Umbilical cord milking in nonvigorous infants: a cluster-randomized crossover trial

Clinical Trials Registration Number: NCT03631940

Umbilical Cord **Mi**lking in **N**on-**V**igorous **I**nfants (MINVI)

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Protocol Summary

Study Title	Umbilical cord milking in non-vigorous infants (MINVI)
Population	Infants 35^0 - 41^6 weeks gestational age
Primary Objective	Compare the incidence of admission to the NICU in 35^0-41^6 week gestation non-vigorous newborns receiving UCM to those receiving ECC
Aims/Hypotheses	**Specific Aim 1** - (PRIMARY): Compare the incidence of admission to the NICU in 35^0-41^6 week GA non-vigorous newborns receiving Umbilical Cord Milking (UCM) to those receiving Early Cord Clamping (ECC). **H1:** Compared to ECC subjects, UCM subjects will have a decreased incidence of NICU admission (based on predefined criteria). **Specific Aim 2** (SECONDARY): Compare the safety and efficacy profiles in 35^0-41^6 week GA non-vigorous newborns receiving UCM to those receiving ECC. Compared to ECC subjects, UCM infants will have: **H2**: Higher cerebral oxygen saturations in the first 10 minutes of life (sub-study at two (2) sites, n=20). **H3:** Receive a greater placental transfusion as estimated by hemoglobin levels by 48 hours of life and better blood pressure; will not have increased rates of hyperbilirubinemia compared to ECC subjects; will have decreased resuscitation interventions, level of HIE, use of therapeutic hypothermia, use of volume expanders, and length of hospitalization. **H4**: Will have improved developmental outcome scores on the Ages & Stages Questionnaire, Third Edition (ASQ-3); UCM subjects will have a lower rate of medium to high risk scores on the MCHAT at 2 years of age. **H5**: Better cardiac function as measured by echocardiography at 12 hours of life (sub-study at two (2) sites, n=200).
Design and Sample Size	This prospective multi-national cluster randomized crossover (CRXO) trial randomizes by hospital wherein each institution is randomized over time to each arm of the study n=1200 infants – 600 UCM/600 ECC
Inclusion Criteria	• Non-vigorous newborns born between 35^0-41^6 weeks gestation
Exclusion Criteria	• Known major congenital or chromosomal anomalies of newborn • Known cardiac defects other than small ASD, VSD and PDA • Complete placental abruption/cutting through the placenta at time of delivery • Mono-chorionic multiples • Cord anomaly (i.e. avulsion or true knot) • Presence of non-reducible nuchal cord • Perinatal providers unaware of the protocol • Incomplete delivery data • Infants born in extremis, for whom additional treatment will not be offered

Efficacy Endpoints	**Primary:** • Rate of NICU admission **Secondary:** • Use of therapeutic hypothermia • Use of volume expanders • Hemoglobin • Bilirubin levels • Death • Cerebral oxygenation at 10 minutes (substudy) • Echocardiogram - cardiac function/hemodynamic (substudy) • Length of hospitalization (exploratory) • Blood pressure (exploratory) • Resuscitation interventions (exploratory) • HIE; Mild Moderate Severe (exploratory) • ASQ-3 Score (follow-up) • M-CHAT-R Score (follow-up)
Safety Evaluations	Adverse events
Statistical Methodology	See Data Analysis section.
Enrollment Period	2 years
Study Duration	5 years
Webpage	http://www.minvitrial.org
ClinicalTrials.Gov Trial	MINVI NCT03631940 NIRS Substudy NCT03621956 Echo Substudy NCT03798093 MINVI Follow-up NCT03621943

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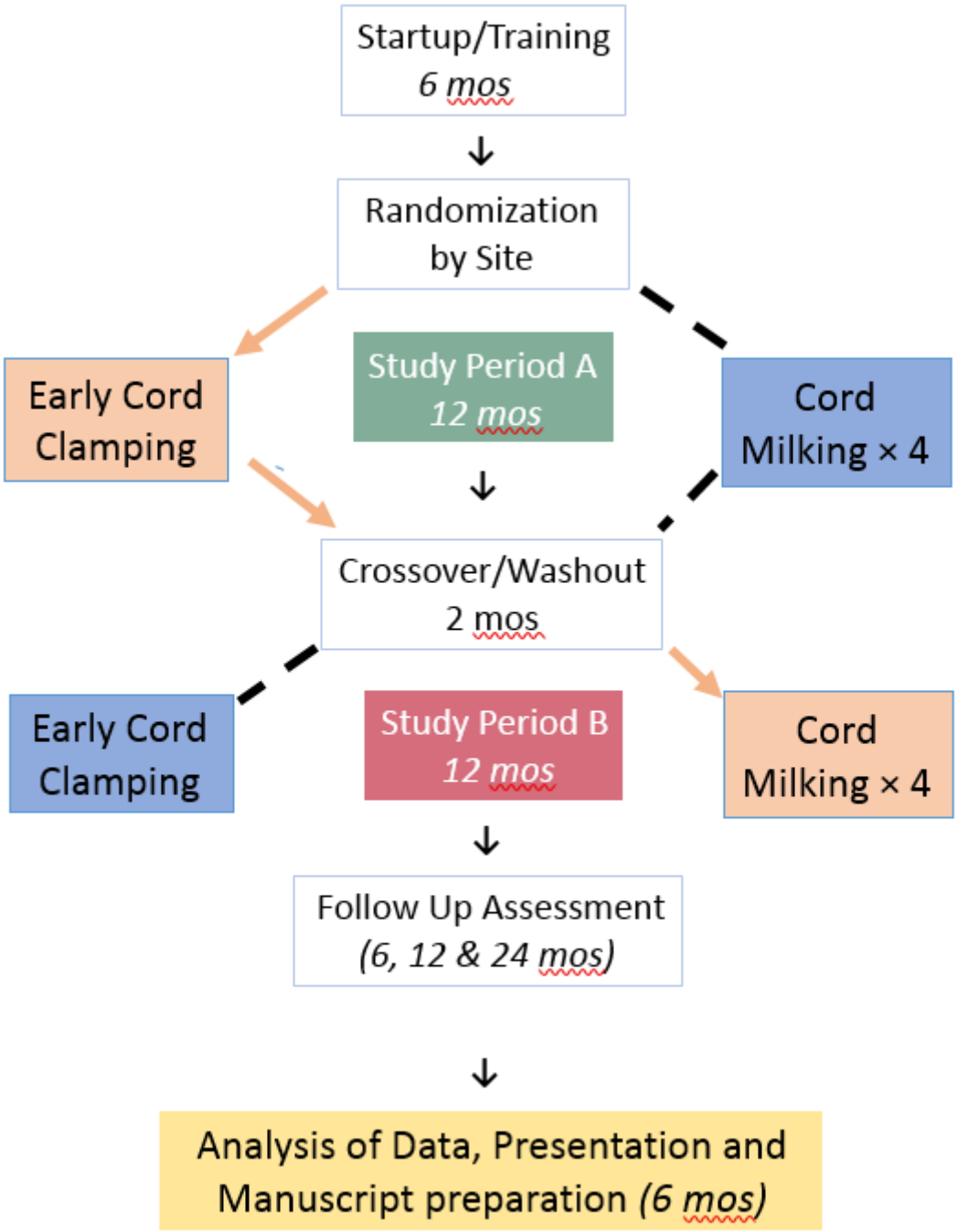
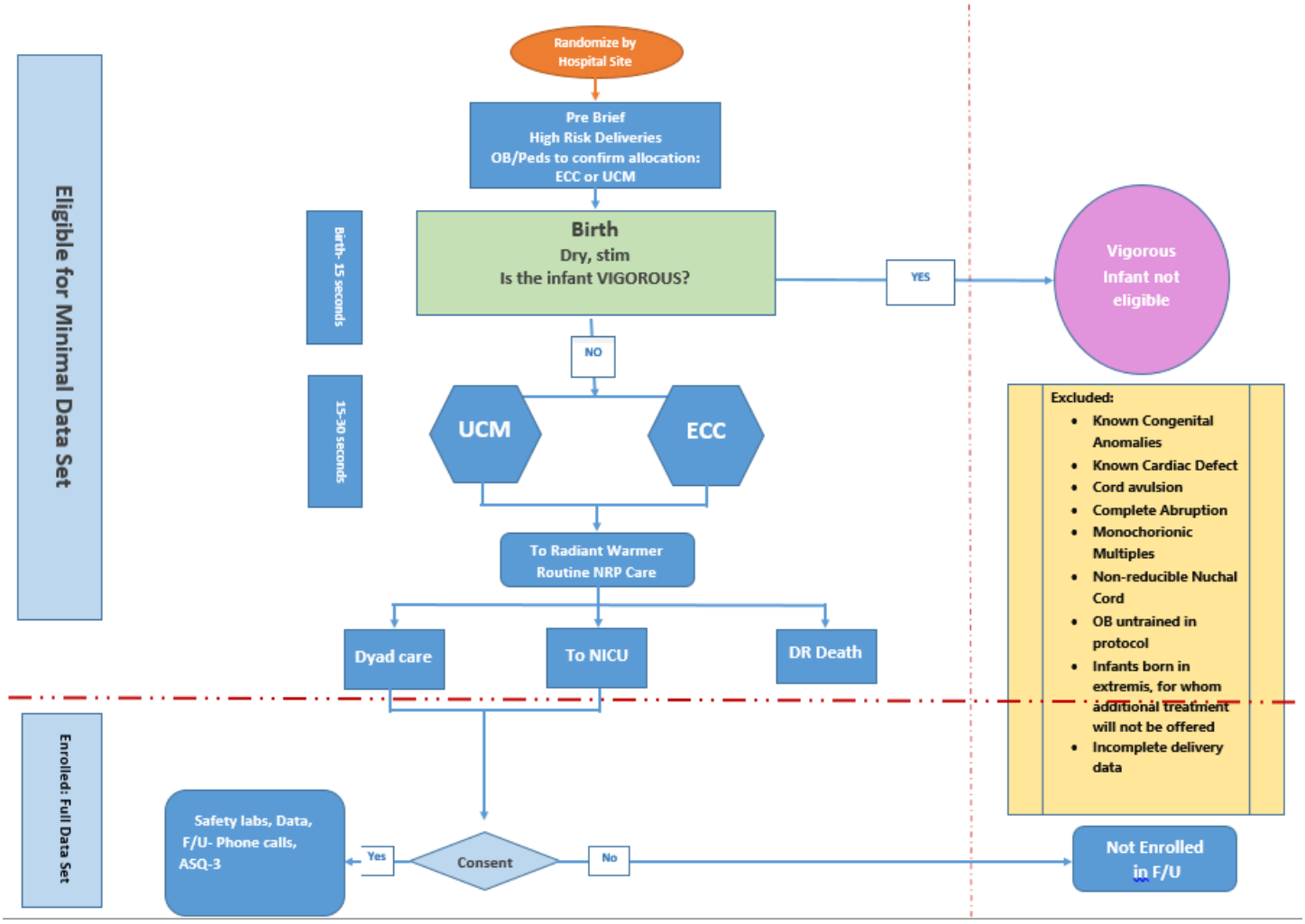
Randomization Overview



Intervention Flow Diagram



List of abbreviations

CRXO	-Cluster Randomized Crossover
ACOG	- American College of Obstetricians and Gynecologists
ECC	- Early Cord Clamping
UCM	- Umbilical Cord Milking
NIRS	- Near Infrared Spectroscopy
DCoC	- ACTRI Data Coordinating Center, UCSD
DSMB	- Data and Safety Monitoring Board
ILCOR	- International Liaison Committee on Resuscitation
HIE	- Hypoxic Ischemic Encephalopathy
ASQ-3	- Ages & Stages Questionnaire, Third Edition
SAE	- Serious Adverse Event
WHO	- World Health Organization
ASQ-3	- Ages and Stages, 3rd ed. Questionnaire
M-CHAT-R	- Modified Checklist for Autism in Toddlers

I. INTRODUCTION

ABSTRACT

We are proposing a study to determine if umbilical cord milking (UCM) for non-vigorous infants can improve outcomes compared to immediately clamping and cutting the umbilical cord at birth. In 2016, the American College of Obstetricians and Gynecology Committee recommended a delay in umbilical cord clamping in vigorous term infants. They also stated that infants requiring resuscitation may benefit considerably from placental transfusion, but their need for immediate attention raises questions about whether they should undergo immediate or delayed umbilical cord clamping and whether umbilical cord milking may offer a unique benefit. Due to the lack of a clear recommendation for non-vigorous infants, obstetricians are currently milking or immediately clamping the cord despite no evidence demonstrating benefit for one over the other. It is imperative that a trial to demonstrate whether there is any benefit for providing the extra infant's blood from the placenta at the time of delivery to non-vigorous infants.

