Delayed Cord Clamping with Oxygen In Extremely Low Gestational Age Infants

Protocol

Version 2.0. – March 29, 2024

Sponsors:	Eunice Kennedy Shriver National Institute of Child Health and Human Development
Protocol contributors:	Felix Ines, A.S. RCP-RRT (Sharp Mary Birch Hospital for Women & Newborns) Rebecca Dorner, MD (Sharp Mary Birch Hospital for Women & Newborns) Katherine Coughlin, MD (Sharp Mary Birch Hospital for Women & Newborns) Jenny Koo, MD (Sharp Mary Birch Hospital for Women & Newborns) Neil Finer, MD (Sharp Mary Birch Hospital for Women & Newborns) Wade Rich, BSHS, CCRC (Sharp Mary Birch Hospital for Women & Newborns)
Trial identifiers:	NCT04413097 1R03HD105224

ABBREVIATIONS

ASQ-3	Ages and Stages Questionnaire, 3rd edition
BSID-4	Bayley Scales of Infant Development, 4th edition
CBCL	Child Behavior Checklist Questionnaire
CGA	Corrected Gestational Age
CO2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
CSV	Comma-separated values
DCC	Delayed Cord Clamping
DCoC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report forms
FiO2	Fraction of inspired oxygen concentration
GA	Gestational Age
GMFCS	Gross Motor Function Classification System
HI Group	High Oxygen concentration group
HIPAA	Health Insurance Portability and Accountability Act
LO Group	Low Oxygen concentration group
MOL	Minutes of Life

NICHD	National Institute of Child and Human Development
NICU	Neonatal Intensive Care Unit
NIRS	Near-Infrared Spectroscopy
NRN	Neonatal Research Network
NRP	Neonatal Resuscitation Program
PAO2	Alveolar partial pressure of oxygen
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
PPV	Positive pressure ventilation
ROC curve	Receiver operating characteristic curve
SAE	Severe adverse event
sIVH	Severe intraventricular hemorrhage
SpO2	Peripheral oxygen saturation
SPSS	Statistical Package for the Social Sciences
StO2	Tissue oxygen saturation
TCM	Transcutaneous carbon dioxide monitoring

REVISION HISTORY

Version	Date	Amendment Text	Description
1.2	11/10/2021	• Added PPROM prior to 20 weeks gestation to exclusion criteria • Revised Recruitment status to "Recruiting" • CRIB-II (Clinical Risk Index for Babies) • NeoBeat Heart Rate Meter • Definition of BPD • Definition of CLD	Preterm Premature Rupture of Membranes prior to 20 weeks gestation added to exclusion criteria Updated recruitment status to recruiting Revised obtaining SNAPPE-II score to obtain CRIB-II score Neobeat HR meter is added as a device to collect the infant's HR during DCC Bronchopulmonary Dysplasia as defined and categorized by: Jensen, Dysart, Gantz, *et al*: Defining Bronchopulmonary Dysplasia) Chronic Lung Disease (mode of respiratory support at 36 weeks' post-menstrual age as defined and categorized by: Jensen, Dysart, Gantz, *et al*: Defining Bronchopulmonary Dysplasia)
1.3	03/14/2022	• Secondary Objective • Added ASQ-3	To compare the incidence of neurodevelopmental impairment and abnormal neurologic outcomes at 22-26 months' corrected age, as assessed by the Bayley Scales of Infant Development (4th ed) and standardized neurologic exam, for infants born between 22-28+6 weeks GA receiving a FiO2 of .30 versus a FiO2 of 1.0 during 90-seconds DCC Ages and Stages Questionnaire, 3rd edition
1.4	05/09/2022	• Include lab test collection at two different time points	Blood samples will be collected at two different time points: Cord blood sample (T1: Cord blood collected after the cord is cut) and at 2 hours of life or NICU admission (T2). This is an extra few drop of blood that are drawn from the baby for medical purposes (cord blood from cord gases and admission blood workup) Samples will be tested for oxidized and reduced glutathione which are the most reliable and comprehensive biomarkers of oxidative stress

1.5	11/25/2022	• Updated Timeframe for the following Secondary Outcome Measures: -Surfactant Administration -Severe ROP -Use of Inhaled Nitric Oxide -Ages and Stages Questionnaire • Removal of sub-site enrollment goal • Addition of NEC and SIP as Expected Adverse Events • Updated Primary Outcome	Timeframes for Secondary Outcomes updated to be consistent with information under Clinical trials registration website. To minimize amendments due to sub-site inability to reach enrollment goal in due time Added NEC (stage >/=2) and Spontaneous Intestinal Perforation Updated Primary Outcome Measure
1.6	06/08/2023	• Concord Birth Trolley • Addition of DSMB recommendation of tracking sepsis, blood and/or CSF infection	The Concord Trolley is a stabilization bed that provides heat by a radiant warmer during DCC. The Concord trolley also has the improved functionality of infant positioning during DCC, specifically for infants with a very short umbilical cord. Addition of an updated process on implementing the recommendations from the DSMB on tracking sepsis, blood and/or CSF infection.
1.7	09/27/2023	• There were no changes to the protocol. Version adjusted to coincide with current ICF	There were no changes to the protocol. Version adjusted to coincide with current ICF.
1.8	09/27/2023	• Added CBCL Assessment to Secondary Objectives	Child Behavior Checklist Questionnaire will be collected at 2-year follow-up
2.0	02/14/2024	• Specified ASQ-3 scores at 24 months chronological age.(22-26 months) • Peripheral oxygen saturation of $\geq$ 80% by 5 minutes of life • Removed the comparison of BSID-4 versus ASQ-3 scores	Specified ASQ-3 scores at 24 months chronological age. (22-26 months) Clarification on peripheral oxygen saturation of $\geq$ 80% by 5 minutes of life The score comparison of BSID-4 and ASQ-3 is incomparable, therefore, this item has been removed.

		• Specify thresholds on borderline or clinical range scores from the CBCL assessment	Scores will be used as an estimate of behavioral and emotional problems

Table of Contents

1. TRIAL SUMMARY 10
2. INTRODUCTION 14
2.1. Background and rationale 14
2.2. Objectives 15
2.3. Trial design 16
3. METHODS 17
3.1. Study setting 17
3.2. Eligibility criteria 17
3.2.1. Inclusion criteria 17
3.2.2. Exclusion criteria 17
3.3. Interventions 18
3.3.1. Intervention description 18
3.3.2. Modifications 19
3.3.3. Adherence 20
3.3.4. Concomitant care 21
3.4. Outcomes 21
3.5. Participant timeline 26
3.6. Sample size 28
3.7. Recruitment 28
3.8. Allocation 28
3.9. Blinding (masking) 29
3.9.1. Blinding mechanism 29
3.10. Data collection 29
3.10.1. Trial procedures and evaluations 29
3.10.2. Retention 30
3.11. Data management 31

