Protocol

PREMOD2

Premature Infants Receiving Milking or Delayed Cord Clamping: Randomized Controlled Multicenter Non-Inferiority Trial

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	See Manual of Operations for complete list of additional sites			

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35 **Protocol Summary**

Study Title	Premature Infants Receiving Milking or Delayed Cord Clamping: Randomized Controlled Multicenter Non- Inferiority Trial [PREMOD2]
Population	Premature Infants 23^0 - 31^6 weeks gestational age
Primary Objective	To compare the incidence of severe IVH and/or death in premature newborns 23^0 - 31^6 weeks delivered by C/S receiving UCM to those receiving DCC.
Aims/Hypotheses	**Aim 1**. Compare the incidence of severe IVH and/or death in premature newborns 23^0 - 31^6 weeks GA delivered by C/S receiving Umbilical Cord Milking to those receiving Delayed Cord Clamping. ***Hypothesis 1:*** Demonstrate infants in the Infants Receiving Milking (UCM) group are not inferior to the Delayed Cord Clamping (DCC) group with regard to severe IVH and/or death. ***Hypothesis 2****:* If H1 is true, demonstrate lower incidence of severe IVH and/or death in UCM infants compared to DCC. **Aim 2.** Compare the safety and efficacy profiles of premature newborns <32 weeks GA delivered by C/S receiving UCM vs. DCC during their hospitalization and at 24 months corrected age. ***Hypothesis 3****:* UCM group will have a decreased need for resuscitation interventions with no difference in bilirubin or polycythemia compared to DCC. ***Hypothesis 4****:* In the NIRS sub-study, the UCM group will have improved early cardiac and cerebral hemodynamics in the delivery room and first 24 hours of life compared to DCC. ***Hypothesis 5****:* Infants in the UCM group will have improved long term outcomes such as less Neurodevelopmental Impairment (NDI) at 24 months corrected age compared to DCC. **Aim 3** (***Exploratory, hypothesis-generating*****):** To compare the outcomes of premature newborns 23^0 - 31^6 weeks GA delivered by C/S (from Aims 1 and 2) with those born by vaginal delivery receiving UCM or DCC.
Design and Sample Size	This prospective multi-national randomized controlled trial (RCT) is a two-arm parallel design of two alternative approaches of treatment. 1500 infants – 750 Delayed Cord Clamping / 750 Milking
Inclusion Criteria	• Infants delivered at 23^0 - 31^6 weeks GA based on ultrasound of the fetus up to 13+6 weeks of gestation, if assisted reproductive technology (ART) resulted in the pregnancy, the ART derived date, if neither then the best obstetric estimate at the time of delivery). • Infants without known major congenital malformations prior to delivery • Multiples (unless monochorionic) will be randomized to same group

Exclusion Criteria	• Congenital anomalies of newborn • Cardiac defects other than small VSD and PDA • Maternal HIV, Hepatitis B and C • Placenta abruption or previa with active bleeding, cutting through the placenta (Note: Partial abruptions are not excluded) • Cord prolapse • Hydrops • Bleeding Accreta • Monochorionic twins (Di/Mo or Mo/Mo) • Fetal risk or maternal risk for severe compromise at delivery identified by obstetrician or neonatologist • Families unlikely to return for neurodevelopmental testing at 24 months
Efficacy Endpoints	**Primary:** The rate of severe IVH (grade 3 or 4) or death **Secondary:** • Incidence of death or neurodevelopmental impairment at 22-26 months corrected gestational age • All Grade Intraventricular Hemorrhage • Severe IVH (Grade 3 or 4) • Hemoglobin/Hematocrit at 4 hours • Incidence of Severe IVH or death in infants <28 weeks gestation • Cerebral StO2 during Resuscitation – Sub-study • Cerebral StO2 in the NICU – Sub-study
Safety Evaluations	Adverse events
Statistical Methodology	See Data Analysis section.
Enrollment Period	3 years
Study Duration	5 years
Webpage	http://www.Premod2.org
ClinicalTrials.Gov Trial	NCT03019367

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Yasser El-Sayed, MD	Stanford University
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Sponsor: Eunice Kennedy Shriver National Institute of Child Health and Human Development

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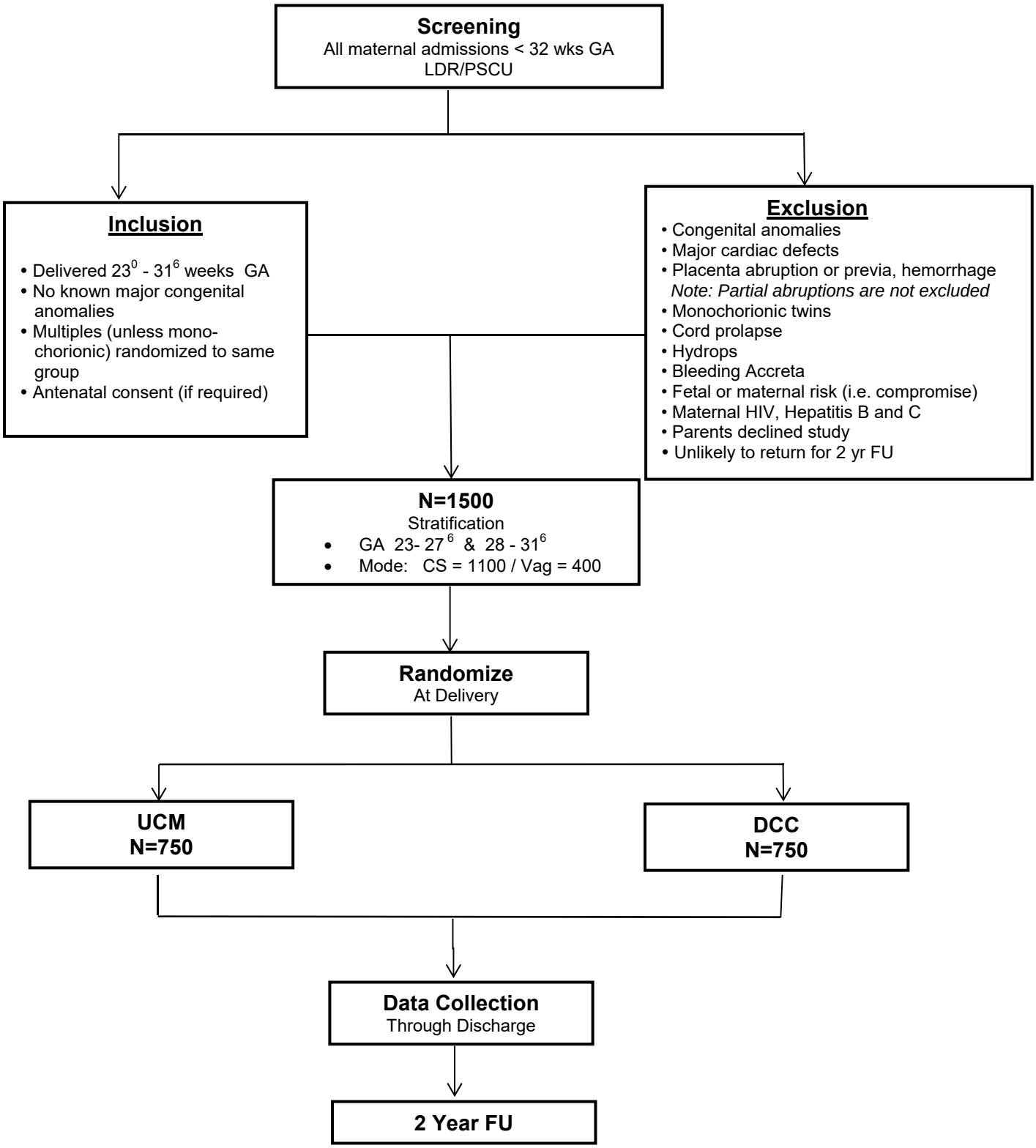
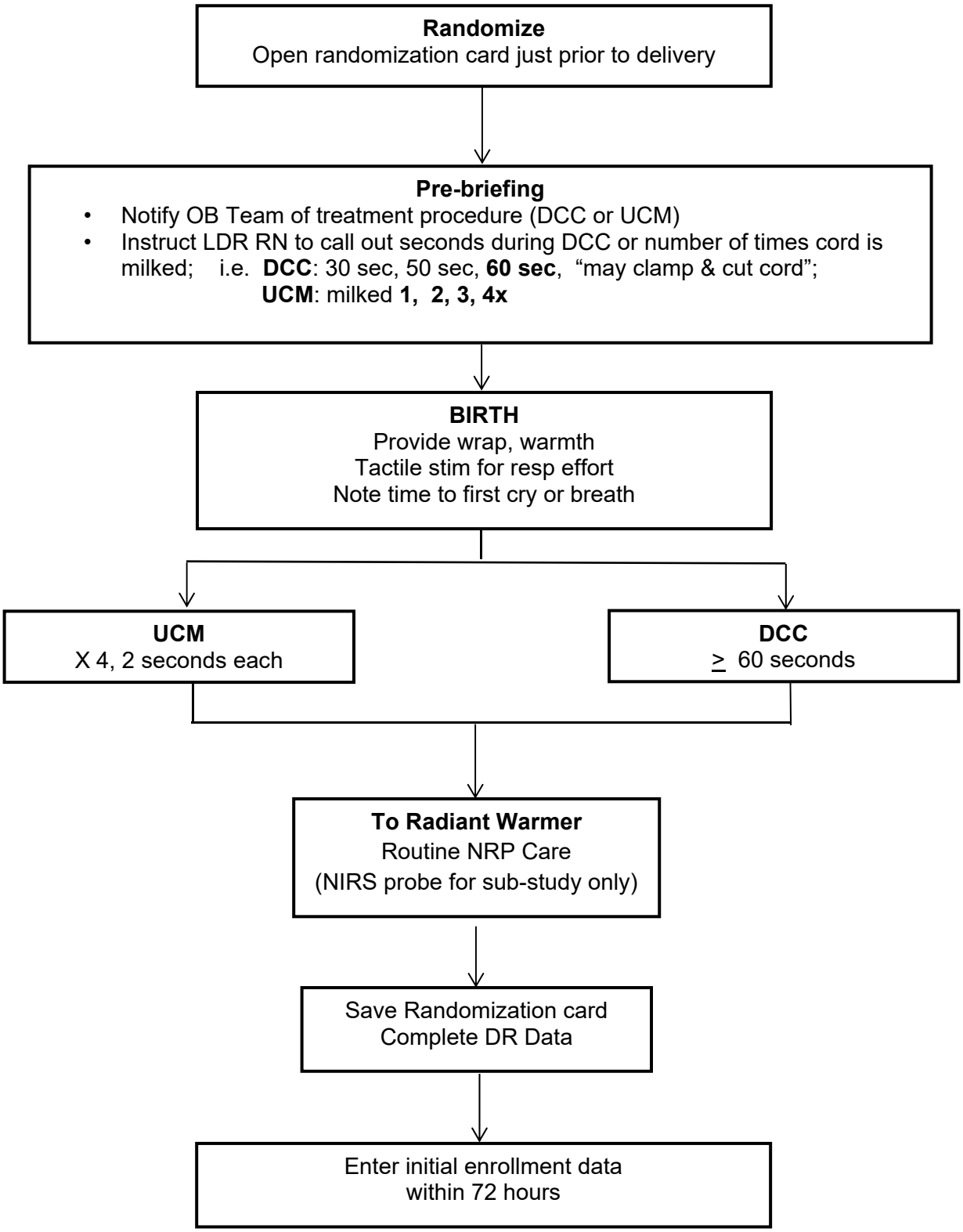
Study Overview Diagram