We are hypothesizing that umbilical cord milking will reduce admission to the NICU compared to early cord clamping (ECC). In addition, it may reduce developmental problems by two years of age. At birth, it is critical that an infant begins breathing quickly. The infant has to switch from relying on the placenta for oxygen to using its lungs for the first time. Worldwide each year, almost 10 million babies do not breathe immediately at birth, and about 6 million of these infants need resuscitation. The usual practice for infants who need resuscitation is to immediately clamp the umbilical cord. Animal studies show that clamping the cord before the baby breathes can cause the heart beat to slow and can decrease the amount of blood being pumped out of the heart each minute. This study will test whether infants will benefit from UCM as compared to ECC. For UCM infants, the cord will be quickly milked four times before cutting and will not delay the resuscitation procedures. Our prior work has shown that, compared to early cord clamping, UCM results in better heart rate, blood pressure, less early anemia, and more oxygen in the brain, however whether these benefits will occur in non-vigorous infants and whether such benefits will improve clinical outcomes (like admission to the NICU and neurodevelopment) is unknown.

It is impossible to predict which infants will be non-vigorous prior to delivery and it is anticipated that about 3 percent of deliveries will be non-vigorous. It is also stressful for expectant parents to be approached for a study where it would be unlikely that their child would be non-vigorous at birth. In addition it would be unethical to add additional time for individual patients to be randomized at birth where a rapid decision for cord management would be needed. Therefore, we are proposing a cluster crossover randomized controlled trial where all sites would perform one method of cord management for one year and then cross over to the other approach. This study involves comparing 2 approaches to treatment that are currently in widespread use. We will be comparing outcomes of current practice variation applied with a standardized approach. All infants that were non-vigorous for each study year would be included in the study with collection of a minimal de-identified data set similar to a delivery room registry. The majority of these deliveries are emergent/urgent so we are requesting a waiver of antenatal consent in order to perform this cluster randomized cross-over trial. Parents will be able to opt out prior to delivery by review of handouts, fliers and post-delivery when approach to collect long term follow-up data. The parents will be consented after delivery for permission to collect ongoing information about their infant.

This trial will involve 1200 term newborns needing resuscitation at birth at ten (10) hospitals in San Diego, CA; La Mesa, CA; Loma Linda, CA; Sacramento, CA; Washington, DC; Portland OR; Salt Lake City UT; Edmonton, Alberta, Halifax, Nova Scotia, and Poznan, Poland. This trial will provide evidence to promote a change in guidelines supporting the use of UCM – a simple, no-cost intervention as standard of care in term and near-term newborns needing resuscitation.

II. BACKGROUND AND SIGNIFICANCE

Need for Research with Infants Requiring Resuscitation. Each year approximately 6 million infants require resuscitation globally(1). Neonatal morbidity and mortality remain high (2-4). Several large epidemiologic studies from around the world identified the need for resuscitation as a risk factor for hypoxic-ischemic-encephalopathy, cerebral palsy, attention deficit hyperactive disorder, autism, and neonatal stroke (5-8). Improvements in delivery room management could significantly affect long-term outcomes. The recommended umbilical cord management for non-vigorous infants (limp, pale and not breathing) who need resuscitation is to immediately clamp the umbilical cord at birth due to insufficient evidence for UCM (9).

Umbilical Cord Milking May be Neuroprotective. Preliminary evidence suggests umbilical cord milking (UCM) may be a neuroprotective mechanism that also facilitates cardiovascular transition for non-vigorous infants at birth and thus may reduce mortality and costly NICU admissions. UCM provides a replacement cardiac preload before the placenta is removed from the circulation and increases blood volume which will improve cardiac output and increase pulmonary and cerebral circulation, thus mitigating further ischemia in an already compromised infant (10). At present when there is a need for immediate neonatal resuscitation, neither of the currently practiced methods for facilitating a placental transfusion, UCM or delayed cord clamping (DCC), are recommended (11, 12). Compared to immediate or early cord clamping (ECC), both UCM and DCC demonstrated improvements in systemic and brain perfusion, suggesting neuroprotective benefits (13, 14). DCC and/or UCM have been shown to improve heart rate, blood pressure, urine output and cerebral oxygenation, increase early hemoglobin levels, and prevent anemia in term and preterm infants without adverse effects or harm noted in any of the studies (14-23). In contrast to DCC, UCM can achieve significant placental transfusion without postponing resuscitation and can be completed as quickly as ECC (24). It requires minimal training and no additional staff. **The proven benefit for UCM in vigorous infants and the lack of studies in non-vigorous newborns is identified as a major knowledge gap** by the American Congress of Obstetricians & Gynecologists (**ACOG**)**,** which states “infants requiring resuscitation may benefit considerably from placental transfusion, but their need for immediate attention raises questions about whether they should undergo immediate cord clamping” or “**whether umbilical cord milking may offer unique benefits**” (11).

Facilitating a placental transfusion at birth improves iron stores and long-term neurodevelopmental outcomes in healthy term infants (25, 26). However, there are no published trials on non-vigorous newborns at birth preventing a recommendation for providing a placental transfusion in this highly at-risk population. This study intervention will allow us to examine whether we can reduce this burden of morbidity and mortality in non-vigorous infants via umbilical cord milking (UCM).

Cord Milking is a practical method to provide blood volume to non-vigorous infants at birth.

Umbilical cord milking consists of gently grasping the uncut umbilical cord and squeezing the cord from the placenta several times toward the infant. The available studies on cord milking for vigorous term infants, when compared to Early Cord Clamping (ECC), include one systematic review five RCTs (15-17, 27) and five older controlled trials (13, 28-31). These studies conclude that cord milking significantly improves blood pressure, hematocrit, and hemoglobin levels within the first few days of life and iron stores out to 6 months of age, with no associated harm. In late preterm infants, higher ferritin levels at 6 weeks of age are reported after UCM (32). None of the studies demonstrated harm from UCM in these vulnerable infants, but also have not shown any clinical benefit. A recent study (PREMOD2) was stopped due to increased severe IVH in infants receiving UCM less than 28 weeks gestation compared to delayed cord clamping. There were no differences in death, or total IVH between the two groups. Cord milking in the most immature infants may be inferior to delayed cord clamping where a vascularized germinal matrix may be prone to bleeding with cord milking.

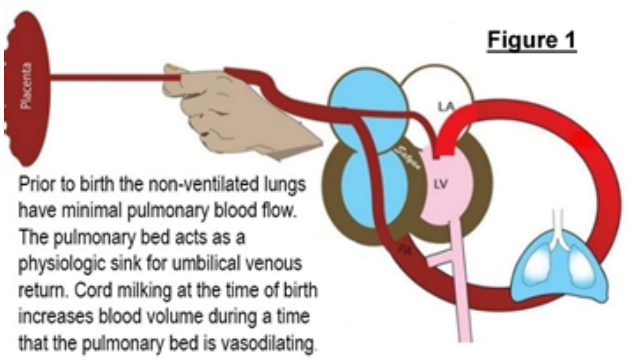


Figure 1

Physiology of Umbilical Cord Milking.

UCM provides a replacement preload before removing the placenta from the circulation, increasing pulmonary and cerebral circulation, and thus may mitigate further ischemia to an already compromised infant. Successful transition for non-vigorous infants may require active transfer of blood directed towards the pulmonary circuit by UCM. (see **Figure 1**, courtesy S. Lakshminrusimha) Increased pulmonary blood flow has been shown with recordings of electrocardiographic changes—vigorous newborns that had UCM had a longer P wave, PR, and QTC interval when compared with those who had early cord clamping (28). UCM may enhance alveolar patency compared to DCC or ECC by improving pulmonary capillary blood flow (33). Our recently completed retrospective study of term/near-term newborns with acidemia at birth suggested **decreased need for resuscitation, and ongoing respiratory support** after UCM compared to ECC (34). Whether a similar benefit will result from UCM in non-vigorous term/near-term infants is unknown. Based on currently available literature there is no foreseeable risk to the baby or to the mother with either ECC or UCM.

Are OB Providers Using Cord Milking?

While UCM is not currently recommended by any national or international body of experts for healthy or non-vigorous newborns, (35, 36) many providers who are comfortable practicing DCC are milking the cord when DCC is not feasible in term and preterm infants. Our retrospective study from two centers demonstrated that 30 percent of non-vigorous term/near term infants are receiving cord milking (34). A recently completed survey of 124 perinatologists indicated that 51 percent perform cord milking despite the lack of evidence for clinical benefit. ACOG acknowledges "infants requiring resuscitation may benefit considerably from placental transfusion, but their need for immediate attention raises questions about whether they should undergo early cord clamping (ECC) or whether umbilical cord milking may offer unique benefits" (11). **Before UCM in non-vigorous infants becomes widespread without any evidence, it is imperative that a clinical trial be performed to determine its potential benefit compared to ECC.**

Early Cord Clamping has become the standard of care for practical reasons in non-vigorous infants.
To perform resuscitation, infants must be moved to a separate location, typically a radiant warmer. This arrangement provides advantages to the neonatal team. All resuscitation equipment is readily available in a familiar setup with adequate lighting and a secure, warm, flat platform for resuscitation and space for the team to work. Physical separation from the mother allows the team to focus on the neonate, but requires ECC. These logistic considerations for resuscitation in a separate location preclude DCC.

Delayed Cord Clamping is not practical or as effective as UCM for non-vigorous infants.
Infants who receive a placental transfusion by DCC or UCM have more favorable outcomes than infants who do not receive a placental transfusion (37). One of the main differences between DCC and UCM is the source that drives placental blood to the infant. In healthy infants receiving DCC, the baby's heart continues to be the driver as it was in utero until the umbilical arteries close. This is represented by the pulsations felt in the cord. Uterine contractions also play a major role especially as the fibers contract and reduce the size of the cavity after the fetus is out of the uterus. Caldeyro-Barcia documented contractions of 100 mmHg during third stage which would squeeze the placental blood out into the infant. When the infant is bradycardic and non-vigorous, blood may not be transferred as expected with DCC. In addition, many of these infants may require delivery by Cesarean Section (C/S). During C/S when the uterus is cut open, pressure on the placenta may be diminished and the infant may not receive much placental transfusion even if delay were possible. It has been demonstrated that DCC at C/S provides an inferior placental transfusion compared to UCM in preterm infants(38).
Some studies suggest that opening the lungs with ventilation during delayed cord clamping might mitigate some of these limitations (39, 40). The SMBHWN group has performed the only RCT to date of ventilation during delayed cord clamping in preterm infants born by C/S which did not show any benefit compared to DCC alone. In addition, it validated previous findings that 30% of providers had difficulty placing the baby on the resuscitation platform. The research team at SMBHWN also recently demonstrated the feasibility of resuscitation during DCC in term infants but due to these logistical issues excluded C/S (41). However, this approach excluded 1/3 of infants that needed resuscitation. In both studies there was a reduction in the resuscitation team from 3-4 to 1-2 persons due to spatial constraints. Training of the obstetrical and neonatal teams was labor intensive requiring 24/7 research attendance limiting the generalizability of this approach.

In contrast during UCM, the blood volume in the cord is manually pushed into the infant. The cord refills quickly (about 2 seconds) and can be milked again. After 3-4 times milking the cord, an infant receives about 17 mL/kg (42). Our group has demonstrated that UCM provides a similar blood volume to a 2-minute delayed cord clamping in term infants as measured by residual placental blood volume (21). Unlike DCC, milking at C/S provides increases in placental transfusion in term and preterm infants making it ideal in this population (15, 38). While the concept of resuscitation with an intact cord is appealing, UCM may be a simpler, more efficient, pragmatic, and time-sensitive technique that is effective following C/S or vaginal birth. UCM requires little training and no additional personnel.

The risk for long-term neurodevelopmental impairment (NDI) in non-vigorous infants is high.

