once the cesarean has begun. In the intervention group, the thermal mattress will be activated immediately prior to hysterotomy and placed on the sterile field with delivery of the infant directly onto the mattress. The infant will be dried, stimulated and bulb suctioned as deemed necessary per standard of care followed by wrapping. In the non- intervention group, the infant will be delivered onto the sterile field, dried and suctioned as deemed necessary per OU standard. Cord clamping will be delayed for 60 seconds in all infants under the supervision of both the obstetrician and the neonatal resuscitation team. If either team believes delayed cord clamping is no longer considered safe, as is our usual protocol, the cord will be clamped and cut and the baby will be handed off to the neonatology team. After the infant is handed to the neonatology team along with all group assignment specific materials (wrap and thermal mattress, if in the intervention group), neonatal temperature will be assessed immediately upon arrival to the resuscitation warmer using a digital thermometer placed in the axillary space. Infant temperature will be recorded at 1) arrival to the warmer, 2) after the neonatologist deems that in-room resuscitation is complete and 3) at admission to the Neonatal Intensive Care Unit (NICU), Mother Baby Unit (MBU) or Post-Anesthesia Care Unit (PACU) depending on the baby's needs; determined by the resuscitating physicians. These measurements will be recorded by research nurses in a data collection sheet. Further, the research nurse will record the time from delivery to the time it takes for the infant to arrive at the warmer. Upon arrival at the warmer, the mattress and wrap will be removed as neonatal evaluation takes place.

As immediate neonatal temperature is not generally discussed with patients unless there is an issue such as concern for infection, neonatal temperature will not be routinely discussed with all participants. Only if there is concern for neonatal infection or if there is hyperthermia (>37.5 degrees C) will the study results be discussed with the patient.

Identifiers might be removed and the de-identified information may be used for future research without additional informed consent from the subject.

E. Chart Review

All outcomes will be recorded in a REDCap database by research nurses and data managers on the OUHSC campus in prospective fashion. Data will be obtained from maternal and neonatal electronic medical records and only de-identified data will be analyzed from the REDCap database. The primary outcome will be the proportion of hypothermic newborns. Secondary outcomes will include temperature at completion of resuscitation, need for NICU admission, temperature upon leaving the delivery room, temperature upon admission to the NICU (if required), hypoglycemia (less than 30mg/dL in the first 24 hours), highest bilirubin level, maximal respiratory support and duration of respiratory support including but not limited to supplemental oxygen and mechanical ventilation, pulmonary hemorrhage, hyperthermia (>37.5 degrees C), days in the NICU, and composite neonatal morbidity and mortality outcome inclusive of 1) death, 2) intraventricular hemorrhage (all grades), 3) sepsis (determined by treating neonatologist) and 4) Necrotizing enterocolitis . Confounders that will be assessed will include delivery room temperature as reported on the room thermostat, maternal temperature as recorded by anesthesia at the time of delivery, time from delivery to arrival at the neonatal warmer, indication for delivery, indication for cesarean, infant weight, timing of betamethasone administration (time for administration to delivery) and gestational age. Access to the database will be controlled and logged using REDCap's internal systems. Finally, at the completion of the study, the data will be stored for 7 years in order to complete analysis and apply for additional grants prior to being destroyed.

F. Inclusion / Exclusion Criteria

Inclusion criteria: Patients who have non-emergent cesarean deliveries, gestational age between 32 weeks and 0 days and 36 weeks and 6 days determined per usual clinical parameters.

Exclusion Criteria: Fetal anomalies or death, neonates with blistering skin conditions, reversed end diastolic umbilical artery flow, placental abruption, chorioamnionitis, monochorionic multifetal pregnancies, inability to provide consent, provider perception that patient is in significant pain and provider perceived contraindications to delayed cord clamping.

Since this is a pilot trial, we will not establish early termination criteria. However, if the DSMB asks us to stop the trial due to concern for patient safety we will comply.

G. Gender/Minority/Pediatric Inclusion for Research

Since this study aims to optimize outcomes for newborn preterm neonates with an intervention that is performed at the time of delivery such a study cannot be completed without participation of neonates or their mothers. As mentioned, the risks to mothers

should not be increased because of this intervention as there are no additional interventions beyond standard of care delayed cord clamping that will be required of mothers. On the neonatal side, there is a risk for neonatal iatrogenic hyperthermia defined as temperature >37.5 degrees Celsius; however, no clinically important adverse outcomes have been identified in previous studies[1].