Intervention Flow Diagram



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List of abbreviations

ACOG	- American College of Obstetricians and Gynecologists
BSID	- Bayley Scales of Infant and Toddler Development, Edition 3
DCC	- Delayed Cord Clamping
DCoC	- Data Coordinating Center, UAB
DSMB	- Data and Safety Monitoring Board
EAPM	- European Association of Perinatal Medicine
ILCOR	- International Liaison Committee on Resuscitation
IVH	- Intraventricular Hemorrhage
SAE	- Serious Adverse Event
SOGC	- Society of Obstetricians and Gynaecologists of Canada
UCM	- Umbilical Cord Milking
WHO	- World Health Organization

Background

Extremely premature infants can experience severe bleeding in the brain, or severe intraventricular hemorrhage (IVH) which usually occurs within 72 hours after birth. Approximately 65% of all severe IVH are in infants < 28 weeks gestation, though only 1-2% of overall births are at this gestation. This has significant public health implications, by causing increased death and long-term morbidities in this high risk population. The study intervention is poised to understand if we can reduce this burden, and the trial will provide data on a not yet established therapy. If the strategy is indeed successful, potential benefits for preterm infants are life-long.

The etiology of IVH is multifactorial and is primarily attributed to the intrinsic fragility of the germinal matrix vasculature and the disturbance of cerebral blood flow. Physiological studies have demonstrated an association between low blood flow and low blood pressure within the first 24 hours resulting in the development of IVH and neurological impairment later in childhood. Hence, stabilization of the germinal matrix vasculature and the maintenance of normal cerebral blood flow on the first day of life is a potential strategy to reduce severe IVH. Fifty percent of the feto-placental circulation resides in the placenta.[1] It seems logical to assume that providing premature newborns with a sufficient placental transfusion by delaying clamping of the umbilical cord for 30 to 60 seconds would reduce IVH by improving blood flow at birth. Delayed cord clamping (DCC) has been shown to reduce overall grades (mainly lower grades 1 and 2) of IVH but has not had an effect on severe IVH (grades 3 and 4). While there may be uncertainty about the long-term outcomes of premature newborns with low grade IVH, there is a clear need to prevent severe IVH.

Recently, we evaluated umbilical cord milking (UCM), a technique which provides a placental transfusion by grasping the unclamped umbilical cord and pushing blood towards the newborn several times before the cord is clamped. Our Phase 1 pilot trial (PREMOD: PREmature infants receiving Milking Or Delayed clamping; n=154) compared UCM to DCC in premature newborns delivered by C/S and demonstrated that UCM improved blood flow and organ perfusion (as measured by cardiac ultrasound and improved urine output) by providing a greater placental transfusion (measured by a higher admission haemoglobin). A meta-analysis has demonstrated benefits in premature newborns, and a recent survey done by our group has demonstrated that over 50 percent of perinatologists perform cord milking in premature infants.

Knowledge to date

Severe IVH may be closely related to perinatal hemodynamic changes, including an increase in the afterload on the left ventricle of the heart after the infant is separated from the placenta.[2] The left ventricle of a preterm myocardium has limited ability to respond to such an increase in afterload, and

this can result in cardiac dysfunction and hemodynamic deterioration. The severity of IVH increases with decreasing systemic blood flow as measured by superior vena cava (**SVC**) flow.[3,4] Low SVC flow over the first 24 hours of life (**HOL**) is also significantly associated with an increase in death or survival with any disability in later childhood. Improving perfusion during this critical time period may reduce or prevent these serious complications in preterm infants. Delayed umbilical cord clamping (**DCC**) and umbilical cord milking (**UCM**) have both been shown to maintain optimal blood pressure and systemic blood flow as measured by SVC flow, when compared to early cord clamping.[5-8] We recently compared UCM to DCC and demonstrated that infants receiving UCM during Cesarean section (**C/S**) had higher SVC flow (**PREMOD**).[9] While our trial was not powered to detect a difference in severe IVH or death, UCM infants had a lower incidence of severe IVH and death compared to DCC infants.