While establishing respirations and independent breathing are critical for survival, reducing long-term neurological impairment is essential for quality of life. Non-vigorous infants born with severe respiratory depression may have asphyxia leading to hypoxic ischemic (HIE) or neonatal encephalopathy. Of the 3-6/1000 infants who develop HIE each year, over half die or are disabled despite receiving the only treatment available – therapeutic hypothermia. If we show that UCM improves developmental outcomes, even slightly, this study may contribute to a change in delivery room practices. Dr. Katheria's completed 2-year neurodevelopmental follow-up trial (PREMOD) demonstrated improved language and cognitive scores with UCM compared to DCC in preterm infants (43).

Preliminary work that led to this proposal

The interventions (UCM versus ECC) and population (non-vigrouous infants) were chosen carefully based on prior work by Dr. Katheria. In a trial of infants receiving [i]UCM compared to ECC, UCM infants had increased heart rate and peripheral arterial oxygen saturation within the first 5 minutes of birth, suggesting improved breathing/aeration (44). We also found that UCM increased serum hemoglobin at 12 hours, reduced the need for a blood transfusion, decreased the median duration of oxygen therapy from 17 to 2 days, and reduced the incidence of chronic lung disease from 41 percent to 14 percent (19). Dr. Katheria and others also established that UCM is at least on par with DCC regarding clinical outcomes in both term (17) and preterm infants). (45, 46). A second trial provided evidence for increased placental transfusion as demonstrated by a higher hemoglobin, blood pressure, urine output, and improved systemic blood flow as measured by echocardiography with UCM compared to DCC C/S delivered infants <32 weeks(47). Our completed 2-year neurodevelopmental on this cohort demonstrated improved language and cognitive scores which further supports the safety of UCM in preterm infants. (43).

Dr. Katheria recently performed studies of UCM and DCC on term infants at risk for resuscitation. The trial was a pilot RCT of vaginally born term infants at risk for resuscitation comparing DCC with resuscitation compared to early clamping (34). While there were no differences in clinical outcomes, there was non-significant reduction in our proposed primary outcome for a reduction in NICU admission. Although not proven, UCM could demonstrate similar improvements. A recent retrospective study of term infants with fetal acidemia (the majority of which were delivered by emergent C/S) who were all admitted to the Sharp NICU received either UCM or ECC. In this cohort, UCM demonstrated a non-significant reduction in a number of our proposed secondary outcomes of the need for resuscitation, and respiratory support. We propose our intervention will reduce the outcome of NICU admission and have outlined our approach below.

***Project Goals*:** The main goals of this trial are to determine if infants who are non-vigorous at birth and receive UCM before cord clamping will have a decreased incidence of admission to the NICU and improved short and long-term outcomes compared to infants who receive ECC.

III. METHODOLOGY

Trial Design The planned cluster randomized crossover design has several innovations and benefits over a traditional individual patient randomized controlled trial. Using this design, we will randomize by hospital so that each institution is

randomized over time to each arm of the study. This procedure eliminates institutional and selection bias, minimizes site differences and number of study sites in deriving treatment effect, and improves generalizability as the sample should be more representative of the actual population (22). We chose this design because a traditional RCT would add cost and would take 2-3 times as long to complete enrollment. In the interim, cord management practices may change.

Cluster randomization offers several theoretical advantages over individual randomization (48, 49). The treatments occur in a more realistic delivery room setting—reproducing the way deliveries would function if the intervention was found to be effective and then applied to practice. It allows for recruitment of every patient of interest as an automatic default process that will markedly increase efficiency. It simplifies the consent process, as all patients of interest in that unit will receive the intervention or control during each epoch and parents can 'opt-out' of the system if they wish. It will decrease the cost of the trial because of the decreased burden of antenatal consent and screening. This is possible given that both cord management options are currently performed by providers relatively indiscriminately based on their individual interpretation of related data. The blocks will be standard of care for the year interval at the institution, and there is no more than minimal risk.

In conventional cluster-based trials, the major determinants of statistical power are the number of clusters (in this case the number of labor units) and the variation in outcome within clusters (operationalized by the so called intra-cluster correlation coefficient). Depending on the variations in outcomes at each site, the number of patients in each cluster could have far less impact on statistical power.

We plan to reduce these challenges by using a crossover of clusters. According to this approach, clusters are randomly allocated to receive Treatment A or Treatment B for a suitable period (12 months) and then swap to the other treatment (50). Thus, units randomly allocated to treatment A would then receive treatment B and those initially randomly allocated to treatment B would swap over to treatment A. This cluster randomized crossover control trial (CRXO) design is significantly more powerful than the conventional parallel group cluster RCT, because comparisons are made within the cluster, thereby removing the variation between clusters that can confound conventional cluster trials and leaving only the variation in *changes* in outcome over time between clusters (e.g., how clusters vary in their *changes* in morbidity and mortality rates over time). When there is little such variation, the CRXO design can be remarkably powerful and negate a large proportion of the loss of power due to the clustering in conventional parallel-cluster trials.

Risk

One important premise for CRXO is that the intervention and the control arm are of equal risk. We believe the current evidence supports the concept that UCM is as beneficial as DCC when DCC is not feasible. There is no current evidence for any risk or benefit for UCM or ECC in non-vigorous infants. The pediatric and obstetric co-investigators and administrators at each institution where the study will be conducted support this premise.

Timeline

Each site has provided the 1-minute Apgar score of 3 or less over the past three years in infants greater than or equal to 35 weeks. The ten sites selected for the trial have an approximate total of 1500 depressed newborns (1-minute Apgar ≤3) at 35-41+6 weeks GA in 2016. Assuming a cluster crossover design will allow 90 percent of infants to be enrolled. Initially it would require about 6 months for training and standardization of all sites. This CRXO study has recruited hospitals that are willing to be randomized for 12 months to one arm of the trial with a cross-over period of up to 2 months for training and education, followed by implementation of the second arm of the trial. Once IRB approval has been obtained, sites will receive randomization by letter from the data center (UCSD ACTRI). They will immediately begin standardizing their cord management to the assigned intervention. As soon as the site PIs have achieved 100 percent compliance over at least 1 month (all non-vigorous infants received assigned intervention) they will let the data center know they are ready to begin the trial. After 50 percent of the subjects are enrolled, all sites will pause enrollment, and immediately begin training and using the alternate cord management (the cross-over period). Enrollment will occur over approximately 26 months (12 months per arm cross over to ensure minimal drift or changes in practice. Based on estimated enrollments, sites will cross over when they have achieved 50 percent of their targeted enrollment or after 1 year of enrollment whichever comes first. We believe using this cluster randomized crossover design with each unit performing the same intervention for infants considered at risk, will result in either intervention (ECC or UCM) being performed with minimal variation for the period of that intervention.

Preparation of sites for the trial

Each site will be randomized prior to study initiation using a computer-generated scheme prepared by the data center. The lead Biostatistician will inform each site of its randomization status before they begin the trial for education on the intervention. They will also receive another crossover period before beginning the second epoch. Site and investigator standardization will be carried out by the site PIs using a variety of teaching methods and/or video certification process. Each site PI (perinatal provider and neonatologist) will orient their colleagues, delivery room and operating room staff to the study and its protocols. The site PIs will train their providers and staff to ensure that the cord is milked in a consistent method (if in the cord milking epoch), and record time elapsed from delivery until the clamping and cutting of the umbilical cord (both UCM and ECC epoch). This may include review of approved videos, study laminates and protocol. This will also include new staff at sites being trained in the protocol procedures. OB's who have not been trained and are not aware of the protocol, will be excluded from enrolling. Site PI's have agreed to make training new staff a priority to minimize any loss of subjects.

Standardize UCM Procedure

To ensure compliance and adherence of the different sites to the same study intervention(s), the following steps will be taken:

- The detailed process of UCM will be explained and shown in a real time manikin simulated video clip distributed by the Clinical Coordinating Center to the PIs of all participating centers.
- Each sites Neonatal and OB PI will educate their involved staff (OBs, family physicians and midwifes) before the launch of the study. This will be accomplished by using the central site video clip, handouts and simulation workshops using manikins.

- The simulation video clip will be available to all sites for download to ensure its availability to the staff all the time.
- Reinforcement of the procedure education will be carried out by the local research team every 1-2 months to ensure compliance of the OB practitioners to the same procedure.

Each site PI (perinatal provider and neonatologist) will orient their colleagues, delivery room and operating room staff to the study and its protocols. The site PIs will train their providers and staff to ensure that the cord is milked in a standard manner (if in the cord milking epoch), and record time elapsed from delivery until the clamping and cutting of the umbilical cord (both UCM and ECC epoch).

Protocol for the Control and Intervention Procedures

UCM: The delivering practitioner will place the newborn below the level of the incision (at the edge of the table) at C/S and a second team member will milk the cord four times. For vaginal delivery, the delivering obstetrician, midwife or perinatal provider will hold the infant against their body or place the infant on the mother's abdomen and the cord will be milked either four times by the obstetrical provider or by a second team member. For the cord milking procedure, the obstetrical provider will milk the entire length of umbilical cord over two seconds, repeating three additional times as described previously. This time is not significantly different from the time for ECC as we have demonstrated in our previous trials.

ECC*:* This will occur by clamping the umbilical cord as soon as possible. Since both ECC and UCM will occur after a brief assessment, it is important to note that the cord clamping time will be longer than in previously conducted preterm trials (average 20 seconds) which performed the intervention on all subjects regardless of whether or not they were vigorous. In all cases, the cord clamping time will be documented to ensure consistency.

Protocol Deviations include: a) patient did not receive correct treatment arm, b) cord clamping time of ≥60 seconds.

IV. SPECIFIC AIMS AND HYPOTHESES

Specific Aim 1 (PRIMARY OUTCOME) Compare the incidence of admission to the NICU in 35-41+6 week gestation non-vigorous newborns receiving UCM to those receiving ECC.

H1: Compared to ECC subjects, UCM subjects will have a decreased incidence of NICU admission.

Rationale. Given the knowledge gap, ECC continues to be recommended in non-vigorous newborns. We have shown that UCM is associated with immediate improvements in the delivery room and long-term benefits in preterm infants. There was a non-significant reduction in NICU admission in infants who received a placental transfusion with DCC in our pilot study compared to ECC. Dr. Katheria's recently completed cohort study demonstrated up to 30 percent of non-vigorous newborns with fetal acidemia are already receiving UCM at birth. In these infants, there was a trend for a reduction in morbidities such as the need for resuscitation and ongoing respiratory support. Therefore, we chose NICU admission as an outcome variable as infants with increased resuscitation and poor transition will be admitted for ongoing respiratory or neurological support. It is also a meaningful outcome for providers to change practice.

Standardized criteria for assessing the need for resuscitation: Per currently recommended guidelines for resuscitation, infants that are apneic with hypotonia, pallor or cyanosis should receive immediate resuscitation (and therefore would be ineligible for delayed cord clamping).

The collaborating perinatal providers in this trial will use their clinical judgment when determining if an infant is non-vigorous. Since both UCM and ECC are practiced at all of the participating hospitals, they have all agreed to perform one intervention on all qualified infants for one year and then crossover to the other arm for the subsequent year. They are comfortable and experienced with performing both procedures. Infants that are not vigorous will not be treated differently than if they were not the study.

As part of this study, half of these infants will receive UCM and the other half will receive ECC.

Pragmatic trial vs Protocol Deviations: It is important to note we designed this trial to be pragmatic and left to the judgment of the perinatal provider for the need for resuscitation, in order to ensure the trial is minimal risk.

Expectations, Limitations & Alternatives

We expect to find a lower incidence of NICU admission in the UCM group. A limitation of these outcomes is based on an assumption that the multicenter trial would show a similar treatment effect as observed in our pilot data of NICU admission (ECC 25% versus UCM 16.25%). The proposed large sample size will provide sufficient power to detect a clinically significant reduction in proportion of infants requiring admission to the NICU for multiple reasons such as poor transition, concern for neurological depression, and ongoing respiratory support. A reduction in NICU admission with UCM will justify the use of UCM in non-vigorous infants. There is a lack of knowledge regarding what effects UCM may have in the situation of significant fetal blood loss (i.e. unrecognized maternal abruption). Failure to reject the null hypothesis will cause us to examine potential reasons the hypothesis was not rejected, thus allowing us to make evidential recommendations for UCM.