This study involves viable neonates (gestational age ≥32 weeks) and pregnant women. The proposed interventions are aimed at neonatal resuscitation, as such they should not impact maternal wellbeing. The intervention will be completed in a sterile fashion similar to all the procedures of the cesarean delivery. The research is aimed at directly improving neonatal outcomes, and this particular intervention has been demonstrated to be safe if applied at a different time point in the neonatal resuscitation process[1]. The informed consent process will include the risks and potential benefits associated with the proposed study. As expected, assent cannot be obtained from neonates. When obtaining consent from mothers younger than 18 years old, we will obtain consent from the patient and her parents, as she will be making decisions regarding her child's wellbeing immediately after birth and is considered empowered to do so under Oklahoma law. The overall risk level for pregnant patients is low as the procedures do not affect their wellbeing. The risk for neonates is also low because similar interventions have been investigated in the past at a different time point in the neonatal resuscitation process without evidence of significant adverse consequences1.

H. Recruitment and Enrollment

Women who are admitted to the University of Oklahoma Children's Hospital Labor and Delivery or Antepartum unit will be screened by study personnel for eligibility. They will be approached about voluntary participation by trained study personnel. Research nurses are independent of the treatment team. Patients to be screened will be identified from the EMR by research nurses or by phone call from admitting physicians. If the patient is eligible the study will be introduced by research nurses independent of the treating/admitting physicians and they will be provided with an informed consent form. Interested participants will be consented either on the antepartum unit or the labor and delivery unit.

Last, it is impossible to recruit patients outside of the inpatient setting for a study investigating preterm delivery, as such deliveries are rarely predictable in the outpatient setting. There will only be one site for this study, the OU Children's Hospital labor and delivery and antepartum units. Patients who are imminently delivering, or in significant pain per the judgement of treating physician or nurse will not be approached to minimize the risk of coercion. Study personnel will administer an informed consent interview with each participant, which includes a verbal explanation of the study in lay terms. Participants will also receive a written informed consent form. Potential participants are told that they need not participate in this research study, that the study may or may not benefit them directly, that they would be contributing toward a better understanding of treatments for preterm newborns, and that they may decline participation. The consent process also describes alternative options for the person considering research participation (including the right to decide not to participate in any research), privacy protections, potential circumstances involving loss of privacy, and what to do in case of adverse events. All potential participants are given adequate time to make a decision, have a chance to have their questions answered prior to making a decision, and are encouraged to include trusted relatives, friends, and/or other healthcare providers when making a decision. Once the informed consent has been signed, the participant is considered enrolled in the study. At this time, study-specific procedures may be

performed. Informed consent forms will be available in both English and Spanish, and if required hospital translator services will be used to assist in translations during the consent process. A patient's capacity to consent will be determined by her treating physician, if in their opinion they cannot consent to clinically relevant procedures they will not be approached for consent.

Enrollment will be stratified by gestational age with a goal recruitment of at least 44 pregnancies at 32-34weeks and 6 days gestation and 20 pregnancies between 35-36weeks gestation.

I. Risks and Benefits

This intervention has been previously evaluated at a different time point in the neonatal stabilization process in various studies. A previous study where infants were wrapped from the initiation of resuscitation until admission to the neonatal intensive care unit a 7% risk of hyperthermia with no associated adverse neonatal clinically important consequences4. Hyperthermia in this population is defined as temperature >37.5 degrees C. The effect of a combination of warming mattresses and polyethylene wraps is mixed as one study notes a 28% risk of hyperthermia at admission to the NICU in neonates born at less than 31 weeks, while another did not identify any children with hyperthermia[1-3]. Neither study reported adverse clinical consequences. Perlman and colleagues evaluated 3 observational studies for a total of 8985 patients showing no increase in the risk of hyperthermia[1]. Certainly, we would expect a lower rate of hyperthermia, as the intervention will only be applied until the infant can be brought to the neonatal warmer for a total of 2-3 minutes, contrasted with a longer exposure in the above studies. Of note, none of the above studies have demonstrated an increased risk of adverse clinical outcomes in the setting of iatrogenic hyperthermia. As such, the risk level from the proposed study is likely very low. Similarly, since the study will involve extraction of identifiable data there is an extremely low risk of violating privacy and confidentiality as all staff involved are trained to follow HIPAA and the data will be stored on a secure server.