A recent Neonatal Research Network (**NRN**) trial compared the neurodevelopmental outcomes at 18 to 22 months in extremely preterm survivors and found no difference in outcomes between mild IVH (Grade 1 and 2) and no IVH (Cerebral Palsy 8 vs 9%, Cognitive Impairment 27 vs. 30 percent, p=0.92 and 0.75, respectively).[10] Those with severe IVH (grade 3 and 4) had significantly greater incidence of cerebral palsy (28%) and NDI (46%), p<0.05. Bolisetty et al found that even mild IVH may contribute to increased neurodevelopmental impairment (**NDI**) in extremely premature infants,[11] but Calisici found no such effect.[12] Despite uncertainty about the long-term outcomes of premature newborns with low grade IVH, there is a clear need to prevent severe IVH. **Reducing the incidence of severe IVH will have a significant impact on reducing NDI, thus enhancing quality of life.**

The inability to reduce the incidence of severe IVH during DCC may reflect an inadequate placental transfusion for premature newborns delivered by C/S.[13-15] Aladangady et al reported lower circulating red cell volume with DCC in neonates delivered by C/S compared with vaginal delivery (**V/D**).[15] They also found that blood volume improved as duration increased up to 60 seconds in infants with V/D but not C/S delivery. Strauss et al found C/S delivered newborns who received DCC for 60 seconds had decreased red cell volume compared to V/D infants.[13] McDonnell et al failed to show any difference in hemoglobin levels with a 30-second DCC in those delivered by C/S.[14] **It is important to note that all of these trials comparing DCC to immediate cord clamping after C-section suggested minimal to no transfusion occurred.** The American College of Obstetricians and Gynecologists (**ACOG**) acknowledges the need for more research regarding the method for a cord blood transfusion in newborns delivered by C/S.[16] Given the C/S rate of up to 75% for very premature newborns,[17] it is critical that we determine the optimal method for an adequate placental transfusion during C/S.

<u>UCM vs. DCC in Premature Newborns.</u> Our PREMOD pilot trial demonstrated that UCM at C/S improved blood flow and organ perfusion by providing a greater placental transfusion, as measured by

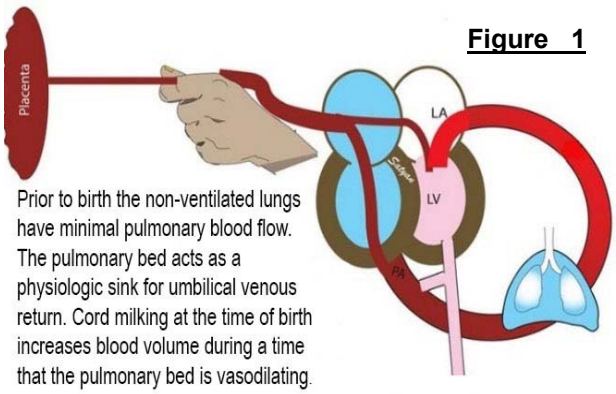
improved SVC flow (by echocardiography) and higher admission hemoglobin compared to DCC.[9] This is the first trial to suggest that UCM may be superior to DCC in premature newborns delivered by C/S. Despite these results and a recent meta-analysis demonstrating a reduction in IVH in premature newborns with UCM,[18] it has not yet been recommended by any organization for infants of any gestation because of a cited lack of sufficient evidence.[16,19-22] A recent survey done of perinatologists revealed that up to 50 percent perform cord milking in premature newborns (Faksh et al, unpublished). In addition, several centers continue to use cord milking as their exclusive standard of care based on reduction in morbidities such as death and IVH after implementation of cord milking.[23,24] Thus, there is an urgent need for Class I evidence comparing DCC and UCM which includes long-term follow-up. If either of these **simple, no-cost interventions** provide a superior placental transfusion or improve neonatal outcomes then a large impact on the burden of disability may be realized. **If UCM is found to be non-inferior or superior, it will be preferred due to the lack of delay in resuscitation.**

DCC in Premature Newborns. ILCOR and other organizations recommend a 30-60 second delay in cord clamping during preterm birth.[19,25] Several randomized controlled trials, cohort studies,[26] and meta-analyses have been published on DCC in premature newborns.[13-15,27-38] Although DCC decreases the overall incidence of IVH, enthusiasm for DCC is tempered by the lack of benefit for severe IVH and/or death in addition to the small numbers of newborns included in these trials and concerns about reporting bias.[39] Recently, the largest DCC trial (n=208) did not show any difference in severe IVH.[40] The lack of benefit could also reflect the inadequate placental transfusion during DCC for newborns delivered by C/S. Three trials of DCC vs. immediate cord clamping (**ICC**) stratified by mode of delivery found no difference in hematocrit levels or tagged red blood cells in newborns delivered by C/S.[9,41,42] ACOG acknowledges that there are limited data indicating whether DCC performed during C/S can improve placental transfusion.[43] Various trials have had significant protocol violations, with 14-22 percent of newborns randomized to DCC actually receiving ICC.[9,40] Two trials attempted to compensate for this by using cord milking as an alternative method when DCC could not be performed.[5,8] In a recently published trial DCC was combined with a one-time milking of the umbilical cord.[40] Our team demonstrated the ability to **minimize protocol violations (<5 percent)** in our most recently completed trial of delayed cord clamping (Neonatal Resuscitation with Intact Cord (**NRIC**), n=150). Therefore, we are confident our proposed trial will address and reduce protocol violations by a number of previously adopted mechanisms, including video recordings and certification of obstetrical site investigators. The true effect of DCC will not be realized until a definitive trial of UCM compared to DCC is performed with sufficient power to determine the benefit for infants born by C/S and to account for contamination and protocol violations using intention to treat and per protocol analyses.

Importance of Breathing. Animal studies and one epidemiological study suggest cord clamping should not occur until the newborn is breathing.[44,45] Breathing in premature newborns can be established with either positive pressure ventilation or gentle stimulation during DCC. In our feasibility trial (NRIC) newborns were randomized to receive DCC with stimulation or ventilation. We found no difference between the provision of early continuous positive airway pressure (**CPAP**), positive pressure ventilation (**PPV**), or gentile tactile stimulation (rubbing the back) during DCC of 60 seconds. However, the median [IQR] time to establish breathing was 16 [10,30] and 19 [7,35] seconds in each arm, with over 90 percent of infants establishing breathing prior to cord clamping. These results suggest that the provision of gentle tactile stimulation during DCC may hasten the establishment of spontaneous respirations and provide a similar placental transfusion compared to CPAP with PPV during DCC. The advantage of this approach (stimulation) is that it can be done by a single person (often the obstetrician) without the need of respiratory equipment or a neonatal provider. We will require that stimulation with DCC is performed to ensure that infants are breathing before the cord is clamped.

A.4 UCM in Premature Newborns. In UCM the unclamped umbilical cord is grasped and blood is pushed toward the infant 4 times before it is clamped. This procedure infuses blood into the preterm neonate and can be done in 20 seconds, equivalent to the time it takes for ICC.[7] We have shown in our PREMOD pilot study that UCM yields increased systemic blood flow compared to DCC in premature newborns delivered by C/S.[9] A recent meta-analyses of seven randomized controlled UCM trials in premature newborns delivered at <33 weeks demonstrated that neonates who undergo UCM have higher hemoglobin (**Hb**) and lower risk for chronic lung disease and IVH of all grades compared with those who undergo ICC.[18] **Despite several meta-analyses on DCC and UCM, the trials and number of events are small. The difference may be exaggerated due to a possible Type 1 error.**

Figure 1



Prior to birth the non-ventilated lungs have minimal pulmonary blood flow. The pulmonary bed acts as a physiologic sink for umbilical venous return. Cord milking at the time of birth increases blood volume during a time that the pulmonary bed is vasodilating.

Critics of UCM cite that the cord clamping would occur before the establishment of respirations and pulmonary blood flow.[2] However, this may not be correct. UCM improves the pulmonary blood flow immediately at birth and the onset of respirations. (**Figure 1**) This has been shown with recordings of electrocardiographic changes; newborns who had cord milking had a longer P wave, PR and QTC interval when compared with those who had early clamping of the cord.[46] Jaykka et al demonstrated that the alveolar patency occurs in response to the filling of the surrounding capillaries,

which may accelerate onset of respiration.[47] This could explain why UCM may enhance earlier onset of breathing compared to DCC. In our pilot study there were more infants breathing by the time the cord was clamped with milking compared to a 45 second DCC (74 vs. 53 percent).[9] Our prior work has demonstrated that UCM increased heart rate and oxygen saturation within the first 5 minutes of birth suggesting optimal transition compared to ICC.[7] UCM decreases the number of days on oxygen therapy and reduced chronic lung disease which may be related to enhanced pulmonary blood flow at birth. Current published guidelines regarding the management at delivery of premature newborns only recommend DCC if "the infant does not require resuscitation." But, it is these unstable newborns who are at the highest risk of severe IVH and death.[48,49] ***Cord milking may offer an advantage over DCC in newborns that are deemed too unstable to wait the 30-60 seconds required for DCC***. UCM can be performed in any low-resource setting and provides adequate placental transfusion to the premature newborn without delay.