Potential confounders of non-vigorous infants such as general anesthesia, other non-reversible insults such as chronic hypoxia of placental insufficiency will be collected and analyzed for effects on our primary outcomes. We acknowledge some sites may have infants admitted for other causes not related to the primary intervention (i.e., need for antibiotics). The crossover of each site should account for site differences. The proposed large sample size also allows us to control for such variables in determining treatment differences. Involvement of multiple hospitals both helps increase sample size, and affords the opportunity to examine potential heterogeneity across different sites and determine the extent to which the findings are generalizable.

Prevention of Bias in an unblinded trial

Our pre-specified inclusion criteria will minimize selection bias since infant appearance at birth, rather than actual cord management, determines which infants are included. Allocation bias will be prevented since all non-vigorous infants will receive the same treatment during the prescribed epoch. It is impossible to blind obstetrical providers or parents to the assigned treatment arm. To avoid clinical team bias we will request documentation of the specific intervention (UCM or ECC) not be included in the infant's medical record. Since cord management is not routinely provided in the medical record we have specifically avoided any inclusion of the management to avoid downstream bias once the study has begun. In order to prevent admission bias in either of the prescribed epochs, we have outlined pre-specified criteria that will constitute a NICU admission for purposes of this study, see appendix 2.

Specific Aim 2 (SECONDARY) Compare the safety and efficacy profiles of non-vigorous newborns 35-41+6 weeks GA delivered receiving UCM vs. ECC during their birth hospitalization and at 24 months corrected age.

H2: Compared to ECC subjects, UCM subjects will have higher cerebral oxygen saturations at 10 minutes of life (sub-study at three (3) sites, n=20).

Rationale: Caregivers and researchers raised theoretical concerns that the UCM technique may deliver blood rapidly toward a non-vigorous newborn predisposing them to higher rates of brain injury or dislodging cellular debris into the brain. However, of the 13 studies on term infants comparing UCM to ECC, none have reported adverse outcomes. All demonstrated improvements similar to DCC with increased red cell mass (measured by hematocrit or hemoglobin) improved blood pressure, increased pulmonary blood flow and improved ferritin at 6 weeks to 6 months of age with UCM. Nevertheless, careful assessment of safety is essential. Immediate physiological measurements on a subset (n=20) of infants of the three sub-study sites where the use of NIRS is standard of care, University of Alberta, SMBHWNand SGH to establish the safety and efficacy of UCM. This aim will further test our hypotheses that infants in the UCM group will have improved early cardiac and cerebral hemodynamics within the first 10 minutes.

The Near-infrared spectroscopy (NIRS) is a technology that allows non-invasive continuous real-time measurement of the regional tissue oxygen saturation (StO_2) of organs such as the brain. There are well-established reference cerebral StO_2 values for uncomplicated term and preterm deliveries; however, there are no completed RCTs using NIRS in the delivery room. Our group is currently leading the first multicenter trial (1R01HD088646-01A1) comparing DCC and UCM measuring NIRS at birth in premature infants. If cerebral oxygenation is improved, it will provide one plausible explanation for the long-term benefits expected with UCM. While published data exists on cerebral oxygenation directly comparing UCM with DCC, some studies demonstrated increases in cerebral oxygenation at 4 hours of age with DCC, and a decrease in cerebral oxygenation at birth with DCC compared to immediate cord clamping. To our knowledge, no studies using cerebral oxygenation in non-vigorous term/near-term infants have ever been performed. This sub-study (n=20) will yield the largest available sample of specific measurements of cerebral oximetry in non-vigorous term newborns.

Substudy Sites (only for sites that routinely record NIRS in the resuscitation room).

Three sites experienced with NIRS (**University of Alberta**,**SMBHWN and SGH**) will obtain and report the physiological changes with UCM and ECC in the first 10 minutes of life. Data from the non-invasive monitoring devices are recorded using

a continuous real-time data acquisition system that provides a second-by-second record of the resuscitation that is also time-linked to the video recordings. All sites have 24/7 research team coverage that attend all high-risk deliveries. The research team will ensure accurate sensor placement and data collection. These exceptional settings will allow us to collect significant data regarding resuscitation outcomes linked to cerebral oxygenation.

Protocol for NIRS Sub-Study

At the three sub-study sites, the use of NIRS is standard of care and therefore will be collected along with other data as part of the minimal data set. As part of the NIRS sub-study, sites will collect physiological and resuscitation data from birth (mean airway pressure, fractional oxygen) in addition to cerebral oxygenation. Once the newborn is delivered, receives the intervention (UCM or ECC), and is stabilized during resuscitation, a NIRS sensor (Fore-Sight, CAS Medical, Branford, CT) will be placed on the right forehead within 10 minutes of life. While arterial saturation and heart rate data will be available to the clinical team, data from NIRS will be blinded. Data on all study infants will be recorded for the first 10 minutes in the delivery room at the three sites. Heart rate, oxygen saturations, and cerebral oxygenation will be downloaded as per site's practice for neonatal resuscitation. If an enrolled infant has recovered and is stable enough for maternal bonding, NIRS may be discontinued prior to 10 minutes of life and will not be a protocol deviation.

H3: UCM subjects will receive a greater placental transfusion as estimated by hemoglobin levels by 48 hours of life and beter blood pressure; UCM subjects will not have increased rates of hyperbilirubinemia compared to ECC subjects; UCM subjects will have decreased incidence and severity of HIE, decreased resuscitation interventions, decreased use of therapeutic hypothermia and use of volume expanders, and a shorter length of hospitalization.

Rationale: These variables are chosen to assess the efficacy (hemoglobin) as well as safety (bilirubin) of both cord interventions. Data will be collected from the subject's chart.

H4: UCM subjects will have improved developmental scores on the Ages & Stages Questionnaire at 2 years of age and UCM subjects will have a lower rate of medium to high-risk scores on the MCHAT at 2 years of age.

Neurodevelopmental Follow-up Strategy

Although our hypothesis specifies 24 months as a primary endpoint, we will complete developmental assessments at 6, 12 and 24 months using the age and language appropriate Ages and Stages, 3rd ed. Questionnaire (ASQ-3). The parent or care giver completes the questionnaire with assistance by the site follow-up team as needed. At 24 months of age children will also be screened with the Modified Checklist for Autism in Toddlers (M-CHAT-R), a screening tool for autism. Various methodologies to enhance retention are described below.

The ASQ-3 is a developmental screen used worldwide for children 2 to 60 months of age and covers five developmental subscales (communication, problem-solving, fine motor, gross motor, personal-social). It has been shown to have good internal consistency and validity. Compared with the gold-standard Bayley Scales of Infant Development-II (BSID-II), sensitivity of the ASQ-3 is moderate (78%) for any delay and very high (92-100%) for severe delay. Compared to more recently published BSID-III norms, the ASQ-3 questionnaire has excellent negative predictive value (NPV, 98%) with subscale specificities ranging from 92% to 96%.

All parent questionnaires will be offered online via ASQ-3 online. In the event that a family prefers or does not have

access, a paper copy can be mailed. Survey results and feedback will be provided to the parents by the follow-up team. If a problem is identified, participants will be referred to their pediatrician or the site's High-Risk Infant Follow Up clinic for further evaluation. All surveys are published in both English and Spanish, but will be translated into those languages most commonly spoken at each site. Non-English translations, and certification of translation, will be provided for IRB review and approval upon PI receipt of the stamped IRB approved English versions prior to use in the study.

The M-CHAT-R is a parent-report screening tool used to screen for autism. Its goal is to maximize sensitivity and thus to detect as many cases of ASD as possible. Is has a high false-positive rate meaning that not all children who score at risk will be diagnosed with ASD. The 20-item questionnaire asks for yes or no answers. If the total score is 0-2, the child is considered low-risk. If the score is 3-7, the child is considered medium-risk while a score of 8-20 indicates high risk.

All infants that qualify for additional neurodevelopmental assessments (i.e. abnormal cord gases and/or receipt of therapeutic hypothermia) will also have their 2 year Bayley Scores collected when available. This subgroup will inform us as to whether UCM attenuates or improves long-term outcomes in infants with HIE.

Expectations, Limitations & Alternatives of Neurodevelopmental Follow-up

Each site will include a designated neurodevelopmental follow-up team responsible for maintaining periodic contact with the child's family, facilitating completion of ASQ-3 at 6, 12 and 24 months and MCHAT-R at 24 months, questionnaires scoring, data collection and entry. The follow-up team will also provide feedback to the family concerning developmental screening results and will refer children to appropriate resources whenever significant problems are identified. To enhance the follow up rate, a tracking system will be developed at each study site in which the neurodevelopmental follow-up team, or research coordinator, will maintain ongoing contact by text, phone, e-mail and/or written communication (letter, greeting cards, etc) with the family during initial hospitalization and at 3, 6, 9,12,18, and 24 months. Our goal is 90% follow-up.

Procedures

At Participant Enrollment

The coordinator at each site who consents the parents at the time of enrollment, will explain the need for follow-up, and describes the process we will use.

3 and 18 Month Follow-Up

The Follow-Up coordinator will contact the parent by phone. After appropriate greetings and general inquiry about the mother's wellbeing, s/he will ask about the infant's wellbeing, feeding methods, hospitalizations, health problems, or any follow-up with specialists. This information will be captured in Redcap. Any change of address or name should be requested and noted and the parent or caretaker should be reminded of the upcoming ASQ-3.

6, 12 and 24 Month Follow-Up

Approximately 1 month before the infant reaches each ASQ-3 milestone, the research team member will contact the parent by phone to discuss the upcoming ASQ-3 completion. This will include obtaining the parents preference of administration

(computer, paper copy, phone completion with assistance). The same health information will be solicited and contact information will be confirmed. Study personnel will contact the parent if the form is not returned within 1 month and will assist in completing over the phone.

H5, UCM subjects will have better cardiac function at 12 hours of life (echo Substudy n=200).

Rationale: UCM has demonstrated improved blood pressure, increased pulmonary blood flow cardiac function in preterm infants. However it is unclear whether there are hemodynamic changes in term infants, physiological cardiac measurements on a subset (n=200) of infants of the two sub-study sites (Sharp Mary Birch and Sharp Grossmont Hospital), will be conducted to establish the safety and efficacy of UCM. This aim will further test our hypotheses that infants in the UCM group will have improved early hemodynamics.

Two sites experienced with echocardiography will obtain and report the physiological changes with UCM and ECC at 12 hours of life.

Protocol for Echo Sub-Study

Non-vigorous infants enrolled in the MINVI trial will be approached for consent for ongoing data collection. As part of the data collection, an optional echocardiogram will be performed if the parent consents. The consent will have a check box to indicate if they consent to the additional test.

Echocardiographic measurements will be performed on all infants at 12 hours +/-6 hours of age by our research sonographers who are blinded to infant randomization. Measurements will be taken according to a standard operating procedure to assess systemic blood flow, by superior vena cava (SVC) flow (ml/kg/min), right ventricular output (ml/kg/min), and left ventricular output (LVO) (ml/kg/min). These measurements will be performed off line at a later time. Data will be entered into REDCap.

If any structural abnormalities are found, the attending pediatrician will be notified of the abnormal echocardiogram. The consent will clearly state that this echo is not for diagnostic purposes. Any additional studies including an official complete echocardiogram and or cardiology consultation will be left to the discretion of the attending pediatrician, as he/she deems necessary.

Maintaining Adherence to Algorithms and Minimizing Deviation from Protocol

As this is a cluster randomized crossover trial where the standard of care for every non-vigorous infant will be the same over a year at each site it is unlikely there will be a significant portion of newborns that will receive the wrong allocation based on the cluster. The inclusion/exclusion criteria were designed to be minimal and pragmatic for providers to decide readily if the infant should receive the treatment arm. The outcomes for infants with protocol violations will be measured and analyzed according to original allocation by intention-to-treat principles. Only newborns who meet pre-defined exclusion criteria (i.e. cord avulsion or congenital anomaly) will be excluded from the primary analyses, although we will verify that there is not a differential occurrence by treatment from procedure. This strategy was successful in our previous trials.