3.12. Statistical methods 31
3.12.1. Outcomes 31
3.12.2. Additional analyses 32
3.12.3. Analysis population and missing data 32
3.13. Data monitoring 32
3.13.1. Formal committee 32
3.13.2. Interim analysis 33
3.14. Safety/harms 33
3.15. Auditing 34
4. ETHICS AND DISSEMINATION 34
4.1. Research ethics approval 34
4.2. Protocol amendments 35
4.3. Informed consent process 35
4.4. Confidentiality 35
4.5. Declaration of interests 36
4.6. Access to data 36
4.7. Ancillary and post-trial care 36
4.8. Dissemination policy 36
4.8.1. Trial results 36
4.8.2. Authorship 36
4.8.3. Reproducible research ..... **Error! Bookmark not defined.**
5. STUDY ADMINISTRATION 37
5.1. Key contacts 37
5.2. Funders 37
5.3. Roles and responsibilities 37
5.3.1. Protocol contributors ..... **Error! Bookmark not defined.**
5.3.2. Sponsor and funder 37
5.3.3. Trial committees 37

6. APPENDICES .....**Error! Bookmark not defined.**

6.1. Informed consent materials .....**Error! Bookmark not defined.**

6.2. Biological specimens.....**Error! Bookmark not defined.**

1. TRIAL SUMMARY

World Health Organization Registration Data Set

Title	Delayed Cord Clamping with Oxygen In Extremely Low Gestational Age Infants
Primary registry and trial identifying number	ClinicalTrials.gov NCT04413097
Secondary identifying numbers	1R03HD105224
Sources of monetary or material support	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Primary sponsor	Eunice Kennedy Shriver National Institute of Child Health and Human Development
Secondary sponsors (if any)	
Central contact	Anup Katheria, MD Sharp Mary Birch Hospital for Women & Newborns 3003 Health Center Dr. San Diego, CA 92123 858-939-4170 anup.katheria@sharp.com
Study officials/Investigators	
Brief title	Delayed Cord Clamping with Oxygen In Extremely Low Gestational Age Infants
Acronym	DOXIE
Countries of recruitment	United States of America
Condition(s) or focus of study	IVH-Intraventricular Hemorrhage, Extreme Prematurity, Hypoxia Neonatal, Hyperoxia, Respiratory Insufficiency
Interventions	Intervention type: Procedure/Surgery Intervention name: Delayed Cord Clamping with Low Oxygen concentration Other names: DCC LO group Intervention description: During 90 seconds of delayed cord clamping, the infant will receive gentle stimulation

	and start CPAP by 30 seconds of life at an FiO2 .30, with CPAP of 5 cmH20. If the infant is apneic or there is no Pedicap color change the team will begin positive pressure ventilation (starting PIP of 20 cmH20) by 60 seconds of life. The infant will remain on this support up until the umbilical cord is clamped at 90 seconds of life. Once the cord is clamped the infant resuscitation will continue according to unit protocol.
DCC and High Oxygen Concentration	Intervention type: Procedure/Surgery Intervention name: Delayed Cord Clamping with High Oxygen concentration Other names: DCC HI group Intervention description: During 90 seconds of delayed cord clamping, the infant will receive gentle stimulation and start CPAP by 30 seconds of life at an FiO2 1.0, with CPAP of 5 cmH20. If the infant is apneic or there is no Pedicap color change the team will begin positive pressure ventilation (starting PIP of 20 cmH20) by 60 seconds of life. The infant will remain on this support up until the umbilical cord is clamped at 90 seconds of life. Once the cord is clamped the infant resuscitation will continue according to unit protocol.
Key eligibility criteria	Age eligibility: 28 weeks or younger Sex eligibility: Both Accepts healthy volunteers: No Inclusion criteria: 1. up to 28+6 weeks gestational age 2. Single and Multiple pregnancy 3. All Modes of delivery (vaginal delivery or caesarean section) Exclusion criteria: 1. Parents decline consent 2. Congenital anomalies of the newborn 3. Bleeding Accreta 4. Monochorionic multiples with evidence of TTTS 5. Fetal or maternal risk (i.e., compromise) 6. Preterm Prolonged Rupture of Membranes prior to 20 weeks gestation 7. Parents request no resuscitation

Study design	Study type: Interventional trial Allocation: Randomized Intervention model: Parallel group Primary purpose: Treatment Phase: N/A
Masking	Trial participants, Care providers, Outcome assessors
Date of enrollment	November 17, 2021
Target sample size	140
Recruitment status	Recruiting
Primary outcomes	Outcome: Feasibility of administration of oxygen during delayed cord clamping and its impact on the incidence of preterm infants (up to 28 +6 weeks) who achieve a peripheral oxygen saturation of $\geq$ 80 percent by 5 minutes of life Timeframe: by 5 minutes of life
Secondary outcomes	Outcome: All Grade IVH Timeframe: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA) Outcome: Frequency of Grade III and IV intraventricular hemorrhage Timeframe: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA) Outcome: Resuscitation interventions Timeframe: In the first 10 minutes of life Outcome: Changes in heart rate (BPM) in the first 10 minutes of life Timeframe: In the first 10 minutes of life Outcome: Changes in SpO2 (%) in the first 10 minutes of life Timeframe: In the first 10 minutes of life

	Outcome: Changes in cerebral oxygen saturation, StO2 (%) Timeframe: In the first 10 minutes of life

2. INTRODUCTION

2.1. Background and rationale

Current delivery room practice is to delay clamping and cutting of the umbilical cord to allow for hemodynamic stabilization. Supported by numerous randomized controlled trials(1-10) and meta-analyses(11, 12), this practice is endorsed by neonatal and obstetrical governing bodies. (13-15) Yet, data are very limited in extremely low gestational age infants.

The period when delayed cord clamping (DCC) is performed needs careful examination. Immediately after delivery, extremely low gestational age infants must attempt to initiate lung aeration and gas exchange. Animal studies demonstrate that delaying clamping of the umbilical cord until breathing is established avoids adverse cerebral and cardiac hemodynamics, which may reduce bleeding in the brain or severe intraventricular hemorrhage (sIVH). (16-19) In a multicenter trial comparing DCC to umbilical cord milking, 76 percent of 23^0 – 27^6 weeks gestation age (GA) preterm newborns receiving DCC without respiratory support had initiated respirations prior to cord clamping. (20) Despite the onset of breathing in the majority of DCC infants, relative hypoxemia was common as demonstrated by a low 5-minute of life arterial oxygen saturation (SpO_2, 73 percent (95% CI 71.4, 75.6)). (21) The significance of this observation is evident from two recent analyses establishing those preterm infants with a 5-minutes of life (MOL) SpO_2 <80 percent were more likely to have sIVH or death. (22, 23)

Providing respiratory support to aerate the lung prior to umbilical cord clamping has been advocated as an alternative to immediate umbilical cord clamping. To date, all studies of ventilation during DCC have used room air or low levels of oxygen (0.21-0.30), and none have shown reduction in morbidities. (24-26) Ventilation through a mask with low levels of oxygen may not be sufficient in extremely preterm infants. Non-invasive respiratory support during transition requires a patent airway, allowing air to enter the trachea and aerate the lung. Spontaneous breathing is the most effective method of opening the airway for a newborn. Hypoxia inhibits breathing movements and contributes to a closed glottis (27), which prevents lung aeration and subsequent benefits of DCC.