We need to establish the safety and efficacy UCM. A pragmatic approach for two similar, but inadequately tested interventions would be to first demonstrate substantial equivalence or non-inferiority. Our pilot study provides evidence of superiority. However, a small variation of 4 vs. 6 percent in our primary outcome of death or severe IVH could have significant effects on our estimated sample size and/or our estimated rates from the pilot trial. If UCM is shown to be non-inferior to DCC, it will **provide evidence to support a change in guidelines which make UCM on par with DCC, with the additional benefit of providing placental transfusion to infants who need resuscitation.**

The primary objective for this study is to demonstrate infants in the UCM group are not inferior to the Delayed Cord Clamping (DCC) group with regard to severe IVH and/or death. It is critical that we employ accurate, delivery specific techniques to provide an adequate placental transfusion for the premature newborn. DCC at C/S may result in a failure to increase blood volume resulting in widespread under-perfusion to the organs, especially the brain, of the newly born preterm infant.[29] If we establish the short and long-term benefits of UCM in a definitive large randomized trial, we will provide solid evidence to recommend the use of cord milking at the delivery of premature newborns; potentially resulting in significantly decreased long-term morbidity and costs for this vulnerable population. This evidence has been called for by national and international organizations (ILCOR[25], WHO[19], SOGC[22], EAPM[21], AAP[50]) regarding umbilical cord management in regards to milking and the need for resuscitation at birth.

NIRS Sub-Study. Early hemodynamic effects (within 3 hours of life) of DCC compared to UCM are still unknown. Four sites experienced in the use of NIRS and who have appropriate data collection equipment in the delivery room (Alberta, Ulm, Cork and San Diego) will obtain and report the physiological changes with UCM and DCC from birth until 24 hours of life. This data will yield the

largest available sample of continuously recorded heart rate, cerebral tissue oxygenation, peripheral oxygen saturation, airway pressure, and administered FiO2 to delineate the short term responses to two methods of placental transfusion. While there are published data on cerebral oxygenation directly comparing UCM with DCC, some studies have demonstrated increases in cerebral oxygenation at 4 hours of age with DCC,[51] and a decrease in cerebral oxygenation at birth with DCC compared to immediate cord clamping.[52] In our initial trial we demonstrated increased blood pressure from 3-15 HOL with UCM compared to DCC in premature newborns <32 weeks, but did not show any differences in cerebral oxygenation.[9]

Methodology

Ethics

This multi-center randomized clinical trial will be reviewed and approved by the appropriate Research Ethics Committee/IRB at all participating sites. Sites that can, will obtain a waiver for deferred consent (see parental consent paragraph for details). In circumstances when antenatal consent was not obtained, sites will explain the cord management procedure performed at delivery, and request permission to continue monitoring and use information collected for the study.

Inclusion Criteria

- Infants delivered at 23^0 - 31^6 weeks GA based on ultrasound of the fetus up to 13^6 weeks of gestation, if assisted reproductive technology (ART) resulted in the pregnancy, the ART derived date, if neither then the best obstetric estimate at the time of delivery).
- Infants without known major congenital malformations prior to delivery
- Multiples (unless monochorionic) will be randomized to same group

Exclusion Criteria

- Congenital anomalies of newborn
- Cardiac defects other than small VSD and PDA
- Maternal HIV, Hepatitis B and C
- Placenta abruption or previa with active bleeding, cutting through the placenta
  Note: Partial abruptions are not excluded
- Cord prolapse
- Hydrops
- Bleeding Accreta
- Monochorionic twins (Di/Mo or Mo/Mo)
- Fetal risk or maternal risk for severe compromise at delivery identified by obstetrician or neonatologist

- Families unlikely to return for neurodevelopmental testing at 24 months

Patient discontinuation and withdrawal

The participant's parents are free to withdraw the participant from the trial entirely at any time, and this will not have any consequences for the participant's further treatment. When possible, the parents will be asked if they will allow their child to participate in the remaining follow-up assessments, and allow already collected data to be used in a database, a registry, and/or a publication.

The attending clinician can withdraw the participant from the trial at any time. The reasons will be documented. There are no pre-specified criteria for discontinuation of participants from trial. The discontinuation of participants in the trial will not result in replacement with new participants.

Sample Size and Power calculation

Our initial pilot study of 154 newborns delivered by C/S was recently completed to determine the feasibility and efficacy of this study and revealed a 6 percent difference in the combined outcomes of severe IVH/death between newborns treated with UCM and DCC (4.1 vs. 10.1 percent, respectively). The pilot study was mainly conducted at SMBHWN. However, since severe IVH rates and death may vary from center to center, we compared our data to the most recent Vermont Oxford Network (VON) data (over 900 NICUs). For 2015, our center had a severe IVH or death rate of 16 percent, close to the 50th percentile for the VON network. However, this includes very high risk-babies who would have been excluded from our trial (e.g., di-amniotic monochorionic twins, placental abruptions, hydrops, and congenital anomalies which have a higher IVH/mortality risk. This likely explains why our Phase 1 pilot PREMOD study had a lower composite number of severe IVH and/or death (10.1 percent vs. 4.1 percent, DCC and UCM respectively). We anticipate UCM and DCC subjects in this trial would have a similar incidence of this outcome.

The sample size for non-inferiority testing for infants born by C/S in each group is 502 (overall sample 1500), a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level will have 90% power to reject the null hypothesis that the UCM is inferior to DCC (the difference in proportions, pUCM – pDCC, is 0.01 or higher, a 1% non-inferiority margin) in favor of the alternative hypothesis that the proportions in the two groups are not inferior, assuming that the expected difference in proportions is -0.04 and the proportion in the DCC group is 0.10. (Note using 0.101 yields 485, so we round the proportion difference down to be conservative).

Further, to show our sample size for C/S is adequate we examined the power to detect the difference between 0.10 for the DCC group and 0.04 for the UCM arm with 502 newborns per group. A two group Chi square test with a 0.05 one-sided significance level will have 98% power to detect the difference between the DCC group proportion, p1, of 0.10 and the UCM group proportion, p2, of 0.04 (odds ratio of 0.375) when the sample size in each group is 502 and 75% power to show superiority, if

the rate is 0.06. Both non-inferiority and superiority will use the same sample and will have the ability to test two hypotheses in a systematic manner for each aim.

Randomization, Stratification and Allocation Concealment

Pregnant women who are dated by their earliest ultrasound or last menstrual period at <32 weeks gestation will be identified and recruited from the labor and delivery floor or perinatal special care unit at each site. Parents will be approached and consented prior to delivery when possible. At sites that have IRB approval for waiver/deferred consent in situations where antenatal consent cannot be obtained (i.e., imminent delivery), the caregivers will be approached after delivery to use the data collected, ensuring all subjects receive some form of placental transfusion at birth. Prior to delivery, the research staff or neonatal delivery team will open the randomization envelope for the proper GA group. Subjects will be stratified by gestational age and mode of delivery (23^0-27^6 or 28^0-31^6 weeks) to ensure an approximately equal number of infants born at <28 weeks gestation are in each arm. Multiples will be randomized to the same treatment group for ease of consent and family considerations. There is no crossover allowed between UCM and DCC groups, subjects should receive their randomized treatment. If the physician abandons the procedure for the safety of the mother or infant, they should receive only immediate cord clamping i.e. do not milk the cord if randomized to DCC.