In prior cord milking trials conducted by Dr. Katheria, protocol violation rates for UCM (milking <4 times) were <5 percent. To ensure optimum compliance, he conducted extensive education and certification of our obstetricians in the delivery room. For the proposed trial, the site investigators all have significant experience with UCM and have equipoise of both cord management techniques. All lead perinatal investigators agreed on the techniques and will ensure their colleagues are adequately trained on the maneuvers to minimize site variability. Sites also agreed on institutional policies to video record the UCM techniques at initial startup to minimize site-to-site and inter-observer variations. Videos will be kept at local sites and used solely for study specific training purposes. Videos will be kept secure per local intuitional policies. Site PIs will be considered 'certified' upon agreement of the lead site PI (AK). Training videos and materials will be disseminated to be used as a refresher for delivery room staff, fellows, and attending neonatologists. Monthly teleconference meetings will be conducted to examine site comfort with, and performance of UCM techniques, as well as record keeping, and other study or regulatory issues.

V. STATISTICS

Sample size and power calculation We estimated that a sample size of 1200 across ten sites would be needed to test efficacy of UMC versus ECC for the primary outcome. This was based on the following assumptions: a clinically meaningful 35% reduction in NICU admissions (16.25% for UCM versus 25% for ECC), a two-sided type I error alpha = 0.05, 85% power, 0.02 rho (within cluster within period correlation), 0.02 eta (within cluster between period correlation), and a correction factor (4 x cluster size) for the small number of clusters(51).

For the longer-term neurodevelopment outcome scores, we estimated that a sample size of 1200 across ten sites, with an assumed two-sided type I error alpha = 0.05, 0.02 rho, 0.02 eta, a correction factor (4 x cluster size) for the small number of clusters, and Cohen's d = 0.25, power ranges from 79% to 87% when assuming a range in lost to follow-up from 20% to 10%. The original sample size for this trial was 1000. However, at the first DSMB meeting in May 2019 only four sites had begun enrollment and enrollment was nearing completion of the crossover point (nearly 2/3 complete in the first arm), and two sites were unable to obtain IRB approval. Therefore in conjunction with the DSMB, the decision was made to reassess the sample size calculation for ten sites.

Feasibility Based on the numbers of newborns at each of ten sites, we expect a total of approximately 1500 newborns with a 1-minute Apgar of ≤3 per year. Estimating conservatively that at least 50% will be classified as non-vigorous, a 2-year period of recruitment would be required. The ten sites agree to recruit and each one has provided an estimated number 35-41+6 weeks infants delivered per year.

Statistical Approaches for Testing Hypotheses

All statistical analyses will be based upon the total cohort of patients randomized into the trial. Patients will be included in the treatment group to which they were randomly assigned. We will use the intent-to-treat analysis to determine treatment difference between the UCM and ECC groups.

Descriptive statistics (counts and proportions for categorical variables and means and standard deviations or medians and interquartile ranges for continuous outcomes) will be used to compare baseline demographic, physiologic and clinical

outcomes between the two treatment groups. All statistical tests are two-sided with alpha = 0.05.

Analysis of Primary Outcome (NICU Admission)

The primary endpoint to be used for efficacy evaluation is the rate of NICU admission (by predefined criteria). The primary hypothesis to be tested is whether the UCM group's results show a lower event rate compared to the ECC group. The primary analysis will estimate relative risks and 95% confidence intervals, accounting for the cluster randomized crossover study design, with fixed or random effects for treatment group effect, period effect, cluster effect and cluster by period interaction effect. The analysis will also account for multiple gestations and clustering within a pregnancy if more than one neonate of a multi-gestation pregnancy meets eligibility. If the treatment groups are found to differ on a pre-treatment factor known to be a risk factor for the outcome, the statistical analysis will adjust for these differences. An evaluation of treatment by site interaction will be included. The percent of patients missing information to define the primary outcome is expected to near 0%. Death is not an anticipated competing risk for the primary outcome as it is expected that all randomized newborns requiring NICU admission will be admitted immediately. However, a sensitivity analysis will be conducted using a composite outcome of NICU admission (by predefined criteria) or death.

Subgroup analyses should be pre-specified and interpreted with care. Prior studies offer no basis for assuming a priori interactions between treatment groups, strata and subgroups defined by sex, race/ethnicity, gestational age, site or a combination of these groups, beyond that already controlled for in the randomization. For these reasons, preplanned tests for interactions with treatment assignment are not warranted and are not powered for with the sample size. However, in accordance with NIH guidelines, an evaluation of consistency across racial/ethnic subgroups will be included.

Analysis of Secondary Outcomes

Secondary outcomes (use of therapeutic hypothermia, use of volume expanders, hemoglobin, bilirubin, death, and neurodevelopmental follow up scores) will be analyzed using similar multivariable procedures accounting for the study design as for the primary outcome to test treatment effects. Analyses will estimate relative risks and 95% confidence intervals for binary outcomes and means or mean differences and 95% confidence intervals for continuous outcomes. Secondary outcomes will be evaluated for missing data and those with and without missing data will be compared. Multiple imputation analysis will be conducted as warranted. Analyses will also evaluate death as a competing risk. No adjustment for multiple comparisons of secondary outcomes is planned.

Exploratory Analyses

Several outcomes are identified as exploratory (level of HIE, blood pressure, length of hospitalization, resuscitation interventions, and placental pathology). These analyses will focus on descriptive statistics rather than hypothesis testing. Likewise any evaluations of subgroup differences by treatment group (other than race/ethnicity as mentioned previously) will be explored in secondary analyses for descriptive purposes and solely for purposes of generating hypotheses for future studies.

Follow up Study- While all secondary and exploratory outcomes that occur during the delivery hospitalization will be presented in the primary paper, all subjects will continue to be followed until 24 months of age to determine their long-term outcome. The sample size is powered to detect differences in their Ages and Stages Composite and MCHAT scores.

Substudies for cerebral oxygenation and echocardiography will be reported as separate projects on clinical trials.gov and analyzed independently.

VI. Recruitment

Eligibility criteria

The eligibility will be determined for each child at birth. Any vigorous or crying infant will receive usual care and will not be included in the study. All high-risk deliveries attended by the Pediatric team will be screened. If the infant is determined to be non-vigorous and needs resuscitation, the baby receives the treatment arm as assigned per the trial and will be added to the screening log as eligible for follow up. If the infant did not meet any exclusion criteria, the site's designated research coordinator or their designee will approach parents following delivery and resuscitation to explain the remaining portion of the study (ongoing data collection, and periodic contact via phone, text, letter or email for developmental follow-up studies). Each site will be responsible for maintaining their own master screening log. The purpose is for each screened patient to be assigned a study number to track eligibility, informed consent and data collection. The log with the study numbers and site patient identifiers will be kept in a secure, limited access area at each center. Only investigators and research personnel who are involved with the study will have access to the site specific log.

Inclusion Criteria

As a pragmatic trial, all deliveries that do not meet exclusion criteria will be included. We acknowledge that anticipating resuscitation based on fetal (abnormal fetal heart rate tracing) or delivery (need for instrumentation or meconium) criteria do not accurately predict the need for resuscitation. The determination for eligibility will be determined for each child at birth by the obstetrical provider. Any vigorous or crying infant will receive usual care (i.e., delayed cord clamping) and will not be included in the study. If the infant is non-vigorous as determined by usual practice the baby receives the treatment arm as assigned per the trial. **Non-viable infants or infants of unknown viability will not be included in the trial, only viable infants in distress. Infants born in extremis for whom no additional treatment will be offered by the attending neonatologist will not be enrolled in this trial. The individuals making the assessment of the infant at birth (Obstetrical Residents, Obstetrician, Midwife or other perinatal provider) are not co-investigators or key personnel so they will have no conflict of interest regarding enrollment.** Based on annual deliveries and the number of infants with a low Apgar score ≤3, we anticipate this will occur in about 3 percent of all term/near-term deliveries at each site.

- Non-vigorous Infants delivered at 35-41+6 weeks GA

Exclusion Criteria

- Known major congenital or chromosomal anomalies of newborn
- Known cardiac defects other than small ASD, VSD and PDA
- Complete placental abruption/cutting through the placenta at time of delivery
- Monochorionic multiples
- Cord anomaly (i.e. cord avulsion, true knot)
- Presence of non-reducible nuchal cord
- Perinatal providers unaware of the protocol

- Incomplete delivery data
- Infants born in extremis, for whom additional treatment will not be offered

This protocol will not adversely affect the rights and welfare of subjects, and will involve no more than minimal risk to subjects. This study meets the criteria of 45 CFR 46 Subpart D a) 404 the research is not greater than minimal risk.

No infant will be excluded or specifically included in this trial due to sex, race, or ethnicity. For this reason, the enrollment in this trial should closely match the overall combined demographics of the ten trial sites. There is currently no data to suggest that any gender or race/ethnicity differences exist relative to the endpoints of this trial. Due to the design of this pragmatic crossover cluster-randomized trial, all infants born at any given institution who qualify by way of being non-vigorous term/near term infants will be enrolled in the trial. For this reason, there is no possibility of selecting out specific populations for inclusion or exclusion.

VII. Ethical Considerations

The MINVI trial will be conducted in compliance with the guidelines of the Declaration of Helsinki in its latest form, the International Conference on Harmonization of Good Clinical Practice Guidelines. In case of modifications in the study protocol that are not merely of a formal nature but contain changes pertinent to the study participants, a renewed vote of the ethics committee will be obtained.

We collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. We have incorporated their suggestions and they enthusiastically support the study and would like to provide ongoing community awareness both locally and abroad. All other institutions will present this protocol to their appropriate parent and patient committees for collaboration and community support, if applicable.

The primary research team convened a meeting of all study sites and personnel on June 20, 2018. At this meeting all providers agreed to use their own clinical definition of non-vigorous but agreed to collect data on reasons which were unanimous (tone, color, and breathing).

Parental consent/waiver

Waiver of Consent

This protocol will not adversely affect the rights and welfare of subjects, and will involve no more than minimal risk to subjects. We will be comparing the outcomes of two current practice variations with a standardized protocol. Based on the current literature to date there are no known risks with early cord clamping or umbilical cord milking in near term and term non-vigorous infants. If the subject is non-vigorous they would receive the assigned standard of care for that year. All subsequent medical care would remain per hospital protocol in both years of enrollment. The only difference would be the standardization of cord management for the year in non-vigorous infants. If parents were to ask if anything would have been different if their baby was not in the study the answer would be no because subjects who are enrolled in the study will receive the same cord management that they would have received if they were not enrolled. The study design requires each delivering hospital to adopt one standard of care for each year of enrollment. However, this may have been a different

cord management than they would have received had the delivering hospital not elected to participate in this study or if the practitioner chose a different cord management based on the clinical situation. Therefore, the permission is to collect ongoing and follow-up data. The majority of these deliveries are emergent/urgent so we are requesting a waiver of consent. This allows the provider and/or research staff to carefully review the study intervention and data collection with the parents after the initial anxiety of an urgent delivery has decreased. We believe this is the correct approach for this trial. Requiring antenatal consent would also adversely affect the generalizability of the data obtained. Without the waiver of consent sites would require antenatal consent and this has been shown to limit the enrollment of the sickest infants in studies by eliminating the ability to obtain consent from mothers with limited prenatal care and/or emergent deliveries. This results in excluding some of the sickest infants that could potentially benefit the most from a trial intervention in which there are minimal risks.

Parents will be notified about the study with the ability to opt out of the trial prior to delivery by the following: 1) Expectant mothers will receive a brochure and discuss the study with the obstetrical provider at the prenatal visits. 2) Brochures will be included in the hospital admission packets 3) Posters and signs will be displayed at admission areas. Every effort to notify all expectant families will be made prior to delivery. While routine practice will be to perform the assigned intervention for that year. A family that opts out can discuss with the clinical team whether they have a different preference for cord management other than the routine practice in the event resuscitation is needed. However, umbilical cord management is ultimately at the discretion of the practitioner based on the clinical situation. If families opt out of the study, the research team will track them on the screening log and the electronic chart may be flagged to not approach the families for consent and ongoing data collection. Each site's PI will be responsible for training their research team members on this process to ensure that no families are approached for ongoing data collection.

Waiver of HIPAA Authorization

Partial waiver of HIPAA Authorization is requested for screening. The use or disclosure will not adversely affect the rights and welfare of the subjects. This research protocol cannot be conducted without partial waiver because investigators would be unable to identify eligible subjects. This will involve no more than minimal risk to the privacy of subjects. Only research investigators/assistants will access PHI for eligibility and screening purposes. The site specific screening log will include: names of subjects, date of birth, medical record number, eligibility based on cord management, admitted to NICU, date consented, reason not enrolled. For all eligible infants, parents will be approached for informed consent and HIPAA authorization.