It would seem logical that provision of higher amounts of supplemental oxygen at birth would eliminate early hypoxia. Historically, too much oxygen during resuscitation of the very preterm infant is associated with death or organ injury. (28, 29) A recent trial demonstrated that stabilization with a brief period of 100 percent oxygen post-delivery led to greater minute ventilation, higher tidal volumes, and improved oxygenation compared to 30 percent oxygen. (27) Despite this data, several multicenter trials of resuscitation with intact umbilical cord start with low oxygen levels (31-33). Also, many trials required 3-5 minutes to establish breathing during DCC. To test feasibility and safety, 100 percent oxygen was administered to seven preterm infants during 60 seconds of DCC. All infants who received continuous positive airway pressure (CPAP) and 100 percent oxygen at birth achieved a saturation above 80 percent by 5 MOL, and

all survived without sIVH. A higher alveolar oxygen tension may be critical to initial stabilization and oxygenation of the extremely preterm infant**.** Preliminary animal work suggests 100 percent oxygen during DCC provides an optimal increase in pulmonary blood flow without a large increase partial pressure of oxygen (PaO_2), due to the simultaneous streaming of umbilical venous blood with relatively low PaO_2. A pilot study with detailed assessments of hemodynamics and organ function immediately after birth is needed to determine the efficacy and safety of providing 100 percent oxygen during DCC.

DCC for up to 3 minutes has been practiced internationally and locally by OB providers because of the known benefits to term and preterm infants.

This study is conducting at least 90 seconds of DCC to allow time to establish lung recruitment with continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV).

2.2. Objectives

2.2.1 Primary objective:

To assess the feasibility and compare the incidence of extremely low gestational age infants (up to 28+6 weeks GA) who achieve a peripheral oxygen saturation of $\geq$ 80 percent by 5 minutes of life (MOL) given mask CPAP/PPV with an FiO2 of 1.0 during DCC for 90 seconds (HI Group) to infants given mask CPAP/PPV with an FiO2 of 0.30 during DCC for 90 seconds (LO Group).

Hypothesis 1: A greater number of infants randomized to the HI group will achieve a peripheral oxygen saturation of 80 percent by 5 MOL compared to those randomized to the LO group.

Hypothesis 1a: If H1 is true, demonstrate that high alveolar PAO2 during DCC enhances pulmonary hemodynamic transition without causing systemic oxygen toxicity (due to “dilution” by placental blood) resulting in a dramatic reduction in morbidities and mortality.

2.2.2 Secondary objective:

I. To compare the incidence of neurodevelopmental impairment and abnormal neurologic outcomes at 22-26 months’ corrected age, assessed by the Bayley Scales of Infant Development (BSID,4th ed) and standardized neurologic exam, for infants born between 22+0-28+6 weeks GA receiving an FiO2 of .30 versus an FiO2 of 1.0 during 90-seconds DCC as:

- Neurodevelopmental Impairment:
  -Mod-Severe Neurodevelopmental impairment: Defined as having at least one of the following: Cognitive score <70, GMFCS greater or equal 2,

blindness (vision <20/200), or hearing impairment interfering with the ability to communicate with amplification.

-Mild Neurodevelopmental Impairment: Defined as having at least one of the following: Cognitive score 70-84, GMFCS =1, unilateral blindness (vision <20/200 in only one eye) or hearing impairment which does not interfere with the ability to communicate.

- Gross Motor Function Classification System (GMFCS) score: A validated system used to describe the severity of motor dysfunction. Scale measured from Level 0-5 with Level 0 being normal and Level 5 being the worst score. Measures ability to walk, sit, head control, voluntary movements and postures.

- Cerebral Palsy: Classified as None, Mild, Moderate or Severe per GMFCS and neurologic examination

II. Compare developmental and neurologic outcomes, assessed by the Bayley Scales of Infant Development (BSID, 4th ed) standardized neurologic exam at 22-26 months' corrected age, and ASQ-3, at 22-26 months' chronological age, in extremely low gestational age infants born at 22-28+6 weeks GA receiving an FiO2 of .30 versus an FiO2 of 1.0 during 90-seconds DCC.

III. Compare the neurodevelopmental outcomes as described above for premature newborns 22–28+6 weeks GA delivered by C-Section with those born by vaginal delivery receiving an FiO2 of .30 versus an FiO2 of 1.0 during 90-seconds DCC.

IV. Compare behavior and emotional problems in children as assessed by Child Behavior Checklist (CBCL) scores on infants born between 22-28+6 weeks GA receiving a FiO2 of .30 versus a FiO2 of 1.0 during 90 seconds of DCC.

According to the normative data of the CBCL, a *t*-score ≤ 59 indicates non-clinical symptoms, a *t*-score between 60 and 64 indicates that the child is at risk for problem behaviors, and a *t*-score ≥ 65 indicates clinical symptoms.

V. Compare oxidative biomarkers (GSH, GSSG) as assessed from blood specimens collected from the umbilical cord, after the cord is cut, and upon NICU admission or within 2 hours of life on infants born between 22- and 28+6-weeks GA receiving a FiO2 of .30 versus a FiO2 of 1.0 during 90 seconds of DCC.

2.3. Trial design

This randomized double-blinded pilot trial will enroll 140 extremely low gestational age infants (up to 28+6 weeks GA) who receive DCC of at least 90 seconds with carefully detailed hemodynamic assessments and simultaneous video recordings in the resuscitation suite. The study will evaluate infants receiving continuous positive airway pressure (CPAP) and/or positive pressure ventilation (PPV) by face mask with an

inspired fractional oxygen (FiO2) of 1.0 (HI Group) during DCC compared to infants given mask CPAP/PPV with an inspired FiO2 of 0.30 during DCC (LO Group). Due to the nature of the intervention, both arms receive CPAP/PPV with identical cord clamping times and respiratory support; the study can be blinded by covering the oxygen blender, avoiding any postnatal treatment bias. Once the cord is clamped and cut, each infant is resuscitated as per unit protocol (i.e., CPAP/PPV with a starting FiO2 0.30) by the clinical team. A detailed breathing assessment from a video recording in the resuscitation suite will be collected as well as physiological parameters from birth through the first 24 hours of life. If we reduce hypoxia in extremely preterm infants by providing supplemental oxygen during the period of delayed cord clamping, there may be a dramatic reduction in morbidities and mortality.