Blinding/Bias

All potentially eligible newborns between 23^0 to 31^6 weeks GA in-utero will be screened and logged in order to detect possible selection bias. Randomization will be concealed, preventing allocation bias. It is impossible to blind either caregivers or parents to the assigned treatment arm. Documentation of the intervention will not be in the delivery summary portion of the medical record (i.e. noted as placental transfusion rather than DCC or UCM). In addition all outcome assessments, whether for primary outcome (interpretation of head ultrasounds) or secondary outcome (neurodevelopmental exams), will be performed by blinded team members. Ascertainment of severe IVH will be performed by board certified pediatric radiologists who are blinded to treatment arm.

Description of general interventions

Delayed Cord Clamping - DCC will be performed at C/S by the obstetric team by having the delivering obstetrician hold the infant below the level of the C/S incision for at least 60 seconds in warm, sterile towels. Infant may be dried and given gentle tactile stimulation to promote respiratory effort.

For V/D the delivering obstetrician will hold the infant below the level of the introitus for at least 60 seconds in warm sterile towels and gently stimulated if not breathing.

Umbilical Cord Milking - UCM will be performed by having the delivering obstetrician hold the infant below the level of the C/S incision (or below the level of the introitus for V/D) and milk about 20

cm of umbilical cord over two seconds, repeating three additional times. This will take about 15 seconds to complete before the obstetrician clamps the umbilical cord. For C/S delivery, the assisting obstetrician may need to assist by either holding the infant or performing the milking of the cord.

Resuscitation

Newborns will be resuscitated according to the local unit's protocol.

NIRS Sub-study (Appendix 3)

This will include a subset of 400 subjects less than 28 weeks gestational age, enrolled in the primary trial. Four experienced and instrument compatible sites (Alberta, Ulm, Cork and San Diego) will obtain and report the physiological changes with UCM and DCC from birth until 24 HOL. Once the newborn has been delivered, received the intervention (UCM or DCC), and been placed on the resuscitation bed, ECG electrodes, a NIRS sensor [Fore-Sight, (CAS Medical, Branford, CT). and a pulse oximeter will be placed within 60 seconds. While arterial saturation and heart rate data will be available to the clinical team, data from NIRS will be blinded. Data on all sub-study infants will be recorded for at least the first 10 minutes in the delivery room, and then for 24 hours in the NICU. Heart rate, oxygen saturations, and cerebral oxygenation, will be downloaded as per each site's practice for neonatal resuscitation. Sharp has used NIRS in the delivery room and operating room for the past 2 years, and the other three sites have been performing this procedure for the past 3 (Edmonton), 10 (Ulm), and 5 (Cork) years. Groups will be stratified by site and NIRS device in analysis and the site factor examined.

Outcome measures

Primary outcome

Severe IVH or death

Secondary outcomes

- Incidence of death or neurodevelopmental impairment at 22-26 months corrected gestational age
- Death prior to discharge
- All grade IVH
- Severe IVH (grade 3 or 4)
- Incidence of severe IVH or death in infants <28 weeks gestation
- Hemoglobin/Hematocrit at 4 hours of life (infant)
- Cerebral StO2 in the first 10 minutes of life (Sub-study, Appendix 3)
- Cerebral StO2 in the first 24 hours of life (Sub-study, Appendix 3)
- Other exploratory and safety secondary outcomes are listed in Appendix 1

Compliance with the Protocol

The clinical investigation will be conducted in compliance with this protocol. Modifications to the protocol will not be implemented before agreement from the sponsor and relevant ethics committee approvals are obtained.

Investigators are not allowed to deviate from the protocol. Any serious or safety related deviation will be recorded, summarized and monitored.

Data collection

Infants will be recruited over a period of 36 months or until the requisite sample size is achieved, whichever is earlier. Approximately another six months will be required to collect hospital data on all infants enrolled. Resuscitation data will be documented on the randomization card at the time of delivery. Other medical data on each infant will be collected on an electronic Case Report Forms (eCRF). The eCRF will be designed in collaboration with University of Alabama, Birmingham. Upon enrollment, initial subject randomization allocation and GA should be entered into the electronic database within 72 hours. Trial completion data will be entered from each site within one week after discharge or death of an infant. All information entered into this database will be used for analysis.

Data Security

Access to direct identifiers will be limited to local clinic staff who meet all relevant training requirements and are assigned to (or support) this project, and who must have access to these identifiers for purposes of quality control and monitoring. All investigators, statisticians, and staff will have completed the Human Subjects Protection training. All data with identifiers will be stored on firewall-protected secure servers.

Data analysis

All aspects of data management and analyses will be the responsibility of the Data Coordinating Center (**DCoC**) at UAB working closely with the PREMOD2 Steering Committee as they have in numerous trials. The DCoC is comprised of three parts: Biostatistics, Data Management and Information Systems. Together, the DCoC provides statistical collaboration, data management, and information technology support for the development and conduct of clinical trials. The DCoC will provide data management and and biostatistical support including centralized randomization, data monitoring and quality control, interim analyses and statistical monitoring, and publication support. Data Management will include case report form design, management and entry, data quality assurance, and reporting. Information Systems will include database design, web based data entry and system support including the randomization system.

577

578 **Primary Analysis**

579 The primary endpoint to be used for efficacy evaluation is the rate of severe IVH (grade 3 or 4)
580 and/or death. The primary hypothesis to be tested is whether the UCM group results in a non-inferior
581 event rate compared to the DCC group. The non-inferiority margin is set at 1% (0.01). Although a
582 proportion's test is used for sample size calculations, rates will be compared using logistic regression,
583 which will allow for control of covariates, as well as investigation of effect modification. Potential
584 covariates include gender, gestational age, maternal corticosteroid use, chorioamnionitis,
585 preeclampsia, and small for gestational age.[40,53-55] A formal statistical analysis plan will be written prior
586 to database lock. Differential consent practices at sites (antenatal vs. postnatal) may also skew
587 subject acuity/gestation or maternal complications. Clinical site will be used as a stratifying factor to
588 control for any confounding by site through residual, site-level treatment imbalance. Standard
589 regression diagnostics will be used to assess model adequacy and to examine for potential outlying or
590 influential data points. Since in a non-inferiority trial an intention to treat analysis biases away from the
591 null, in the per protocol analysis, the covariate of the ordinal scale of the quality of the manipulation for
592 UCM or DCC will be included. If non-inferiority is established by rejecting that the outcome event rate
593 is worse by 1% or more in the UCM group, then superiority will be tested at the 5% level following FDA
594 guidelines. For all superiority testing, the intention to treat analysis will be utilized with a per protocol
595 analysis as a sensitivity analysis.

596 Prior studies offer no basis for assuming a priori interactions between treatment groups, strata
597 and subgroups defined by sex, race/ethnicity, gestational age, site or a combination of these groups,
598 beyond that already controlled for in the randomization. For that reason, preplanned tests for
599 interactions with treatment assignment are not warranted, and are not powered for with the sample
600 size. We propose to table all results by subgroups for descriptive purposes and to explore in
601 secondary analyses possible subgroup differences by treatment group, solely for purposes of
602 establishing consistency and/or generating hypotheses for future studies.

603

604 **Secondary Analysis**

605 Secondary outcomes will be analyzed using similar procedures to the primary outcome.
606 Comparisons between treatment groups will use logistic regression (dichotomous outcomes), linear
607 regression (continuous outcomes), or survival analysis (survival time outcomes, such as time to
608 discharge, etc.), as appropriate. Differential practices at sites (criteria for phototherapy or blood
609 transfusions) may also skew these secondary outcomes. Therefore, the clinical site will be used as a
610 stratifying factor to control for any confounding by site through residual, site-level treatment imbalance.
611 Neurodevelopmental follow-up results will be assessed using ANCOVA models with covariates used

for analyses of the primary outcome. BSID-III scaled and composite cognitive, language and motor scores will be compared.

Assessment of safety

The study will be closely monitored for issues of data quality, study conduct, adherence to the prescribed recruitment and treatment procedures, data quality, and adverse events. These analyses will be presented to the DSMB. Interim analyses as determined by the DSMB, will seek to identify results that are sufficiently extreme and precise to offset the goal of obtaining additional data that might lead to more precise results, as well as information about differences in treatment effect by subgroups of patients.[56] Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical practice.(98) As a non-inferiority trial, early termination would likely be the result of unexpected safety concerns and not efficacy. The superiority must be tested in the context of this non-inferiority hypothesis first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority, which we do not anticipate.