A full waiver of individual HIPAA authorization is requested for instances when the research team is unavailable to obtain consent (i.e. infant is born and dies or is discharged before study team could approach). This will allow us to collect minimal data that is coded to protect subject's confidentiality. This will support outcome data for the primary outcome. The minimal data collected under waiver will be collected from the existing medical records and will include: information from the delivery room record, admission to NICU, and information from the study source document (appendix 3). We have an adequate plan to protect the identifiers from improper use and disclosure.

PHI that will be accessed for screening will be identifiable on research-related forms by a study number. We will take the following precautions to maintain the confidentiality of identifiable subject information. We will also keep subject's identity

separate from their data on a Master log and coded. PHI will not be used or disclosed to any other person or entity, except as required by law.

1. Paper-based records will be kept in a secure location and accessible only to persons involved in the study
2. Computer-based files will be available only to persons involved in the study through the use of access privileges and passwords.
3. Prior to accessing any PHI, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information
4. Whenever feasible, identifiers will be removed from study-related information
5. PHI will not be disclosed or re-used for other purposes

Follow-up Survey - When parents are contacted to provide them results for the trial (study publications), they will be asked if they would be willing to participate in a survey. Since research staff has already contact families by email and text for developmental data, no new PHI is required. This brief survey is being done to determine their opinions regarding the process of informed consent for this trial. A similar survey was used for a different study conducted by the lead study site and provided valuable insight. The survey will be sent to parents through email or text with a RedCap link, and only the results will be available to the investigators and staff.

VIII. Risks

Loss of confidentiality: All data will be safeguarded in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the principles and practices of strict confidentiality. Data will be maintained by numerical code rather than personal identifiers and computer-based files will be available only to persons involved in the study through the use of access privileges and passwords. However there is still a potential risk of loss of data and privacy.

Hemoglobin lab draw: will be performed by licensed phlebotomist or RN. As with all blood draws, possible risks include irritation of the vein, such as redness or swelling, pain, bruising or bleeding at the blood draw site, and there is a rare possibility of infection.

Survey Completion: minimal known risks including loss of confidentiality.

As with any study, there may be risks that currently are unforeseeable.

Risk Management

Protection against Risk

Practitioners at all sites have experience with performing UCM and ECC within their normal clinical care. Only research team members (with appropriate research training relevant to protection of human subjects) shall have access to the project's databases.

Management of Risks

Hemoglobin lab draw: Will be performed by clinical staff that are trained and experienced in drawing blood from newborns. Proper techniques will be used at all times to minimize the chance of infection thereby minimizing potential risks related to the collection of blood samples. All efforts will be made to reduce infants discomfort (i.e. warming infants heel, providing oral glucose, or hospital standard practice).

Data Collection and Survey Completion

All data will be safeguarded in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the principles and practices of strict confidentiality. Every reasonable effort will be made to keep the subjects records confidential. Subject's records will be stored in a secure office. Codes, instead of names, will be used to identify the collected information.

Reporting Process

The population being studied is at increased risk of all complications (such as hypoxic ischemic encephalopathy) associated with term and near-term infants who are deemed to require immediate resuscitation. The majority of these events will be expected and included in data collection and reported in all DSMB analyses. However, all SAE's of death, polycythemia/jaundice requiring exchange transfusion, pulmonary hemorrhage and severe IVH (grade 3 or 4) on HUS or MRI will be reported within 3 days of discovery of event, to UCSD DCoC via REDCap.

Monitoring

The DCoC will send out monthly reports detailing enrollment, SAE's, protocol deviations and data queries. Clinical Coordinating Center (SMBHWN) Data team will be monitoring sites as needed throughout the trial. The purposes of monitoring visits, which will generally be done by phone or GoToMeeting, are to:

- Ensure the rights and safety of participants
- Confirm that the study is conducted in accordance with GCP guidelines
- Ensure maintenance of required documents
- Verify adherence to the protocol
- Monitor the quality of data collected
- Ensure accurate reporting and documentation of all AEs and unanticipated problems

Data Safety Monitoring Board (DSMB)

An expert board consisting of perinatologists, neonatologists, outside statisticians and a former NICU parent will be closely reviewing all serious adverse out comes. This group has been established to: 1) protect all study patients, 2) safeguard the interests of all study patients, 3) monitor the overall conduct of the trial, 4) advise the investigators to protect the integrity of the trial, and 5) supervise the conduct and analysis of all interim analyses. The DSMB will review the first 200 enrolled infants. If the first review does not show any evidence of safety signal for adverse outcomes in either group on blinded analyses, additional blinded reviews will be conducted when 50 and 75 percent of subjects are enrolled. If the odds ratio of NICU admission or death between the two arms exceeds a threshold, it will trigger a safety signal. We will suggest to the DSMB the threshold of an odds ratio of 2.5 as the threshold for a formal meeting to discuss potentially stopping the trial. However, the DSMB should discuss and determine the threshold. There is no plan to stop for efficacy as the trial design (cluster randomized cross-over) necessitates that both arms of the trial be completed at each site before efficacy can be

adequately assessed. If the trial were stopped prematurely, we would perform planned analyses on the data collected at the time of the closing of the study. The findings will be communicated to all study staff by the data center in monthly reports via email. According to the study's Statistical Analysis Plan and due to the cross-over design of the study, there will be no planned formal interim analysis for efficacy or futility.

IX. Data Management

Centralized Data Collection

REDCap (Research Electronic Data Capture). All case report forms for the trial will be captured using a secure web-based data capture system REDCap. REDCap under the direction of the UCSD ACTRI Biomedical Informatics division offers and manages REDCap. The ACTRI Biomedical Informatics team will maintain and provide full administration and support for REDCap. Data captured electronically in the delivery room will be uploaded to REDCap for future analysis for all sites. The REDCap application supports many data collection and analysis projects. Data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning and analytic assistance from biostatisticians. The iterative development and testing process results in a well-planned data collection strategy for individual studies. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. The system has been deployed using a highly secure, HIPAA-compliant network design and is housed in a physically secure data center. Back up of data is performed nightly and archived off-site for two years for Disaster Recovery purposes. Principal investigators may opt to archive the data for up to seven (7) years offsite to AWS Glacier.

Data that will be accessed, used and collected will be identifiable on research-related forms by a study number. We will take the following precautions to maintain the confidentiality of identifiable subject information. We will also keep subject's identity separate from their data on a Master log and coded.

1. Paper-based records will be kept in a secure location and accessible only to persons involved in the study
2. Computer-based files will be available only to persons involved in the study through the use of access privileges and passwords.
3. Prior to accessing any PHI, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information
4. Whenever feasible, identifiers will be removed from study-related information

Data Collection

Under waiver of individual HIPAA, we will collect the following minimal data set from all eligible subjects (parents that opt out will not be included):

Screening ID, Month/Year of birth, gestational age, SGA, time of cord clamping, Breathing or crying prior to cord clamping, birth assessment of tone, number of times cord milked, location of infant when milked (i.e. mothers abdomen, below level of introitus) birth weight, gender, APGARS at 1 and 5 minutes,, resuscitation procedures (CPAP, PPV, intubation, chest

compressions, epinephrine, max FiO2), NIRS data, disposition (NICU admission, or stable and staying with parent), pregnancy and delivery risk factors (diabetes, suspected or confirmed Triple I, hypertension, rupture of membranes).

After Informed Consent we will collect the following full data set:
Maternal data from infant's chart: Age, Race/Ethnicity, Level of Education, Mode of Delivery, Anesthesia (general, Spinal Epidural), Medications, Placental Weight. All maternal data will be collected from the infant's chart; the mother's chart will not be accessed for study purposes.
Infant data: Includes all data collected under waiver, plus Race/Ethnicity, Multiple gestation, length (cm), head circumference (cm), Hemoglobin between 12-48 hrs, Venous and/or arterial cord pH (if available), cardiac US, Peak total serum bilirubin (mg/dL)or Transcutaneous Bilirubin level, Polycythemia in the first week of life (Hct >65%), Duration of phototherapy days, Use of cardiac inotropes (dopamine, dobutamine, epinephrine), Early onset sepsis (positive blood or CSF culture at < 72 HOL), Duration of intubated and mechanical ventilation (days), Need for blood transfusion (DOL of 1st transfusion and total number), Length of hospitalization (total days), ASQ3, MCHAT, MRI white matter injury, HIE: mild, moderate, severe (initial screen completed at 1-6 hours of life), HIE: mild, moderate, severe (highest stage before discharge), Therapeutic Hypothermia, Placental pathology, PPHN.

Notification of Parents prior to enrollment: Both mother and baby will be subjects in this study. We are informing parents in three ways. First, all obstetric practices that refer babies to the study hospitals will have information such as brochures in their offices, at prenatal childbirth education classes and the obstetrician will discuss hospital's participation in the study with their patients. Second, there will be signs (to be developed from handout) about the study at prenatal sites and physician offices. Both will have information for parents about contact information of the researchers. Finally, there will be information about the study on the Sharp website with answers to frequently asked questions. High visibility posters of the study and information brochures will be posted in the hospitals for limited to no prenatal care situations and for those that may not have access to internet resources. All documents created for parent notification will be submitted for IRB approval before use.

Protocol Deviations

The following deviations will be entered on the Deviation Report Form in REDCap as they are identified:

- Cord clamping ≥ 60 seconds will be considered a protocol violation and analyzed due to the confounding effects of delayed cord clamping.
- Patient did not receive correct treatment arm.

Serious Adverse Events (SAE)

All SAE's of death, polycythemia/jaundice requiring exchange transfusion, pulmonary hemorrhage or severe IVH (grade 3 or 4) on HUS or MRI will be reported within 3 days of discovery of event, to UCSD DCoC via REDCap. The DCoC will forward all SAE reports to the DSMB and PI.

Unanticipated Event or Problems

The investigator will be responsible for reporting an unanticipated adverse event in REDCap, if it meets all of the criteria listed below:

1. It is an unexpected event (nature, severity or frequency) and not addressed within the study protocol or informed consent document
2. It is related or possibly related to the research as determined by the PI – there is a reasonable possibility that the event may have been caused by the procedures involved in the research
3. And suggests that the research places the subject or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

If the unanticipated event is determined serious by the PI, it must be reported to the DCoC within three (3) days in REDCap; within 14 days for a Non-serious unanticipated event. The DCoC will report this to the DSMB who will determine if the adverse event changes the known risk to study subjects. If the information changes the known risk to subjects, the DSMB's report regarding the change in risk will be released to all participating investigators. The DSMB may request changes to the DSMP.

Data Safety Monitoring Board (DSMB)

A DSMB has been established to:

1) Protect all study patients
2) Safeguard the interests of all study patients
3) Monitor the overall conduct of the trial
4) Advise the investigators to protect the integrity of the trial, and
5) Supervise the conduct and analysis of all interim analyses.

The DSMB will receive regular reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of pre-determined early stopping rules. All Serious Adverse Events (**SAEs**) will be reported within 3 days of discovery to the Data Coordinating Center **(DCoC)** and forwarded to the DSMB; reports of adverse events and recruitment will be sent monthly; demographics will be included with the interim and final safety and efficacy analyses. The DSMB will conduct interim analyses and project statisticians, independently from the trial leadership and staff. The role of the trial investigators is to notify the IRB of any issues that are relative to patient safety or to early stopping of the study. The study will be closely monitored for issues of data quality, study conduct, and adverse events. These analyses will be presented to the DSMB.