3. METHODS

3.1. Study setting

Sharp Mary Birch Hospital for Women & Newborns
3003 Health Center Dr. San Diego, CA 92123

University of California Davis Medical Center
2315 Stockton Blvd, Sacramento. CA 95817

University of California San Diego Jacobs Medical Center
9300 Campus Point Dr. San Diego, CA 92037

* Please see NCT.gov for Complete Updated List of Sites & Investigators

3.2. Eligibility criteria

3.2.1. Inclusion criteria

1. up to 28+6 weeks gestational age
2. Single and Multiple pregnancy
3. All modes of delivery (vaginally or caesarean section)

3.2.2. Exclusion criteria

1. Parents decline consent
2. Congenital anomalies of the newborn
3. Bleeding Accreta
4. Monochorionic multiples with evidence of TTTS

5. Fetal or maternal risk (i.e., compromise)
6. Preterm Premature Rupture of Membranes prior to 20 weeks gestation
7. Parents request no resuscitation

3.3. Interventions

3.3.1. Intervention description

Prenatal consent will be obtained from parents of infants with estimated gestational age up to 28+6 weeks. Shortly before delivery, infant's will be randomly assigned to receive either Low oxygen concentration (FiO2 .30) or High oxygen concentration (FiO2 1.0) during 90 seconds of delayed cord clamping.

Randomization and intervention will remain blinded to the clinical care team during the entire study period. The research team member will open a randomization card when notified of a subject's impending birth, review the protocol with the obstetric provider performing the procedure, set-up the sterile stabilization bed, and note the time of initial spontaneous breathing and the time it takes from delivery until the clamping and cutting of the umbilical cord in both groups.

The research team member will set the oxygen blender as indicated by the randomization card and cover the blender to blind the FiO2 setting. The research team member will not be involved in the clinical care of the infant. The oxygen blender will be concealed from the clinical care team to ensure resuscitation maneuvers will not be biased.

At delivery, the infant will be placed on a stabilization bed or on the mother's abdomen that allows the infant to be close to the mother and the umbilical cord to remain intact for eDCC. If the infant is resuscitated on the mother's abdomen a separate resuscitation stand will be used. The stabilization bed (or stand) is equipped with an oxygen blender, humidifier, t-piece resuscitator with mask, necessary to provide CPAP/PPV. At some centers the bed will be equipped with a radiant warmer (Ceramotherm, Wyer GmbH, Germany) to maintain thermoregulation on the infant during delayed cord clamping.

If an infant is randomized to DCC and Low Oxygen concentration (DCC LO group), the following procedure will ensue:
During delayed cord clamping, the infant will be gently stimulated by drying the infant with a sterile towel and provide CPAP by 30 seconds of life. During delayed cord clamping, breathing assistance with CPAP of 5 cmH20 and a FiO2 0.3 will be provided.

If an infant is randomized to DCC and High Oxygen concentration (DCC HI group), the following procedure will ensue:
During delayed cord clamping, the infant will be gently stimulated by drying the infant with a sterile towel and provide CPAP by 30 seconds of life. During delayed cord clamping, breathing assistance with CPAP of 5 cmH20 and a FiO2 1.0 will be provided.

Patency of the airway will be assessed by a Colorimetric CO2 detector. Lack of color change will indicate that the airway is obstructed, the pressure is not sufficient to expand the lungs, there was excessive air leak, or there was no or inadequate pulmonary blood flow. If there continues to be no color change, the neonatal provider will reposition and reattempt to open the airway, if there is no improvement, PPV will be initiated by 60 seconds of life (staring with 20 cmH2O). Cord clamping will occur no earlier than 90 seconds of life and the infant will be transferred to a standard neonatal warmer and resuscitated per NRP guidelines.
Additionally, when available heart rate data will be collected using a non-invasive dry-electrode monitor, (NeoBeat, Laerdal Medical, Stavanger, Norway) and applied over the infant's chest or abdomen to provide continuous display of heart rate.

The Near-Infrared Spectroscopy (NIRS) will be applied after cord clamping once the infant is considered stable by the medical team. If available, the NIRS sensor will be placed on the infant's forehead. Cerebral StO2, SpO2, blood pressure (once in the NICU) and heart rate will be recorded every two seconds and linked with other variables. These variables will continue to be recorded for the first 24 hours of life.

Timed echocardiographic measurements will be performed on all enrolled infants at 6 hours +/- 2 hours of age by our research sonographers who are blinded to infant randomization. Every effort will be made to complete the timed echocardiographic measurements within the specified timeframe, however, will still be acceptable if done no later than 12 hours of life. 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 (RVO) (ml/kg/min) and left ventricular output (LVO) (ml/kg/min), and measure pulmonary artery pressure. All obtained data and measurements will be entered into the REDCap database.

Data will be submitted to the statistician, who will remain blinded to the intervention for the duration of the study.

3.3.2. Modifications

To aerate a lung with non-invasive ventilation such as CPAP or mask PPV, a patent airway must be present for air to enter the lung. Spontaneous breathing is the most effective and least traumatic way to open the airway at birth. A closed glottis during apnea hampers the effectiveness of non-invasively applied PPV.

A colorimetric CO2 detector will be used in both groups to assess airway patency. Lack of color change will indicate that the airway is obstructed, the pressure is not sufficient to expand the lungs, there was excessive air leak, or there was no or inadequate pulmonary blood flow. The neonatal provider will reposition and reattempt to open the airway, and if there is no improvement, they will initiate PPV (starting PIP of 20 cmH20) by 60 seconds of life.

This has been demonstrated by both animal and human studies, with the latter showing that a non-invasively applied sustained inflation in preterm infants at birth was

ineffective unless the infant was spontaneously breathing. Interventions aimed at improving effectiveness of non-invasive ventilation should therefore focus on stimulation of spontaneous breathing to open the glottis and enable success of non-invasive respiratory support.

Hypoxia is a potent inhibitor of fetal breathing movements before birth and this inhibitory effect persists for days to weeks after birth. For more effective non-invasive respiratory support, hypoxia should be avoided to facilitate spontaneous breathing and glottic opening, preventing apnea at birth. This, in turn, may reduce the need for invasive respiratory support, thereby reducing the risk of lung and brain injury.

Oxygenation at birth is largely determined by the surface area available for gas exchange within the lung, the gas diffusion distance, and the partial pressure gradient for oxygen between alveoli and adjacent capillaries. To stabilize extremely preterm infants in the delivery room, a higher fraction of inspired oxygen (FiO_2) may be required to compensate for inadequate lung aeration because the surface area for gas exchange is suboptimal. However, international resuscitation guidelines recommend resuscitation in extremely low gestational age infants should commence with a low FiO_2 to reduce the risk of hyperoxia which has been associated with increased production of free radicals and its resultant tissue damage. (30, 31) The downside of this approach is an increased risk of hypoxia with a potential negative effect on breathing effort. It has been shown that hypoxemia (mean peripheral arterial oxygenation SpO_2 < 80 percent) at 5 minutes of life is associated with a higher risk of mortality and the development of sIVH. (23)

3.3.3. Adherence

The clinical investigation will be conducted in compliance with this protocol. The research team is meeting daily with all the providers involved in the delivery of extremely premature infants. Modifications to the protocol will not be implemented before agreement from the primary PI and relevant ethics committee approvals are obtained. In the discussions with the maternal and neonatal providers, every effort is made to optimize processes in the delivery that will not interfere with the providers' workflow nevertheless beneficial for the premature infant. Investigators are not allowed to deviate from the protocol.