All study procedures will follow good clinical practice. Risks of adverse events will be reduced by the study personnel and the investigators regularly monitoring participants' progress, by oversite of the IRB, and the data safety monitoring board (DSMB). Patient participation may be stopped by the delivering physician if there is concern for intrauterine infection or placental abruption. In addition, the neonate will be evaluated by a physician or nurse practitioner trained in neonatal resuscitation during the intervention as is currently the standard of care. The intervention may be discontinued or halted from initiation if the neonatal health care provider deems that there is a blistering skin disease that makes the neonate unsuitable for participation. Immediate access to higher levels of care from staff neonatologists are available at University of Oklahoma Children's Hospital Labor and Delivery 24 hours a day with direct access available via the use of an internal paging system. Finally, both devices to be used during this study (neonatal wrap and warming mattress) will follow FDA labeling.

Participant confidentiality will be protected by our strict adherence to HIPAA guidelines. As specified in the informed consent process, it is not possible to ensure complete protection of a subject's identity. However, any breaches of good clinical practice in this regard would be taken extremely seriously, with appropriate reporting and regulatory actions. All patients will be assigned a study participation number, which will be used to track the patient and their neonate throughout the study. All patient related data will be

stored on secure University servers with access limited to only relevant research personnel and will be password protected (REDCap database). All study personnel are accredited by university-approved online Human Subjects in Research Safety Programs. The PIs will be responsible for steps to protect against risks, including but not limited to training in Protection of Human Subjects for all study personnel, security of database systems, locking of any areas containing medical records, and protection of vulnerable populations.

1. Perlman JM, Wyllie J, Kattwinkel J, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation.* 2015;132(16 Suppl 1):S204-241.
2. McCarthy LK, O'Donnell CP. Warming preterm infants in the delivery room: polyethylene bags, exothermic mattresses or both? *Acta Paediatr.* 2011;100(12):1534-1537.
3. Billimoria Z, Chawla S, Bajaj M, Natarajan G. Improving admission temperature in extremely low birth weight infants: a hospital-based multi-intervention quality improvement project. *J Perinat Med.* 2013;41(4):455-460.
4. Vohra S, Roberts RS, Zhang B, Janes M, Schmidt B. Heat Loss Prevention (HeLP) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants. *J Pediatr.* 2004;145(6):750-753.

J. Statistical Methods

Since this intervention has not been studied previously and requires cohesion between pediatricians and obstetricians, we will plan on hosting in-person and virtual training for key study personnel. Currently, at OU we deliver approximately 250 neonates between 32 and 36 weeks gestation via cesarean each year. Assuming a 33% rate of enrollment, it would take us approximately 11 months to enroll our target sample size of 74 patients.

Two prior studies, one evaluating epidemiology and the other an intervention, demonstrated that 29% of neonates born in the late preterm period were hypothermic in the delivery room with a standard deviation of 8.8. With the proposed enrollment of 74 preterm infants that meet inclusion criteria, we would have approximately 80% power to detect a difference between the two groups of 20%. Since this intervention has not been evaluated previously and we are using indirect data from other institutions and other interventions, we are assuming a 10% increase in sample size (calculated at 68) to account for variations (total of 74). This is a pilot trial to generate the parameters needed to guide the development of the next-step full-scale multicenter trial. Thus, power calculations for the efficacy of the intervention were completed to ensure we did not need to start with a larger or smaller sample size, given the pilot nature of the project.

For this pilot trial, the baseline characteristics of patients assigned to the intervention and control groups will be estimated and compared as means, medians or proportions, as appropriate for the distribution of the data. Descriptive statistics (i.e., proportions, 95% confidence intervals, means, standard deviation, medians, and interquartile range) will be used to characterize the distribution of the primary and secondary outcome measures among the intervention and control groups. Using an intent-to-treat approach, the primary and secondary outcomes will be compared between treatment groups using Student's t-tests, Wilcoxson rank sum tests, chi- square tests or Fisher's exact tests, as appropriate for the variable distributions.