Trial Timeframe

Trial stages	Timeframe
Protocol development	April- June 2018
Protocol finalized	July 2018
Site determination	June 2018, Investigator Meeting
Sites submit IRB application	July-August 2018
Finalize contracts and payment methods	September-October 2018
Site Randomization and education	October – December 2018
Recruitment phase	January 2019- March 2021
Assessment phase	Primary outcome June 2021
Analysis	2021 for primary outcome, 2023 for neurodevelopmental outcomes
Publication	2021 on primary outcome, 2023 for neurodevelopmental follow-up

Publication Plan

The trial will be registered on ClinicalTrials.gov prior to the randomization of the first site. The Publications and Presentations (**P&P**) policies and procedures for this trial can be modeled after those that have been used successfully in other studies. These will be developed, implemented, and enforced by a P&P Committee, chaired by a to-be-named individual for the trial, with representation of study members from the trial. The P&P policies and procedures will be developed as part of the Manual of Operations and communicated to participating sites as part of the site initiation activities. All investigators will be encouraged to participate in opportunities for presentation and publications; resources within the DCoC will be available to facilitate this. These policies will provide for optimizing the use of the valuable data collected by the study and provide an additional non-financial incentive for participating investigators.

Statements of compliance

The clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The clinical investigation will comply with the relevant national regulations of each participating medical center, and will not begin until required approvals from ethical committees have been obtained. Additional requirements imposed by the ethical committees will be followed. The clinical investigation will be conducted in accordance with this protocol.

Appendix 1 Data Collected

DATA COLLECTED ABOUT INFANTS AND MOTHERS

Maternal data from infant's chart:

1. Age
2. Race/Ethnicity
3. Diabetes (gestational, Type 1 or 2) (yes/no)
4. Suspected or confirmed Triple I, chorioamnionitis (yes/no)
5. Hypertension (yes/no)
6. Rupture of Membranes (hours)
7. Mode of Delivery
8. Type of Anesthesia
9. Maternal medications (i.e. magnesium, fentanyl)
10. Placental Weight
11. Level of education
12. COVID-19 confirmed positive

Data collected from all eligible infants under waiver:

13. Screening ID
14. Month/Year of birth
15. Birth assessment of tone
16. ECC or # times Milked
17. Timing of cord clamping
18. Breathing/Crying before cord clamped
19. 1 and 5 min Apgar
20. Resuscitation interventions (cpap, ppv, intubation, compressions, epinephrine, max Fio2)
21. NIRS, HR, SpO2 in del room
22. Gestational Age
23. Birth Weight
24. Gender
25. Disposition(NICU, Death or Dyad care)
26. Infant/delivery risk factors
27. NICU admission Dx
28. Reason Peds called to delivery
29. Multiple Gestation
30. COVID-19 confirmed positive

Infant data collected after consent:

31. Length, FOC (cm)
32. SGA (<10%)
33. Race/Ethnicity
34. Cord Gasses (ven/art)
35. Baby blood gas- First available
36. Hypoglycemia- First 24 hrs
37. Volume Bolus (i.e. NS) First 24 hrs
38. Hemoglobin 12-48 Hrs of life
39. Measures of cardiac function
40. Peak total bilirubin (serum or transcutaneous, Bhutani nomogram)
41. Duration of phototherapy days
42. Polycythemia within 1st week
43. PPHN
44. Therapeutic Hypothermia
45. Seizures (Confirmed by neurologist)
46. HIE: Mild, Mod, Severe (initial screen completed 1-6 hours)
47. HIE: Mild, Mod, Severe (highest stage before discharge)
48. MRI white matter injury
49. NICU admission BP
50. Use of cardiac inotropes (dopamine, dobutamine, epinephrine)
51. Early onset sepsis (positive blood or CSF culture at $\leq$ 72 HOL) (yes/no)
52. Duration of intubated and mechanical ventilation (days)
53. Need for Blood Transfusion (DOL of 1st transfusion and total number)
54. Need for other blood products (PLT, FFP, Cryo)
55. Placental Pathology
56. Length of hospitalization (total days)
57. Concurrent study enrollment
58. Severe IVH (Grade 3-4)

Developmental screening through 2 years of age

59. Medical history at 3 and 18 months
60. ASQ- at 6, 12 and 24 months
61. MCHAT Survey at 24 months
62. BSID III at 2 years of age if done
63. COVID-19 confirmed positive

Appendix 2 Admission Criteria

MINVI Trial Eligible criteria for NICU admission

If an infant has any of the following documented prior to discharge they will be considered as achieving NICU admission for the purpose of the MINVI trial.

Any other reasons will NOT be considered an admission for trial purposes.

- Respiratory Distress (including any of the following: tachypnea, Grunting, Retractions)
- Bradycardia/Tachycardia
- Hypotonia
- Lethargy/Difficult to arouse
- Hypertonia/Irritability
- Poor feeding/Emesis
- Hypoglycemia
- Oxygen Desaturations/Cyanosis, Need for oxygen
- Apnea
- Seizures or Seizure-like activity
- Hyperbilirubinemia
- Temperature instability

Unless any of the above are checked the following are not acceptable criteria for NICU admission for the purposes of the MINIVI trial.

- High WBC, bandemia or CRP
- Abnormal Cord Gas (without abnormal neurological exam)
- Maternal anxiety or unavailability to care for infant
- Congenital anomaly (should be excluded)
- Known Cardiac Anomaly (should be excluded)
- Abdominal mass
- Skin Lesions

Appendix 3 Delivery Room Data Collection

MINVI Delivery Room Data

Treatment Assignment **UCM** **ECC**

Subject ID # _____

Site #_____

GA: _____ Weeks _____Days

Date of Delivery_____

Mode of Delivery: **VAG** **CS** **STAT** **ASSISTED**

Reason Peds team called	
Multiple Gestation	Birth Order A B C
Poor Tone? Poor/No respirations? Pale?	Yes □ No □ Yes □ No □ Yes □ No □
What Tx did patient receive?	ECC(<30sec) Milking (# of times) ___
Timing of Cord Clamping	Seconds
Cry or Breathing prior to clamping?	Yes No
Location of infant during cord treatment	□ Mothers abdomen □ Mothers leg □ OB held at level of introitus □ OB held below level of introitus
Reason Pt did not receive correct Tx	□ Abruption/Cut through placenta □ Cord tear/separation during delivery □ MD refused (OB or Neonatologist) □ Non-reducible nuchal cord (needed to cut) □ Assistance unavailable □ Other reason_____
Respiratory Support in Delivery Room	**Maximum** FiO2: _____ CPAP: □ Yes □ No PPV: □ Yes □ No Intubation: □ Yes □ No Chest compressions: □ Yes □ No Medications: □ Yes □ No
Disposition	□ Admitted to NICU □ Died in DR □ Dyad care

Appendix 4 Summary of Changes

MINVI

Protocol Summary of Changes

To: All Site Participants

FROM: Dr. Anup Katheria, PI

SUBJECT: Updated Protocol Version 1.1, dated September 28th, 2018

Updated Protocol Version 1.2, dated October 10th, 2018

Updated Protocol Version 1.3, dated October 17th, 2018

Updated Protocol Version 1.4, dated November 28th, 2018

Updated Protocol Version 1.5, dated December 20th, 2018

Updated Protocol Version 1.6, dated May 3rd, 2019

Updated Protocol Version 1.7, dated November 11, 2019

Updated Protocol Version 1.8, dated November 12, 2020

DATE:

Version 1.8

I. **Sharp Grossmont Hospital added as NIRS sub-study site**

II. **Confirmed COVID-19 positive results added as data collection point**

Version 1.7

I. Increased overall study n=1200, decreased NIRS substudy n=20
II.
III. Updates to statistical analysis approach
IV. Participating centers updated
V. Updated Data Center and Steering Committee personnel
VI. Specific Aim 2 H3; changed *improved* blood pressure to *better* blood pressure
VII. Edits to formatting and language for consistency and clarification.
VIII. Efficacy Endpoints clarified as exploratory aims:
    a. Resuscitation interventions, blood pressure, length of hospitalization and level of HIE.

Version 1.6 May 03, 2019

I. Updated intervention flowsheet to include added exclusion criteria (from v1.5)
II. Added the following SAE's
    a. Severe IVH (grade 3 or 4) on HUS or MRI
    b. Pulmonary Hemorrhage
III. Increased window for echocardiogram sub-study to 12 +/- 6 hours of life
IV. Site list updated

Version 1.5 December 20, 2018

I. Updated language regarding standards of care and waiver of consent
II. Added the following exclusion criteria:
    a. No delivery data
    b. Cord anomaly (i.e. avulsion or true knot)
    c. Infants born in extremis for whom no additional care will be offered
III. Addition of temperature instability as a NICU admission criteria

Version 1.4 November 28, 2018

I. Updated DSMB members and study stopping rules
II. Addition of echocardiogram sub-study at Sharp Mary Birch and Sharp Grossmont Hospitals
III. Updated terminology "chorioamnionitis" to current recommendation that suggests use of "triple I".
IV. Update to assessment of risk; Language clarified regarding lack of evidence for use of UCM or ECC in the non-vigorous population.
V. Clarification on parents who opt out and their clinical management

Version 1.3 October 17 , 2018

The following edits have been made based on updated information:

I. REDCap was incorrectly left off page 33
II. Training may be simulation based
III. Clarify parent opt out

Version 1.2 October 10, 2018

The following edits have been made based on updated information:

I. Language was either inserted or deleted to reflect the recent findings of the PREMOD2 study to more accurately reflect risk.
II. Updated site list will be maintained on the Manual of Operations
III. A new member was added to the DSMB

Version 1.1 September 28, 2018

The following edits have been made for consistency and clarification of the protocol:

I. Flowchart updated to remove CBCL from follow-up.
II. Added location of infant when milked to Delivery Room Data collection source doc.
III. Revised language regarding waiver of consent.
IV. Deviations:
    i. Clarification: a delay in cord clamping >/= 60 seconds will be deviation
    ii. Deleted: deviation for cord milking <4 or >6 times
V. SAEs:
    i. Deleted: SAE for CPR in del room

References

1. Wall SN, Lee ACC, Niermeyer S, English M, Keenan WJ, Carlo W, Bhutta ZA, Bang A, Narayanan I, Ariawan I, Lawn JE. Neonatal resuscitation in low-resource settings: What, who, and how to overcome challenges to scale up? International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2009;107(Suppl 1):S47-S64. doi: 10.1016/j.ijgo.2009.07.013. PubMed PMID: PMC2875104.
2. Ersdal HL, Linde J, Mduma E, Auestad B, Perlman J. Neonatal outcome following cord clamping after onset of spontaneous respiration. Pediatrics. 2014;134(2):265-72. Epub 2014/07/16. doi: 10.1542/peds.2014-0467. PubMed PMID: 25022738.
3. Mercer J, Erickson-Owens D, Skovgaard R. Cardiac asystole at birth: Is hypovolemic shock the cause? Medical hypotheses. 2009;72(4):458-63. Epub 2009/01/06. doi: 10.1016/j.mehy.2008.11.019. PubMed PMID: 19121560.
4. Menticoglou S, Schneider C. Resuscitating the Baby after Shoulder Dystocia2016;2016:8674167. doi: 10.1155/2016/8674167. PubMed PMID: 27493815.
5. Perez A, Ritter S, Brotschi B, Werner H, Caflisch J, Martin E, Latal B. Long-term neurodevelopmental outcome with hypoxic-ischemic encephalopathy. The Journal of pediatrics. 2013;163(2):454-9. Epub 2013/03/19. doi: 10.1016/j.jpeds.2013.02.003. PubMed PMID: 23498155.
6. Martinez-Biarge M, Cheong JL, Diez-Sebastian J, Mercuri E, Dubowitz LM, Cowan FM. Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period. The Journal of pediatrics. 2016;173:62-8.e1. Epub 2016/04/07. doi: 10.1016/j.jpeds.2016.02.064. PubMed PMID: 27049002.
7. Getahun D, Rhoads GG, Demissie K, Lu SE, Quinn VP, Fassett MJ, Wing DA, Jacobsen SJ. In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics. 2013;131(1):e53-61. Epub 2012/12/12. doi: 10.1542/peds.2012-1298. PubMed PMID: 23230063.
8. Zhu T, Gan J, Huang J, Li Y, Qu Y, Mu D. Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis. Journal of child neurology. 2016;31(10):1235-44. Epub 2016/05/28. doi: 10.1177/0883073816650039. PubMed PMID: 27229008.
9. Pediatrics AAo. Textbook of Neonatal Resuscitation2016.
10. Arcilla RA, Oh W, Lind J, Gessner IH. Pulmonary arterial pressures of newborn infants born with early and late clamping of the cord. Acta paediatrica Scandinavica. 1966;55(3):305-15. Epub 1966/05/01. PubMed PMID: 5960343.
11. Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. Obstetrics and gynecology. 2017;129(1):e5-e10. Epub 2016/12/22. doi: 10.1097/aog.0000000000001860. PubMed PMID: 28002310.
12. Takami T, Suganami Y, Sunohara D, Kondo A, Mizukaki N, Fujioka T, Hoshika A, Akutagawa O, Isaka K. Umbilical Cord Milking Stabilizes Cerebral Oxygenation and Perfusion in Infants Born before 29 Weeks of Gestation. The Journal of pediatrics. 2012. Epub 2012/05/15. doi: 10.1016/j.jpeds.2012.03.053. PubMed PMID: 22578578.