Our ultimate goal is to allow for the greatest benefit while ensuring our intervention is easily implemented. If we can demonstrate that lung aeration and it's resultant improvement in oxygenation could occur earlier in a safe and controlled manner, it would simplify our approach to the extremely preterm infant. This approach would allow for the continuation of appropriate resuscitation with adequate monitoring thus increasing the likelihood that such an approach, if proven advantageous, would be implemented, and replicated by others.

Enrollment in concurrent research trials that may involve patients that are eligible for this DOXIE trial must be approved by the PI for co-enrollment after review of the protocol and a discussion with the site PI.

3.3.4. Concomitant care

All clinical staff involved with implementing the intervention will receive training in protocol adherence and safety measures. Neonatal providers will be in sterile gown during the procedure and use non-sterile masks for ventilation. Every effort will be made to avoid touching any parts of the sterile field while the provider is administering CPAP/PPV.

Umbilical cord milking is prohibited in this proposed group (<29 weeks). Recently, the Neonatal Resuscitation Program has recommended against umbilical cord milking in infants <29 weeks due to an increased risk of intraventricular hemorrhage (IVH). (20)

3.4. Outcomes

Primary Outcome Measure:

To assess the feasibility and compare the incidence of preterm infants (up to 28+6 weeks GA) who achieve a peripheral oxygen saturation of ≥ 80 percent by 5 MOL given mask CPAP/PPV with an FiO2 of 1.0 during DCC for 90 seconds (HI Group) to infants given mask CPAP/PPV with an FiO2 of .30 during DCC for 90 seconds (LO Group) [Time Frame: by 5 minutes of life]

Secondary Outcome Measures:
1. All Grade IVH

Any Intraventricular Hemorrhage (grades 1-4)
[Time Frame: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA)]

2. Frequency of Grade III and IV intraventricular hemorrhage

Intraventricular hemorrhages (grades 3-4) (bleeding in the brain parenchyma and/or ventricular dilation
[Time Frame: Through study completion at hospital discharge, up to 6 months corrected gestational age (CGA)]

3. Resuscitation interventions

Resuscitation interventions including intubation, chest compressions, medications
[Time Frame: In the first 10 minutes of life]

4. Changes in heart rate (BPM) in the first 10 minutes of life

Other Pre-specified Outcome Measures:
1. Changes in Inspired fractional oxygen (FiO2)

[Time Frame: In the first 10 minutes of life]

2. Duration of Hypoxia

Duration of Hypoxia (defined as oxygen saturation<25th percentile of target ranges defined by Dawson et al.) in the first 10 minutes after birth
[Time Frame: The first 10 minutes of life in the delivery room]

3. Duration of Hyperoxia

Duration of Hyperoxia (defined as oxygen saturation>95%) in the first 10 minutes after birth [Time Frame: The first 10 minutes of life in the delivery room]

4. Changes in Mean airway pressure, MAP (cm H20)

[Time Frame: In the first 10 minutes of life]

5. Duration of Positive Pressure Ventilation

[Time Frame: The first 10 minutes of life in the delivery room]

6. Blood pressures in the first 24 hours of life

[Time Frame: In the first 24 hours of life]

7. Cerebral tissue oxygenation in the first 24 hours of life

[Time Frame: In the first 24 hours of life]

8. Average oxygen saturation in the first 5 minutes after birth

Oxygen saturation in the first 5 minutes after birth
[Time Frame: by 5 minutes of life]

9. Average Heart rate in the first 5 minutes after birth

Heart rate in the first 5 minutes after birth
[Time Frame: by 5 minutes of life]

10. Intubation in the Delivery room or Neonatal Intensive Care Unit (NICU)

[Time Frame: Birth through study completion at discharge, up to 6 months of corrected gestational age]

11. Lowest and Highest Hemoglobin and/or Hematocrit

Hemoglobin and/or Hematocrit levels (before transfusion)
[Time Frame: First 24 hours of life]

12. Mean arterial blood pressure

Mean arterial blood pressure (collected hourly)
[Time Frame: First 24 hours of life]

13. Medication for Low Blood Pressure

Medication for Low Blood Pressure (e.g. hydrocortisone or pressors)
[Time Frame: First 24 hours of life]

14. CRIB-II (Clinical Risk Index for Babies)

[Time Frame: First 12 hours of life]

15. Duration of mechanical ventilation and/or CPAP

Number of days on mechanical ventilation and/or CPAP
[Time Frame: Through study completion at discharge, up to 6 months of corrected gestational age]

16. Surfactant administration

[Time Frame: Immediately after intervention through study completion at hospital discharge, up to 6 months of corrected gestational age]

17. Number of RBC Transfusions since birth

[Time Frame: First 10 days after birth]

18. Patent Ductus Arteriosus requiring pharmacological or surgical treatment

[Time Frame: Through study completion at discharge, up to 6 months of corrected gestational age]

19. Spontaneous Intestinal Perforation (SIP) requiring surgery or peritoneal drain

[Time Frame: Through study completion at discharge, up to 6 months of corrected gestational age]

20. Necrotizing Enterocolitis (Modified Bell's stage 2-3)

[Time Frame: Through study completion at discharge, up to 6 months of corrected gestational age]

21. Bronchopulmonary Dysplasia (mode of respiratory support administered at 36 weeks' postmenstrual age: as defined and categorized in; Jensen, Dysart, Gantz, *et al*: Defining Bronchopulmonary Dysplasia)
http://www.ncbi.nlm.nih.gov/pmc/articles/pmc6775872/

[Time Frame: Hospital course until 36 weeks PMA]

22. Severe ROP (stage 3-4 or treated with laser or bevacizumab) prior to 36 weeks PMA

[Time Frame: After the intervention through study completion at hospital discharge, up to 6 months of corrected gestational age]

23. Combined outcome of severe IVH and/or death

[Time Frame: Through study completion at death or discharge, up to 6 months of corrected gestational age]

24. Death

[Time Frame: Through study completion at death or discharge, up to 6 months of corrected gestational age]

25. SVC Flow

Superior Vena Cava flow by echocardiography
[Time Frame: 6 hours of life]

26. RVO

Right Ventricular output by echocardiography
[Time Frame: 6 hours of life]

27. Left Ventricular Output

Left Ventricular output by echocardiography
[Time Frame: 6 hours of life]

28. Ages and Stages Questionnaire

Ages and Stages Questionnaire
[Time Frame: 22 months to 26 months chronological age]

29. Cognitive Composite Score

Composite Score (cognitive 45-155; higher scores are better) as assessed by the Bayley Scales of Infant and Toddler Development Fourth Edition
[Time Frame: 22-26 months' corrected age]