K. Data and Safety Monitoring Plan

Chair: Edgardo Szyld, MD, MSc (Neonatology); Members: Hugh Nadeau, MD, MS (Maternal Fetal Medicine), Statistician to be determined (we are currently in the process of identifying an epidemiologist from the School of Public Health to assist with this aspect of the DSMB).

Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 4, *Reporting of Serious Adverse Events and Adverse Events*) to the sponsor (OSCTI). Appropriate notifications will also be made to principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version *4.0.* http://ctep.cancer.gov/reporting/ctc.html.

Definitions, Grading, and Attribution of Adverse Events

Definitions

Adverse Event (AE)
Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" at http://www.hhs.gov/ohrp/policy/advevntguid.html

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen.** Since the study processes involve only the 2-4 minutes between delivery and arrival to the neonatal resuscitation warmer, adverse events will be collected during this time period.

Suspected Adverse Reaction (SAR)
Any adverse event for which there is a reasonable possibility that the investigational procedure caused or contributed to the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a procedure (21 CFR 312.32(a)).

Unexpected Adverse Event
An adverse event or suspected adverse reaction may be related to the study agent, or study procedures, or may be unrelated. Procedure-related adverse events or suspected adverse events are considered “unexpected” if not listed in the relevant *package insert* or not listed at the specificity, severity or rate of occurrence that has been observed. “Unexpected” also refers to adverse events or suspected adverse reactions that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

Serious Adverse Event (SAE)
An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or OSCTI, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.

2. A life-threatening event: An AE or SAR is considered “life-threatening” if, in the view of either the investigator or OSCTI, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

3. Prolongation of existing hospitalization. Depending on the gestational age, hospitalization for a period of time (at least until the mother’s due date) is expected. If hospitalization is extended beyond this time frame and there is not an alternative medical explanation for this outcome.

4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Grading Criteria
The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute’s Common Terminology Criteria for Adverse Events 4.0**,** referred to herein as the NCI-CTCAE manual**.** This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual: Grade 1 = mild adverse event. Grade 2 = moderate adverse event. Grade 3 = severe and undesirable adverse event. Grade 4 = life-threatening or disabling adverse event. Grade 5 = death.

Events grade 3 or higher will be recorded on the appropriate AE case report form for this study, which will be a printable pdf form that can be filled out electronically or printed on paper, such that the form can be scanned or uploaded into electronic data system(s). For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, ultrasound, electrocardiogram, etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn’t meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the

NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

Attribution Definitions
The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE pdf /printed case report form. Final determination of attribution for safety reporting will be determined by DSMB. The relationship of an adverse event to study procedures will be determined using the descriptors and definitions provided in Table 1. For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 1. Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

Collection and Recording of Adverse Events

Collection Period
Adverse events will be collected from delivery until hospital discharge.

Collecting Adverse Events
Adverse events (including SAEs) may be discovered through any of these methods:

- Interviewing the subject or parent
- Receiving an unsolicited complaint from the subject or parent.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 2, *Definitions, Grading and Attribution of Adverse Events.*

Recording Adverse Events
Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 2.1, *Definitions)* on the uploadable pdf or printed *AE/SAE CRF)* regardless of the relationship to study procedure. Once recorded, an

AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

Reporting of Serious Adverse Events and Adverse Events

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the electronic safety system. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Reporting of Serious Adverse Events to OSCTI

Site investigators will report all serious adverse events (see Section 2.1, *Serious Adverse Event)*, regardless of relationship or expectedness within 24 hours of discovering the event. For serious adverse events, all requested information on the AE/SAE uploadable CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE uploadable CRF will be updated and submitted.

Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 4.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by OSCTI there are two options for OSCTI to report the adverse event to the appropriate health authorities:

Annual Reporting

OSCTI will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 2.1, *Suspected Adverse Reaction* and *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 2.1, *Suspected Adverse Reaction*).

Safety data will be made public in a timely manner on clinicaltrials.gov and through publications.