Early stopping based on inferior safety must be based largely on descriptive data and close examination of adverse events. Given the projected number of subjects, early stopping is unlikely unless the observed effect of UCM is substantially worse than DCC or there are unexpected adverse results potentially seen. We recognize an adaptive design has some attractive features to incrementally enhance the power to obtain a result, but a concern was an increased budget if a greater sample size is needed. Our goal was to conduct an adequately powered trial without inflating our budget. Since we already had to seek and secure additional funds outside of NIH to make this study feasible, this design was not an option given the budget constraints.

While it is true that the sample size re-estimation could lead to a smaller sample size, it is generally unlikely given our non-inferiority approach and assumptions. Our DSMB will be evaluating the trial at multiple time points. If a smaller sample size would be necessary, this will likely result in a larger difference and they could recommend stopping the trial for efficacy (or safety) should there be such a substantial difference in actual event rate of our primary outcome. If the efficacy or safety is not overwhelming, then not terminating early has benefits in assessments of other outcomes and it would be preferable not to stop early.

Adverse and Serious Adverse Events

Expected Adverse Events – captured in data collection **Appendix 1** and reported in DSMB analyses

The following listed adverse events are expected and will be recorded in the electronic database (DCoC). The DCoC will track and report all adverse events and report to the DSMB every 3 months.

The DSMB will report to the Investigators regarding the risks of the study. Safety reports will be provided to all sites for reporting to their local IRBs.

1. IVH grade 1-2
2. Polycythemia, Hct > 65% in first 7 days of life (not requiring treatment)
3. PVL
4. Sepsis (early and late onset)
5. CLD
6. NEC (stage $\geq$ 2)
7. Spontaneous Intestinal Perforation
8. PDA requiring treatment
9. ROP (retinopathy of prematurity)

Serious Events

1. The following SAEs will be reported within 72 hours of discovery of the event to UAB DCoC via fax or email. DCoC will forward all such events to DSMB and PI.
    - Death (maternal or neonatal)
    - Severe IVH – grades III, IV
    - Compressions and/or Epinephrine in Delivery Room
    - Polycythemia requiring exchange transfusion (Hct >65% in first 7 days of life)
    - Hyperbilirubinemia requiring exchange transfusion (during first 7 days of life)
2. Any **Serious** Unexpected Problem will be reported within 72 hours of discovery to UAB DCoC. DCoC will forward such events to DSMB and PI.

Not Serious Unexpected Event

Unexpected events that are Not Serious will be reported not more than 14 days after the PI first learns of the event. DCoC will forward all non-serious unexpected events to the DSMB and PI.

Protocol Deviations

Deviations will be entered on the Deviation Report Form in the eDES system as they are identified. Deviations include: a) patient did not receive correct randomized treatment, b) 4 hour H&H labs not performed between 2-6 hours of life, c) Other, specify. See Manual of Operations for Deviation Form completion.

Data and Safety Monitoring Board

A DSMB will be 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 in order to protect the integrity of the trial, and 5) supervise the conduct and analysis of all interim analyses. To this end

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. The DCoC will inform the DSMB of all expected and unexpected adverse events; recruitment will be sent monthly, demographics will be included with the interim and final safety and efficacy analyses. Interim analyses will be conducted by the DSMB and the project statisticians, independently from the trial leadership and staff.

We have appointed a six member DSMB to work closely with the NICHD using NIH operating rules. This committee will serve as an independent advisory group to the trial and ultimately to NIH via the Project Officer and the Director of the NICHD and is required to provide recommendations about starting, continuing, and stopping the study. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the applicants. It will be the responsibility of the trial investigators to notify the IRB or IRBs involved of any issues that are relative to patient safety or to early stopping of the study. The electronic data entry system will automatically notify all appropriate individuals once an SAE is entered into the eDES. The PREMOD2 Steering Committee will discuss with the DSMB how frequently to review sites at the start-up phase to ensure safety, consent, and enrollment. The DSMB will meet at least every 6 months during the active trial period.

Suspension or premature termination of the clinical investigation

Early stopping based on inferior safety and/or inferior efficacy (futility) must be based largely on descriptive data and close examination of adverse events. With 500 subjects per group at a second early stopping review (n=1000), and assuming that the UCM Group is actually no worse than DCC, observed risk in the experimental group would have to be at most 0.5 (risk of death and IVH) to have 80% power to show non- inferior efficacy (with $\alpha = 0.012$). To justify stopping for non-inferior efficacy and superior safety again will require a substantial observed improvement in the experimental arm at the second early stopping time. Additional analyses will be presented to the DSMB to ensure consistency over and above an appropriate p-value for termination. In summary, given the projected number of patients to be enrolled, early stopping will be unlikely unless the observed effect of UCM is substantially worse than DCC at the planned early stopping assessment times.

Ethical Considerations

The PREMOD2 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. If applicable, the patients (parents) will be informed in the patient information and consent

form about changes in the terms and conditions of the trial. The trial will only start the randomization of participants after approvals from the relevant ethics committees have been received.

Parental consent/waiver

Pregnant women who are dated by their earliest ultrasound or last menstrual period at <32 weeks gestation will be identified and recruited from the labor and delivery floor or perinatal special care unit at each site. Parents will be approached and consented prior to delivery when possible. However, obtaining antenatal informed consent for a delivery room study is not always feasible. Our group demonstrated that antenatal consent excludes many of the sickest newborns because they are delivered emergently and therefore parents are unavailable for antenatal consent.[57,58] UCM and DCC are both considered standard practices at our hospital and are left to obstetrician preference. In the first PREMOD study, the local IRB determined that the trial met minimal risk requirements. When possible, antenatal consent was obtained. In situations where antenatal consent could not be obtained (i.e., imminent delivery) consent was obtained after delivery to use the data collected, ensuring all subjects received some form of placental transfusion at birth.

In a one year follow up survey of the PREMOD study, parents did not express any concerns about the intervention being done prior to obtaining consent. One family refused to have any data collected but had no issue with their child receiving UCM. Our results are similar to a recent publication from Ayers et al describing parental attitudes about participating in a cord trial identical to our PREMOD study (UCM vs. DCC). In our experience, deferred consent allows the provider and/or research staff to carefully review the study intervention and data collected with the parents after the initial anxiety of preterm delivery has decreased. We believe this is the correct approach for this trial. Our IRB Chairs have indicated that a large multicenter trial using similar interventions would be considered for deferred consent. We do not anticipate all centers will be approved for deferred consent. These centers will seek consent when mothers are admitted to the hospital with a potential for preterm delivery in the GA range. We are aware of the notice of proposed rulemaking from the Office of Human Research Protection requiring the use of a single central IRB for multicenter trials in the United States and that this may affect our ability to obtain deferred consent at individual sites.

Data management

Data handling and archiving

Each site will be responsible for maintaining adequate and accurate source documents that support pertinent study data for each subject. Medical information from the participants medical record (paper or electronic), delivery room recordings, and study specific case report forms (CRF) will serve as source documents and entered into the eDES. A web-based eDES will be designed by the Data

Coordinating Center (DCoC) at UAB. Data entry into the central database and handling of medical records is the responsibility of the investigators.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries will be entered, tracked and resolved through the electronic data capture system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented. After the establishment of a 'clean file', the database will be locked; data will be stored for statistical analysis at the DCoC at UAB. The trial database will hereafter be kept according to the respective national laws. After end of trial, the data will be archived for 25 years according to good clinical practice guideline.

Trial timeframe

Trial stages	Timeframe
Protocol development	2015- November 2016
Protocol finalized	December 2016
Site determination	December 2016, Investigator Meeting
Sites submit IRB application	December 2016 – January 2017
Finalize contracts and payment methods	January-March 2017
Recruitment phase	April 2017- April 2020
Assessment phase	Primary outcome May 2020
Analysis	2020 for primary outcome, 2022 for neurodevelopmental outcomes
Publication	2020 on primary outcome, 2022 for neurodevelopmental follow-up

Publication plan

The trial will be registered on ClinicalTrial.gov prior to the randomization of the first participant. Attempts will be sought to publish protocol, all results, positive, neutral, as well as negative, in a peer-reviewed international journals. Authorship will be determined according to the International Committee of Medical Journal Editors. Attempts will be made to publish a list of all investigators with their contributions in all publications.