30. Language Composite Score

Composite Score (language 45-155; higher scores are better) as assessed by the Bayley Scales of Infant and Toddler Development Fourth Edition
[Time Frame: 22-26 months' corrected age]

31. Motor Composite Score

Composite Score (motor 45-155; higher scores are better) as assessed by the Bayley Scales of Infant and Toddler Development Fourth Edition
[Time Frame: 22-26 months' corrected age]

32. Cerebral Palsy

As assessed by Gross Motor Function Classification System (GMFCS) Levels 1-5
[Time Frame: 22-26 months' corrected age]

33. Pulsatility Index

Pulsatility index calculated from Doppler of the Middle Cerebral Artery
[Time Frame: 6 hours of life]

34. Resistive Index

Resistive index calculated from Doppler of the Middle Cerebral Artery
[Time Frame: 6 hours of life]

35. Changes in cerebral oxygen saturation, StO2 (%)

Changes in cerebral oxygen saturation, StO2 (%)
[Time Frame: In the first 10 minutes of life]

36. Changes in SpO2 (%) in the first 10 minutes of life

Changes in SpO2 (%) in the first 10 minutes of life

[Time Frame: In the first 10 minutes of life]

37. Inhaled Nitric Oxide

Use of Inhaled Nitric Oxide for Respiratory Failure or Pulmonary Hypertension
[Time Frame: Immediately after intervention through study completion at hospital discharge, up to 6 months of corrected gestational age]

38. Glutathione (GSH/GSSG ratio)

Assessment of oxidative biomarkers from birth up to 2 hours of life
[Time Frame: From birth up to NICU admission or in the first 2 hours of life]

39. Thermoregulation
Assessment of thermoregulation (axillary temperatures measured in degrees Celsius) during delayed cord clamping on extremely low gestational infants
[Time Frame: From 5 minutes of life up to NICU admission or in the first 2 hours of life]

40. Early onset sepsis

Assessment of early onset sepsis with a positive blood or CSF culture at $\leq$ 72 HOL
[Time Frame: From birth up to 72 hours of life]

41. Late onset sepsis

Assessment of late onset sepsis with a positive blood or CSF culture at > 72 HOL
[Time Frame: From > 72 hours of life through study completion at death or discharge]

42. Child Behavior Checklist (CBCL)

Child Behavior Checklist Questionnaire
[Time Frame: 22 months to 26 months corrected gestational age]

3.5. Participant timeline

TIMEPOINT (state unit)	Maternal Admission	Date/Time of Birth	5 minutes of life	10 minutes of life	NICU admission	6 hours of life	12 hours of life	24 hours of life	Discharge	24 months (22-26 months ' corrected age)
Subject ID:		x	x	x	x	x	x	x	x	x
ENROLLMENT:		x	x	x		x	x	x	x	
Eligibility screen	x									
Informed consent	x									
Allocation		x								
INTERVENTIONS:										
Respiratory Support		x	x	x		x	x	x	x	
DCC LO group(FiO2 .30)		x	x							
DCC HI group(FiO2 1.0)		x	x							
Oxidative Biomarkers: Blood sample		x			x					
ASSESSMENTS:										
Data Collection			x	x	x			x		
Hemodynamic measurements		x	x	x	x	x	x	x		
Electrocardiographic Measurements (CUS)						x	x			
Near-Infrared Spectroscopy (NIRS)			x	x	x	x	x	x		

Expected outcomes of Prematurity(BPD, IVH, ROP, NEC, SIP)									x	
Bayley-4 Scales (corrected gestational age)										x
Ages and Stages Questionnaire, 3rd edition (chronological age)										x
Child Behavior Checklist Questionnaire										x

3.6. Sample size

A total of 140 babies will take part in this blinded-randomized controlled trial study.

3.7. Recruitment

The research team will approach eligible women for consent on a 24-hour basis. Pregnant women who are dated by their earliest ultrasound or last menstrual period at <29 weeks gestation will be identified and recruited. Prior to delivery, infants will be further stratified by gestational age (22+0 to 25+6 weeks to 26+0 to 28+6 weeks) and randomized to DCC-LO or DCC-HI.

3.8. Allocation

After informed consent is obtained from the parents of infants with a gestational age <29 weeks (by best obstetrical dating), participants will be randomized using sealed opaque envelopes opened immediately before delivery to receive either DCC-LO or DCC-HI. Stratification will be blocked in groups of four to allow for an equal distribution of infants (22+0 to 25+6 weeks and 26+0 to 28+6) weeks gestation. Multiples will be included and randomized individually. The randomization cards will contain a subject identification number that will be kept by the Research Coordinator.

The research team member will set the oxygen blender as indicated by the randomization card and cover the blender to blind the FiO2 setting. The research team member will not be involved in the clinical care of the infant. The oxygen blender will be concealed from the clinical care team to ensure resuscitation maneuvers will not be biased.

Pulse oximetry, ECG sensors and Near-Infrared Spectroscopy (NIRS) sensors will be applied after cord clamping. The NIRS sensor will be placed on the infant's forehead. Cerebral StO2, SpO2, blood pressure (once in the NICU) and Heart rate will be recorded every two seconds and linked with other variables. These variables will continue to be recorded for the first 24 hours of life.

3.9. Blinding (masking)

3.9.1. Blinding mechanism

Randomization and intervention will remain blinded to the clinical care team during the entire study period. The research team member will open a randomization card when notified of a subject's impending birth, review the protocol with the obstetric provider performing the procedure, set-up the sterile stabilization bed, and note the time it takes from delivery until the clamping and cutting of the umbilical cord in both groups. Time of initial spontaneous breathing will also be collected.

The research team member will set the oxygen blender as indicated by the randomization card and cover the blender to blind the FiO2 setting. The research team member will not be involved in the clinical care of the infant. The oxygen blender will be concealed from the clinical care team to ensure resuscitation maneuvers will not be biased.

3.10. Data collection

3.10.1. Trial procedures and evaluations

Infants will be recruited over a period of 24 months or until the requisite sample size is achieved. If there is a substantial increase in withdrawal or death the sample size may be increased. Approximately six months after the final participant completes their 24-month developmental visit we will have completed data collection on all infants enrolled. Resuscitation data will be documented on the randomization card at the time of delivery. Medical data on each infant will be collected on an electronic Case Report Forms (eCRF). The eCRF will be designed to collect delivery room data and information not obtained in the participant’s electronic medical record. Upon enrollment, initial subject randomization allocation and GA should be entered into the electronic database within 72 hours.

Echocardiography
As part of the data collection, an echocardiogram will be performed. Echocardiographic measurements will be performed on all infants at 6 hours +/-2 hours of life 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). 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.

Oxidative Biomarkers: Blood Sample
In addition, biochemical determinations on blood will be performed. This is extra few drops of blood that is drawn from the baby for medical purposes (cord blood from cord gases and admission blood work up).