13. Colozzi AE. Clamping of the umbilical cord; its effect on the placental transfusion. The New England journal of medicine. 1954;250(15):629-32. Epub 1954/04/15. doi: 10.1056/nejm195404152501502. PubMed PMID: 13154597.
14. Walsh SZ. Early clamping versus stripping of card: comparative study of electrocardiogram in neonatal period. British heart journal. 1969;31(1):122-6. Epub 1969/01/01. PubMed PMID: 5764957; PMCID: Pmc487456.
15. Erickson-Owens DA, Mercer JS, Oh W. Umbilical cord milking in term infants delivered by cesarean section: a randomized controlled trial. Journal of perinatology : official journal of the California Perinatal Association. 2012;32(8):580-4. Epub 2011/11/19. doi: 10.1038/jp.2011.159. PubMed PMID: 22094494.
16. Upadhyay A, Gothwal S, Parihar R, Garg A, Gupta A, Chawla D, Gulati IK. Effect of umbilical cord milking in term and near term infants: randomized control trial. American journal of obstetrics and gynecology. 2013;208(2):120.e1-6. Epub 2012/11/06. doi: 10.1016/j.ajog.2012.10.884. PubMed PMID: 23123382.
17. Jaiswal P, Upadhyay A, Gothwal S, Chaudhary H, Tandon A. Comparison of Umbilical Cord Milking and Delayed Cord Clamping on Cerebral Blood Flow in Term Neonates. Indian journal of pediatrics. 2015. Epub 2015/05/27. doi: 10.1007/s12098-015-1734-2. PubMed PMID: 26008758.
18. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. JAMA pediatrics. 2015;169(1):18-25. Epub 2014/11/05. doi: 10.1001/jamapediatrics.2014.1906. PubMed PMID: 25365246.
19. Katheria A, Blank D, Rich W, Finer N. Umbilical cord milking improves transition in premature infants at birth. PloS one. 2014;9(4):e94085. doi: 10.1371/journal.pone.0094085. PubMed PMID: 24709780; PMCID: 3978008.
20. Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T, Takahashi S, Harada K. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. Archives of disease in childhood Fetal and neonatal edition. 2008;93(1):F14-9. Epub 2007/01/20. doi: adc.2006.108902 [pii]

10.1136/adc.2006.108902. PubMed PMID: 17234653.
21. Mercer JS, Erickson-Owens DA. Rethinking placental transfusion and cord clamping issues. The Journal of perinatal & neonatal nursing. 2012;26(3):202-17; quiz 18-9. Epub 2012/07/31. doi: 10.1097/JPN.0b013e31825d2d9a. PubMed PMID: 22843002.
22. Rich W, Finer NN, Gantz MG, Newman NS, Hensman AM, Hale EC, Auten KJ, Schibler K, Faix RG, Laptook AR, Yoder BA, Das A, Shankaran S. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. Pediatrics. 2012;129(3):480-4. Epub 2012/03/01. doi: 10.1542/peds.2011-2121. PubMed PMID: 22371462; PMCID: Pmc3289530.
23. Rich WD, Leone T, Finer NN. Delivery room intervention: improving the outcome. Clinics in perinatology. 2010;37(1):189-202. Epub 2010/04/07. doi: 10.1016/j.clp.2010.01.011. PubMed PMID: 20363455.
24. Tarnow-Mordi WO, Duley L, Field D, Marlow N, Morris J, Newnham J, Paneth N, Soll RF, Sweet D. Timing of cord clamping in very preterm infants: more evidence is needed. American journal of obstetrics and gynecology. 2014;211(2):118-23. Epub 2014/04/02. doi: 10.1016/j.ajog.2014.03.055. PubMed PMID: 24686151.
25. Andersson O, Hellstrom-Westas L, Andersson D, Domellof M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. Bmj. 2011;343:d7157. Epub 2011/11/18. doi: 10.1136/bmj.d7157. PubMed PMID: 22089242; PMCID: Pmc3217058.

26. Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellof M, Hellstrom-Westas L. Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. JAMA pediatrics. 2015;169(7):631-8. Epub 2015/05/27. doi: 10.1001/jamapediatrics.2015.0358. PubMed PMID: 26010418.
27. Bora R, Akhtar SS, Venkatasubramaniam A, Wolfson J, Rao R. Effect of 40-cm segment umbilical cord milking on hemoglobin and serum ferritin at 6 months of age in full-term infants of anemic and non-anemic mothers. Journal of perinatology : official journal of the California Perinatal Association. 2015. Epub 2015/08/01. doi: 10.1038/jp.2015.92. PubMed PMID: 26226248.
28. Walsh SZ. Early clamping versus stripping of card: comparative study of electrocardiogram in neonatal period. British heart journal. 1969;31(1):122-6.
29. Siddall RS, Crissey RR, Knapp WL. Effect on cesarean section babies of stripping or milking of the umbilical cords. American journal of obstetrics and gynecology. 1952;63(5):1059-64. Epub 1952/05/01. PubMed PMID: 14923706.
30. Siddall RS, Richardson RP. Milking or stripping the umbilical cord; effect on vaginally delivered babies. Obstetrics and gynecology. 1953;1(2):230-3. Epub 1953/02/01. PubMed PMID: 13037214.
31. Whipple GA, Sisson TR, Lund CJ. Delayed ligation of the umbilical cord; its influence on the blood volume of the newborn. Obstetrics and gynecology. 1957;10(6):603-10. Epub 1957/12/01. PubMed PMID: 13484167.
32. Kumar B, Upadhyay A, Gothwal S, Jaiswal V, Joshi P, Dubey K. Umbilical Cord Milking and Hematological Parameters in Moderate to Late Preterm Neonates: A Randomized Controlled Trial. Indian pediatrics. 2015;52(9):753-7. Epub 2015/11/01. PubMed PMID: 26519708.
33. Jaykka S. Capillary erection and the structural appearance of fetal and neonatl lungs. Acta paediatrica. 1958;47(5):484-500. Epub 1958/09/01. PubMed PMID: 13582626.
34. Katheria AC, Brown MK, Faksh A, Hassen KO, Rich W, Lazarus D, Steen J, Daneshmand SS, Finer NN. Delayed Cord Clamping in Newborns Born at Term at Risk for Resuscitation: A Feasibility Randomized Clinical Trial. The Journal of pediatrics. 2017. Epub 2017/05/21. doi: 10.1016/j.jpeds.2017.04.033. PubMed PMID: 28526223.
35. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, Kim H-S, Liley HG, Mildenhall L, Simon WM, Szyld E, Tamura M, Velaphi S, Collaborators obotNRC. 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-S41. doi: 10.1161/cir.0000000000000276.
36. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, Simon WM, Weiner GM, Zaichkin JG. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):S543-60. Epub 2015/10/17. doi: 10.1161/cir.0000000000000267. PubMed PMID: 26473001.
37. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. Journal of Perinatology. 2017;37(2):105-11. doi: 10.1038/jp.2016.151. PubMed PMID: PMC5290307.
38. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants. Pediatrics. 2015;136(1):61-9. Epub 2015/07/01. doi: 10.1542/peds.2015-0368. PubMed PMID: 26122803; PMCID: Pmc4485011.
39. Bhatt S, Polglase GR, Wallace EM, te Pas AB, Hooper SB. Ventilation before Umbilical Cord Clamping Improves the Physiological Transition at Birth. Frontiers in pediatrics. 2014;2:113. doi: 10.3389/fped.2014.00113. PubMed PMID: PMC4203108.
40. Nevill E, Meyer MP. Effect of delayed cord clamping (DCC) on breathing and transition at birth in very preterm infants. Early human development. 2015;91(7):407-11. Epub 2015/05/20. doi: 10.1016/j.earlhumdev.2015.04.013. PubMed PMID: 25984654.

41. Katheria A, Poeltler D, Durham J, Steen J, Rich W, Arnell K, Maldonado M, Cousins L, Finer N. Neonatal Resuscitation with an Intact Cord: A Randomized Clinical Trial. The Journal of pediatrics. 2016. Epub 2016/08/31. doi: 10.1016/j.jpeds.2016.07.053. PubMed PMID: 27574999.
42. McAdams RM, Backes CH, Fathi O, Hutchon DJR. Revert to the original: time to re-establish delayed umbilical cord clamping as the standard approach for preterm neonates. Matern Health Neonatol Perinatol. 2018;4:13. Epub 2018/07/13. doi: 10.1186/s40748-018-0081-5. PubMed PMID: 29997896; PMCID: PMC6030773 interests.Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
43. Katheria A, Garey D, Truong G, Akshoomoff N, Steen J, Maldonado M, Poeltler D, Harbert MJ, Vaucher YE, Finer N. A Randomized Clinical Trial of Umbilical Cord Milking vs Delayed Cord Clamping in Preterm Infants: Neurodevelopmental Outcomes at 22-26 Months of Corrected Age. J Pediatr. 2018;194:76-80. Epub 2017/12/17. doi: 10.1016/j.jpeds.2017.10.037. PubMed PMID: 29246467.
44. Katheria AC, Leone TA, Woelkers D, Garey DM, Rich W, Finer NN. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. The Journal of pediatrics. 2014;164(5):1045-50 e1. doi: 10.1016/j.jpeds.2014.01.024. PubMed PMID: 24560179.
45. Katheria AC, Brown MK, Faksh A, Hassen KO, Rich W, Lazarus D, Steen J, Daneshmand SS, Finer NN. Delayed Cord Clamping in Newborns Born at Term at Risk for Resuscitation: A Feasibility Randomized Clinical Trial. The Journal of pediatrics. 2017;187:313-7.e1. Epub 2017/05/21. doi: 10.1016/j.jpeds.2017.04.033. PubMed PMID: 28526223.
46. Katheria AC, Brown MK, Rich W, Arnell K. Providing a Placental Transfusion in Newborns Who Need Resuscitation. Frontiers in pediatrics. 2017;5:1. Epub 2017/02/10. doi: 10.3389/fped.2017.00001. PubMed PMID: 28180126; PMCID: PMC5263890.
47. Katheria AC, Wozniak M, Harari D, Arnell K, Petruzzelli D, Finer NN. Measuring cardiac changes using electrical impedance during delayed cord clamping: a feasibility trial. Maternal Health, Neonatology and Perinatology. 2015;1(1). doi: 10.1186/s40748-015-0016-3.
48. Barbui C, Cipriani A. Cluster randomised trials. Epidemiology and psychiatric sciences. 2011;20(4):307-9. Epub 2011/12/29. PubMed PMID: 22201207.
49. Arnup SJ, Forbes AB, Kahan BC, Morgan KE, McDonald S, McKenzie JE. The use of the cluster randomized crossover design in clinical trials: protocol for a systematic review. Systematic reviews. 2014;3:86. Epub 2014/08/15. doi: 10.1186/2046-4053-3-86. PubMed PMID: 25115725; PMCID: PMC4138528.
50. Connolly SJ, Philippon F, Longtin Y, Casanova A, Birnie DH, Exner DV, Dorian P, Prakash R, Alings M, Krahn AD. Randomized cluster crossover trials for reliable, efficient, comparative effectiveness testing: design of the Prevention of Arrhythmia Device Infection Trial (PADIT). The Canadian journal of cardiology. 2013;29(6):652-8. Epub 2013/05/25. doi: 10.1016/j.cjca.2013.01.020. PubMed PMID: 23702356.

51. Arnup SJ, McKenzie JE, Hemming K, Pilcher D, Forbes AB. Understanding the cluster randomised crossover design: a graphical illustraton of the components of variation and a sample size tutorial. Trials. 2017;18(1):381. Epub 2017/08/16. doi: 10.1186/s13063-017-2113-2. PubMed PMID: 28810895; PMCID: PMC5557529.