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.

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Appendix 1

DATA COLLECTED FROM INFANTS AND MOTHERS

Clinical Data collected from all enrolled mothers:

1. Age
2. Race/Ethnicity
3. Antenatal Steroids (yes/no) (include partial course)
4. Antenatal Magnesium (yes/no)
5. *Diabetes (gestational, Type 1 or 2) (yes/no)*
6. Chorioamnionitis (yes/no)
7. Hypertension/Pre-eclampsia (yes/no)
8. Rupture of Membranes (hours)
9. *Labor prior to delivery (yes/no)*
10. *Pitocin prior to delivery (yes/no)*
11. *Pitocin prior to cord clamping (yes/no)*
12. *Postnatal uterotonic administration: Methergine, Cytotec, Hemabate (yes/no)*
13. *Retained Placenta (yes/no)*
14. *Indication for Delivery (check all)*
15. *Presentation (vertex, breech, transverse)*
16. Mode of Delivery
17. General Anesthesia (yes/no)
18. Endometritis (y/n)
19. Placental Weight
20. *Need for blood transfusion*
21. *Maternal Hospitalization/Readmit within 10 days*
22. *Length of Stay*
23. *Maternal Death*

Clinical Data collected from all enrolled infants:

24. Gestational Age
25. Multiple gestation (yes/no)
26. Gender
27. Birthweight (grams), length (cm), and head circumference (cm)
28. APGARS at 1 and 5 minutes
29. *Race/Ethnicity*

Measured Endpoints and Recorded Outcomes

Specific Aim 1

30. Severe IVH or Death (combined outcome)

Specific Aim 2 (Clinical Outcomes)

Intervention (protocol compliance)

31. *Time of cord clamping (seconds)*
32. *Number of times cord milked*
33. *Breathing or crying prior to cord clamping? (yes/no)*

Resuscitation Interventions (Toxicity and Efficacy)

34. Infant's first temperature in delivery room
35. Maximum inspired oxygen (FiO_2) (percentage)
36. DR Interventions: PPV, CPAP, intubation, chest compressions, medications (Y/N)
37. Intubation (yes/no) (indicate Delivery Room or NICU)
38. Surfactant (yes/no) (Delivery Room or NICU)

Clinical Outcomes (Toxicity and Efficacy)

39. SGA (<10%)
40. Admission temperature to NICU
41. *Hemoglobin & hematocrit at 4 (±2) hours of life*
42. *Venous and/or arterial cord gas (pH+BE)*
43. *Worst BE on blood gas within 1 hour of life*
44. *Peak total serum bilirubin (mg/dL)*
45. *Polycythemia in the first 7 days of life (Hct >65%)*
46. *Duration of phototherapy days*
47. *CRIB Score of severity of illness*
48. *Urine output on day of life 2 (ml/kg/day)*
49. *Mean arterial BP on admission, 6, 12,18 & 24 hol*
50. *Use of cardiac inotropes (dopamine, dobutamine, epinephrine) (yes/no)*
51. *Use of postnatal steroids (yes/no) (indicate for blood pressure, extubation or chronic lung disease)*
52. Presence of any intraventricular hemorrhage (yes/no)
53. Presence of severe intraventricular hemorrhage (Grade 3 or 4) (yes/no)
54. Presence of PVL, echodense lesions or ventriculomegaly on any US prior to discharge (yes/no)
55. Early onset sepsis (positive blood or CSF culture at ≤ 72 HOL) (yes/no)
56. Late onset sepsis (> 72 HOL) (yes/no)
57. Chronic lung disease (receiving supplemental O_2 at 36 weeks (yes/no)
58. Duration of intubated and mechanical ventilation (days)
59. Necrotizing Enterocolitis Bell (Stage ≥ 2) (yes/no)
60. Spontaneous Intestinal Perforations (yes/no)
61. Retinopathy stage 3 or greater (yes/no)
62. Patent Ductus Arteriosus requiring treatment (medical and/or ligation) (yes/no)
63. *Need for Blood Transfusion (DOL of 1st transfusion and total number) (yes/no)*
64. *Hemolytic disease of the Newborn (i.e.Rh, ABO)*
65. Length of hospitalization (total days)
66. Death (only)
67. *Neurodevelopmental Impairment at 24 months: BSIDIII,cerebral palsy, blindness or deafness*

Cerebral and Cardiac Hemodynamic Substudy (Toxicity and Efficacy)

68. Cerebral StO_2 by NIRS from birth until 24 hours of life
69. Maximum inspired oxygen (FiO_2) during birth resuscitation.
70. Heart Rate from birth until 24 hours of life
71. Mean blood pressure (at NICU admission) taken by either oscillometry (every hour) or indwelling arterial line until 24 hours of life

72. Oxygen saturation (by oximetry) from birth until 24 hours of life

<u>Specific Aim 3</u> (Comparison of Cesarean Section vs Vaginal Deliveries)

73. Compare all variables from Aim 1, and 2 in vaginal deliveries (UCM and DCC)

Appendix 2: Staff Delegation and Responsibility Log

Premature Infants Receiving Milking or Delayed Cord Clamping: Randomized Controlled Multicenter Non-Inferiority Trial [PREMOD2]

IRB#_____ Site #_____ Principal Investigator: _____

Staff Name		Signature	Title (PI, Coord)	Role & Responsibilities	Date Started	Date Terminated	PI Initials/Date
Last, First	Initials						

1-Subject Recruitment 3-Determine Eligibility 5-AE Assessment 7-Regulatory Documents Maintenance
2-Obtain Informed consent 4-Conduct Subject visits 6-Lab Studies review 8-Data Collection 9-Other-describe

Appendix 3

PREMOD2 – NIRS Sub-study

Background

Early hemodynamic effects (within 3 hours of life) of Delayed Cord Clamping compared to Umbilical Cord Milking are still unknown. Four sites experienced in the use of NIRS and who have appropriate data collection equipment in the delivery room (Alberta, Ulm, Cork and San Diego) will obtain and report the physiological changes with UCM and DCC from birth until 24 hours of life. This data will yield the largest available sample of continuously recorded heart rate, cerebral tissue oxygenation, peripheral oxygen saturation, airway pressure, and administered FiO2 to delineate the short term responses to two methods of placental transfusion. In our initial trial we demonstrated increased blood pressure from 3-15 HOL with UCM compared to DCC in premature newborns <32 weeks, but did not show any differences in cerebral oxygenation.

Hypotheses

- Infants in the UCM group will have increased cerebral StO2 within the first 10 minutes of life compared to infants in the DCC group.
- Infants in the UCM group will have increased cerebral StO2 in the first 24 hours of life compared to infants in the DCC group.