Oxidized glutathione (GSSG) and reduced glutathione (GSH) which are the most reliable and comprehensive biomarkers of oxidative stress, will be determined in the blood collected from the umbilical cord (cord blood sample collected after the cord is cut) during delivery (T1) and in central or peripheral blood upon admission to the NICU or within 2 hours after birth (T2).

Blood samples for both time periods (T1 and T2) require a few drops of blood that are collected on a modified Whatman paper. Blood samples collected from the umbilical cord, after the cord is cut, and blood samples collected upon admission to the NICU will be placed in an EDTA tube and mixed carefully. 10 uL of this blood sample will be transferred onto the modified Whatman paper using a calibrated pipette. The sample will then be allowed to dry on the modified Whatman paper for 5 minutes at room temperature before storing in the freezer (-80 ^{0}C) until shipment on dry ice to The Medical Research Institute Hospital La Fe, Valencia, Spain.

3.10.2. Retention

Participants in this study will be inborn premature infants in the Neonatal Intensive Care Unit (NICU) and will be tracked by our study team out to 2 years of age. Standardized neurologic and developmental assessments [Bayley Scales of Infant Development, 4th ed. (BSID-4)] will be performed at 22-26 months' corrected gestational age, and age-specific developmental questionnaires [Ages and Stages Questionnaire, 3rd edition] will be performed at 24 months chronological age by our follow-up team at a 22–26-month window to ensure comparability with other trials. Neurodevelopmental impairment will be defined as having moderate to severe cognitive or motor impairment or severe neurosensory impairment. The follow-up team includes a designated neurodevelopmental provider(s) and high-risk infant follow-up program support. This certification and neurodevelopmental evaluation process complies with the current standards set by the NRN, with the goal of a ≥ 90% follow-up rate. Neurodevelopmental assessments will be blinded to original treatment group. Details of measuring neurodevelopmental outcomes at 2 years of age are described in section (2.2.2 Secondary objectives).

Additionally, as part of standardized care at the 2-year follow-up clinic visit, a Child Behavior Checklist (CBCL) questionnaire will be obtained. The preschool version of the CBCL (CBCL/1½-5), where the parents or others who interact with the child in regular contexts rate the child's behavior. Respondents rate the child's behavior on a 3-point scale (*not true*, *somewhat or sometimes true*, and *very true or often true*), and are instructed to rate the behavior as it occurs currently or within the previous two months. The CBCL 1.5–5 comprises 100 problem items identified on several subscales, including Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn,

Sleep Problems, Attention Problems, and Aggressive Behavior. Moreover, scores on Internalizing, Externalizing, and Total Problems can be obtained. The Internalizing domain is a broad measure of emotional problems. It is an aggregate of anxiety and depression symptoms that subsumes four more narrowly focused syndrome scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn. The Externalizing domain is an aggregate measure of behavioral problems and includes Attention Problems and Aggressive Behavior. The Total Problems score quantifies the overall extent of both emotional and behavioral problems, based on responses to all CBCL items including those on the one remaining syndrome scale: Sleep Problems. The Total Problems is based on responses to all CBCL items including those on the three remaining syndrome scales: Social Problems, Thought Problems, and Attention Problems.

Our follow-up clinic has an 85 percent follow-up rate. The study PI is also the medical director of the high-risk infant follow-up clinic and has access to ensure adequate retention of subjects.

3.11. Data management

All data will be safeguarded in accordance with 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. All local databases will be secured with password- protected access systems. Forms, lists, logbooks, appointment books and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Only research team members (with appropriate research training relevant to protection of human subjects) shall have access to the project's databases. The final trial data set will remain with the lead PI.

3.12. Statistical methods

3.12.1. Outcomes

SpO_2 values will be converted to dichotomous outcome (sat >80% by 5 MOL, no/yes) and chi-square testing will be used to evaluate the difference between the HI and LO groups. Subsequent analyses will use logistic regression to estimate odds ratios (95% CI) for SpO_2 < 80% by 5 MOL (no/yes) between the HI and LO groups after adjusting for other delivery room/maternal variables found to be significant in univariable testing.

Longitudinal repeated measures modeling with GEE will be used to test the differences in each of the physiologic parameters SpO_2, StO_2, FiO_2 and MAP over the first ten minutes of life between the HI and LO groups. Variables found to be significant in univariable testing with each of the parameters will be considered for inclusion in model fitting.

Area under the curve measurements (AUC) for FiO_2 versus time and Mean Airway Pressure versus time over the first 5 minutes of life and 10 minutes of life will be calculated using receiver-operating characteristic (ROC) curves to evaluate whether subsequent interventions altered the resultant 5 minutes of life SpO_2. Similarly, the time to achieve a saturation of 80 percent will be compared using ROC curves and AUC measurements should both groups no longer have a different saturation by 5 minutes of life. In addition, Kaplan-Meier curves and proportional hazards modeling will be used to model and evaluate time to event outcomes of interest.

Longitudinal repeated measures modeling with GEE will be used to test the differences over the first 24 hours of life for cerebral tissue oxygenation and blood pressure between the HI and LO groups. Variables found to be significant in univariable testing will be considered for inclusion in model fitting.

Measures of systemic and cerebral blood flow will be compared using appropriate tests for normally distributed values means (T-tests).

3.12.2. Additional analyses

3.12.3. Analysis population and missing data

Data will be first verified for accurate entry, formats, coding, and missing information. The largest and smallest values for each variable will be reviewed for accuracy and plausibility. Each variable will be examined for variability and frequency distribution, skewness and kurtosis. A variety of graphical techniques will be used to display and assess data such as histograms, boxplots and scatterplots, etc. All significance tests will be two sided with a critical alpha level of 0.05. Data analyses will use SPSS and R programming package.

3.13. Data monitoring

3.13.1. Formal committee

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. The DCoC will inform the DSMB of all expected and unexpected adverse events; recruitment reports 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.

There are no conflicts of interest with these individuals, who are not research collaborators, and are at separate institutions from the applicants. It will be the responsibility of the trial investigators to notify the IRB of record 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 database. The DOXIE Steering Committee will discuss with the DSMB how frequently to review sites at the start-up phase to ensure safety, consent, and enrollment.

3.13.2. Interim analysis

The DSMB will receive regular reports from DCoC for 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.

3.14. Safety/harms

The population being studied is at an increased risk of all complications associated with prematurity. The majority of these events will be expected and included in data collection and reported in the final analysis. However, SAE of death and severe IVH will be reported to the principal investigator (PI) and the institutional review board within 72 hours of discovery. The following guidelines outline the reporting timeline and procedures for SAE, expected and unexpected events.