Expedited Safety Reporting

This option applies if the adverse event is classified as one of the following:

Category 1: Serious and unexpected suspected adverse reaction [SUSAR] The sponsor shall report any suspected adverse reaction that is both serious and unexpected (see Section 2.1, *Suspected Adverse Reaction* and *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i). The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with procedure exposure (e.g., burns);

2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the procedure.

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3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of the intervention) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.

Category 2: Any findings from studies that suggests a significant human risk
The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the intervention that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

OSCTI shall notify the appropriate health authorities and all participating investigators of safety reporting within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

Reporting of Adverse Events to IRB
All investigators shall report adverse events, including expedited reports, in a timely fashion to the IRB in accordance with applicable regulations and guidelines. All Safety Reports shall be distributed by OSCTI or designee for IRB submission.

Reporting of Other Safety Information
An investigator shall promptly notify the site IRB as well as the OSCTI Safety Officer when an “unanticipated problem involving risks to subjects or others” is identified, which is not otherwise reportable as an adverse event.

Review of Safety Information

Medical Monitor Review
The OSCTI and DSMB shall compile new and accumulating information on AEs, and SAEs recorded by the study site(s) on appropriate, uploadable *CRFs*. In addition, DSMB shall review and make decisions on the disposition of the SAE reports received (See Section 4.1, *Reporting of Serious Adverse Events to Sponsor*).

DSMB Review

The PIs will establish an independent DSMB to review and interpret data generated from the study and to review the protocol prior to their implementation. Its primary objectives are to ensure the safety of study subjects, the integrity of the research data and to provide the PIs with advice on the ethical and safe progression of the study. The DSMB advises on research design issues, data quality and analysis, and research participant protections.

The DSMB members will be invited by the PIs and will include three experts in the following fields: biostatistics, neonatology and obstetrics. The DSMB will schedule regular committee meetings, recording all meeting minutes and summarizing the committee recommendations for the PIs.

The DSMB will have semiannual teleconferences to review the protocol with respect to ethical and safety standards, monitor the safety of the ongoing trial, the integrity of the data with respect to original study design, and provide advice on study conduct. The DSMB will periodically monitor data quality, including accrual, retention, data submission timeliness, data completeness, protocol adherence and adverse events. The DSMB may recommend protocol modifications based on concern for subject welfare and scientific integrity.

Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data semiannually during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will be informed of an Expedited Safety Report within 24 hours by uploading the report to a secure site and informing DSMB members by email that there is a message for them.

Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially affects safety at their own initiative or at the request of the PIs or OSCTI. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study, which is possibly or definitely related to study intervention.
- The occurrence of a Grade 3 or higher unexpected SAE in 3 or more of the study participants who have received the study intervention.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

Temporary Suspension of enrollment for ad hoc DSMB Safety Review

[Please also see below Stopping Rules and Withdrawal Criteria]

In the event of a death or occurrence of Grade 3 or higher related and unexpected SAE in 3 or more study participants, there will be a temporary halt in enrollment.

Interim Analyses

Interim Analysis of Efficacy Data
A formal interim efficacy analysis is not planned**.** Given the timing of recruitment, duration of follow-up, and targeted sample size, interim efficacy findings would not likely impact the conduct of the trial.

Interim Analysis of Safety Data
Safety data will be collected throughout the trial. A DSMB will be formed and will review the blinded data at semi-annual intervals. Formal interim statistical analysis will be performed after every third of the participants have completed the trial using the Lan DeMets (αt) spending function for between-group comparisons.

The following events will be formally monitored among the maternal/infant dyads:

- Wound infections
- Skin burns
- Hyperthermia at arrival to the warmer - Temperature > 37.5 degrees Celsius
- Length of NICU admission
- Sepsis
- Intraventricular hemorrhage
- Death

Each of these events will be monitored separately.

Futility Analysis
No futility analysis will be performed, due to the pilot nature of this trial.

Study Stopping Rules
The study may be prematurely terminated for the following reasons:

1. Unexpected rates of severe or serious adverse events
2. Any other reason deemed appropriate by the DSMB

L. Confidentiality

Electronically recorded patient information will be stored in a REDCap database on University computers with password protection. Paper consent forms will be stored in locked cabinets in the MFM research nurse office. At this point, no entities outside of the research team will have access to the data. The data will be stored for 7 years prior to being destroyed.

M. Literature Cited

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