Methodology

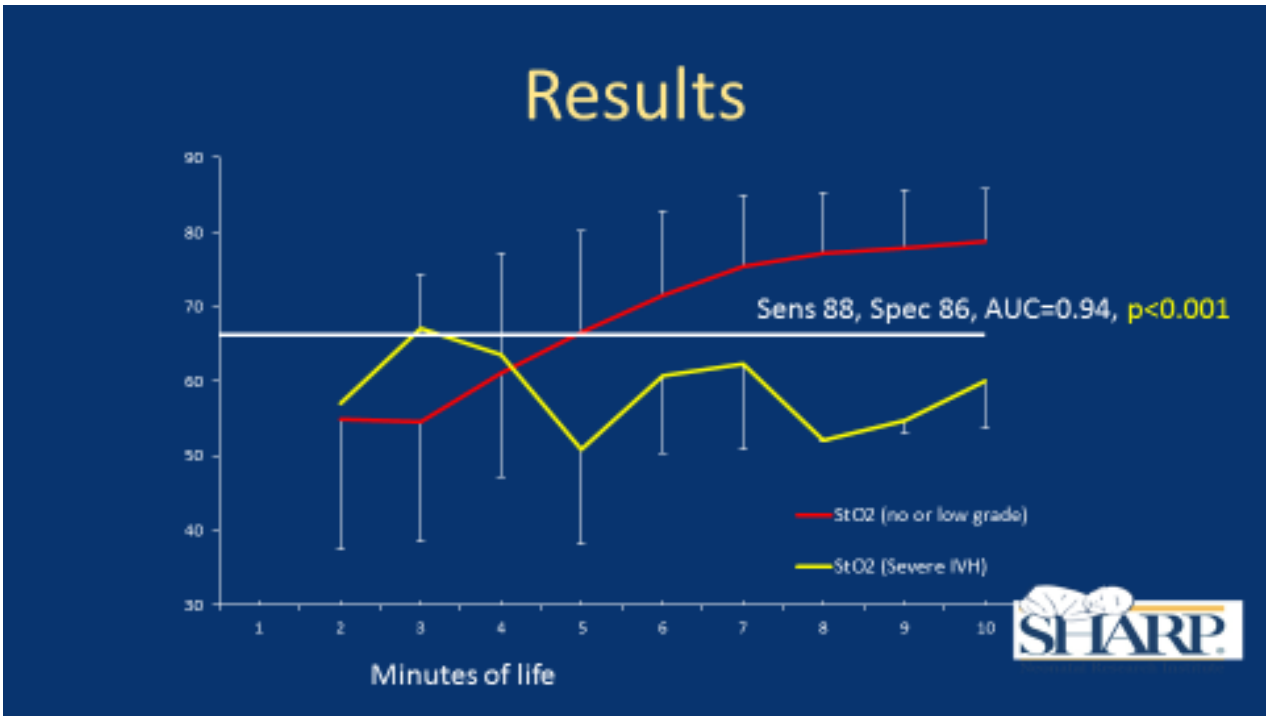
This sub-study will include 400 infants <28 weeks GA enrolled in the PREMOD2 trial. Once the newborn has been delivered, received the intervention (UCM or DCC), and been placed on the resuscitation bed, ECG electrodes, a NIRS sensor and a pulse oximeter will be placed within 60 seconds. While arterial 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 at least the first 10 minutes in the delivery room, and then for 24 hours in the NICU. Heart rate, oxygen saturations, and cerebral oxygenation, will be downloaded as per each site's practice for neonatal resuscitation.

Statistics/Power

A recently completed trial (N=127) by our group demonstrated that premature infants <32 weeks that developed severe IVH or early death (first 72 hours) had a NIRS value of 60 +/-6 at 10 minutes of life. Infants who developed IVH/death were all less than 28 weeks. An ROC curve demonstrated that a NIRS average of <66 between 7-10 minutes predicted severe IVH death with a sensitivity and specificity of 88 and 86 percent respectively (see figure below, AUC=0.94, $p<0.001$). A sample size of 400 (n=200 in each arm) would be able to detect a conservative 3 percent difference between groups with a power of 0.86 and an alpha of 0.05.

Manuscript

This data will be used to publish the hemodynamic/cerebral effects of cord milking compared to delayed cord clamping. This data will also be used to predict which infants are at risk for developing severe IVH and early death (first week of life).



Appendix 4

Here is the summary of changes shown in the boxes below in reverse chronological order.

Version 1.7 May 15, 2018

I. This protocol has been updated with additional NCT numbers for the sub-study & FU, exclusion for parents who request no resuscitation, a change & clarification of deviation reporting, and addition of maternal level of education data which was recommended by the DSMB Chair.

Version 1.6 January 03, 2018

I. This protocol amendment addresses infants in the inclusion GA who are not eligible to be randomized. Data Collection for these infants will not include any HIPPA protected privileged information and can be obtained from the institution's VON Database, pg 21.

II. Updates to Site Participation and clean up of text to match current Manual of Operations.

Version 1.5 August 25, 2017

I. Protocol exclusion criteria deleted throughout text and tables

- Maternal HIV, Hepatitis B and C

Version 1.4 June 1, 2017

I. Protocol Deviation Reporting redefined, pg 23

II. Appendix I Data Collection deleted #12 uterine massage and added uterotonic meds to include Cytotec and Hemabate post delivery

Version 1.3 May 1, 2017

The following edits have been made after review for consistency, clarification of language and, updates to sub-study and data management. DSMB members and Sub-site personnel updated.

I. Participating site update (removed University of Utah)

II. NIRS Sub-study

- Sub-study will monitor NIRS for first 24 hours of life *(change from 72)*
- Subset of 400 subjects < 28 weeks gestational age

III. Aim 2

- Distinct separation made between Hypothesis 3 & 4, safety data (resuscitation interventions and labs) vs. NIRS sub-study

IV. List of Abbreviations

- BSID- Bayley Scales of Infant and Toddler Development, Edition 3 *(added)*
- DSMB- Data and Safety Monitoring Board *(change from Committee)*

V. Methodology

- Blinding- Clarification of procedure blinding

VI. Data Collection

- Upon enrollment, initial randomization and allocation should be entered into the eDES within 72 hours *(change from 48)*

VII. Expected Adverse Events

- Defined polycythemia *with Hematocrit > 65% in first 7 days of life*

VIII. Time period of Serious Adverse Events defined *(first 7 days of life*)

- Polycythemia with Hematocrit > 65% requiring treatment *in first 7 days of life*

- Hyperbilirubinemia requiring exchange transfusion during *first 7 days of life*
- Serious unexpected problems will be reported within 72 hours of discovery *(was 7 days)*

IX. Protocol Deviations

- Deviations will be entered into the eDES system Deviation Log concurrently

X. Appendix 1

- Worst BE on blood gas within 1 hour of life *(added)*

XI. Appendix 3

- NIRS Sub-study Protocol *(added)*

Version 1.2 March 1, 2017

The following edits have been made after review with all Investigators for consistency, clarification of language, hypothesis 3 & 4 and, additional data collection of safety -parameters.

I. Added participating center University of Utah
II. Hypothesis 3, clarified NIRS sub-study
III. Hypothesis 4, edited for Long Term outcomes only. Deleted immediate and delivery room interventions
IV. Expected Adverse events, added ROP

Version 1.1 December 14, 2016

The following edits have been made after review with all Investigators for consistency, clarification of inclusion/exclusion criteria and additional data collection of safety parameters.

I. Inclusion Criteria

Throughout document "Multiples (unless TTT)" was changed to "Multiples unless monochorionic".

II. Exclusion Criteria

Throughout document in Tables and text

- Placenta abruption *(was clarified)* with significant bleeding, cutting through the placenta (Note: Partial abruptions are not excluded)
- Cord prolapse *(added)*
- Hydrops *(added)*
- Bleeding Accreta *(added)*

III. Secondary Endpoints and Outcomes (Edits on pages 5 and 19)

Deleted "See Appendix 1 for safety and efficacy data" and added for clarification:

- Incidence of death or neurodevelopmental impairment at 22-26 months corrected gestational age
- All Grade Intraventricular Hemorrhage
- Severe IVH (Grade 3 or 4)
- Hemoglobin/Hematocrit at 4 hours (infant)
- Incidence of Severe IVH or death in infants <28 weeks gestation
- Cerebral StO2 during Resuscitation
- Cerebral StO2 in the NICU
- Other exploratory and safety secondary outcomes are listed in Appendix 1

IV. Randomization, Stratification, Allocation (Added to page 18)

"There is no crossover allowed between UCM and DCC groups, subjects should receive their randomized treatment. If the physician abandons the procedure for the

safety of the mother or infant, they should receive only immediate cord clamping i.e. do not milk the cord if randomized to DCC."

V. Serious Adverse Events (Clarified on page 26)

- Death (Maternal or neonatal)

VI. Appendix 1

Deleted:

Hemoglobin prior to delivery
Hemoglobin post-delivery (if available)
Estimated Blood loss at delivery

Added:

Uterine massage (yes/no/unknown)
Indication for Delivery
Presentation (vertex, breech, transverse)
Maternal Hospitalization/Readmit within 10 days
Maternal Length of Stay
Maternal Death
SGA (<10%)
Added BE to cord gas