Expected Adverse Events – captured in data collection and reported in final analyses. The following adverse events that are expected and will be recorded in the database. The DCoC will track and report all adverse events to the DSMB every 3 months. After review of the data, the DSMB will report to the PI regarding the risks of the study and whether the risks are consistent with what is described in the informed consent form.
1. IVH grade 1-2
2. Severe Retinopathy of Prematurity
3. Chronic Lung Disease (mode of respiratory support at 36 weeks' post-menstrual age as defined and categorized by: Jensen, Dysart, Gantz, *et al*: Defining Bronchopulmonary Dysplasia) http://www.ncbi.nlm.nih.gov/pmc/articles/pmc6775872/
4. NEC (stage >2)
5. Spontaneous Intestinal Perforation

The DSMB reviewed and discussed the closed report issued on May 19, 2023 (version 2.1) and after examination of the report in detail, the DOXIE DSMB members unanimously recommend that the DOXIE trial continue and further recommend that sepsis, blood stream infections, and CSF infection with identified pathogen be tracked as an adverse event of special interest. The DCoC has acknowledged and made an update to questions in the database for DOXIE to sufficiently track blood and/or CSF infection.

Unanticipated Problem (UP) – Unexpected Problem
An UP is any incident, experience, or outcome that meets ALL the following criteria:
1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm).

The Data Manager will be responsible for reporting to the medical monitor within 14 days of awareness of an UP. The medical monitor will determine if the unanticipated problem changes the known risk to study subjects. If the information changes the known risk to the participants, the IRB and participants will be notified.

Serious Events

All SAEs of death and severe IVH will be entered into the electronic data collection system and reported to the data manager within 72 hours of discovery of event. The data manager will forward all SAEs of death and severe IVH to the lead PI

- Death (maternal or neonatal)
- Severe IVH - grades III, IV
- Compressions and/or Epinephrine in the Delivery Room

Site investigators must assess the seriousness of the event to decide on the timing of the report, as well as to assign the relationship of the event to the study. Each institution is responsible for submitting SAE and Unanticipated Problems to their local IRB in accordance with their specific IRB requirements.

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.

3.15. Auditing

This process will be finalized upon initial meeting with the DSMB

4. ETHICS AND DISSEMINATION

4.1. Research ethics approval

This double-blinded randomized clinical trial 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 regulations of Sharp Mary Birch Hospital for Women & Newborns and will not begin until required approvals from ethical committees have been obtained. Additional requirements imposed by the ethical committees will be followed.
A copy of the IRB approval and consent forms, including all languages, must be sent to the local IRBs. Copies of each site approval will be provided to the main site. The local PI and study coordinator are responsible for ensuring that continuing IRB approval is obtained each year.

4.2. Protocol amendments

All protocol changes must be sent to the IRB of record as a protocol amendment. In case of modifications in the study protocol that are not merely of a formal nature but contain changes pertinent to the study participants. The trial will only start the randomization of participants after approvals from the relevant ethics committees have been received.

4.3. Informed consent process

Consent will be obtained by the primary investigator or a delegated sub-investigator or a research associate. Written informed consent must be obtained before entry into the randomized trial. Full disclosure of the nature and potential risks of participating in the trial will be made. All potential participants will undergo the informed consent process as approved by the Institutional Review Board at each participating center.
Only pregnant mothers or her legally authorized representative can sign a HIPAA authorization providing access to her medical record for data collection purposes. The subject or their legally authorized representative will be given ample time to read the informed consent, ask questions of the research team, and discuss the study with their family and/or the subject's physician. The informed consent process will be documented in the EMR and copies of the signed and dated consent will be given to the participant or their representative, placed in the participant's physical chart, and stored in a locked cabinet in the offices of the local research department.

4.4. Confidentiality

All data will be safeguarded in accordance with 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. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

4.5. Declaration of interests

The Principal Investigator for the overall trial and each study site declare no financial or other competing interests.

4.6. Access to data

The study staff will make every effort to keep the participants information private. All data collected will be identified with a study number, not names or medical record numbers. The code that links this number with the participant will remain in the research office in a password protected electronic file accessible to only the research staff.

4.7. Ancillary and post-trial care

4.8. Dissemination policy

4.8.1. Trial results

Delayed Cord Clamping with Oxygen In Extremely Low Gestational Age Infants (DOXIE) is registered and is posted on the ClinicalTrials.gov public website. The ClinicalTrials.gov Identifier is NCT04413097. The trial results will be reported in a manner consistent with U.S. Public Law 110-85. Consistent with the default adverse events reporting provisions of section 801(a) of the FDA Amendments Act of 2007 (FDAAA) [as it amends 42 U.S.C. 28 2(j) (3) (I) (ii)-(iii)], we will submit summary adverse event information when providing study results to ClinicalTrials.gov.

Any informed consent documents for the clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov.

Several strategies will be implemented to broadly disseminate the study results. First, the primary audience will include Neonatologists and Perinatologists, and Obstetricians. Providers will be targeted by submission of an abstract to the Pediatric Academic Societies (PAS) and the Annual Pregnancy meeting for the Society of Maternal Fetal Medicine (SMFM) for presentation.

4.8.2. Authorship

Authorship will be based on number of recruitments. The PI will be senior author followed by the lead site PI and the other sites, additional key personnel (lead coordinator, data managers, and Co-I) will be listed, followed by the steering committee. FI and AK developed the initial protocol and manuscript. KC, JK, NF, SL, RS, WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript.

5. STUDY ADMINISTRATION

5.1. Key contacts

Central contact

Anup Katheria, MD
Sharp Mary Birch Hospital for Women & Newborns
3003 Health Center Dr. San Diego, CA 92123
858-939-4170
anup.katheria@sharp.com

Sponsor

Eunice Kennedy Shriver National Institute of Child Health and Human Development

5.2. Funders

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

5.3. Roles and responsibilities

5.3.1. Sponsor and funder

A grant to support the DOXIE trial has been obtained from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and with this financial support, the primary study site maintains ultimate authority overall study activities.

5.3.2. Trial committees

Dr. Anup Katheria, Principal Investigator (PI) will be responsible for the overall conduct of the trial and will serve as the chair of the Steering Committee. He will coordinate all clinical research activities and will continue to work with the other Co-Investigators to ensure completion of the project. Dr. Katheria has been performing single and multicenter RCTs of umbilical cord management since 2007. He currently leads two multicenter international trials on cord management (RO1HD088646 and R01HD096023) and completed several cord clamping trials including resuscitation on the cord.

Dr. Neil Finer is an experienced neonatologist and will serve on the Steering Committee, with the PI as the Chair. He led and designed numerous single and multisite clinical trials and is considered one of the world's neonatal resuscitation experts in the field. As the PI's mentor over the past 14 years, Dr. Finer serves on the Steering

Committee for his two current multicenter trials and was also the PI for the NICHD Neonatal Research Network SUPPORT trial. He will assist with ensuring the protocol design and implementation are successful and help with conducting the quarterly meetings as well. He will continually work with the PI to ensure the protocol is followed. In addition, he will respond to problems with the protocol implementation as part of the steering committee.

Dr. Satyan Lakshminrusimha is collaborating with Dr. Katheria on an ongoing cord milking trial (R01HD096023) and is directly involved with this trial design and implementation. He is the PI for a multicenter proposal through NICHD-Neonatal Research Network, and his current NIH research project grant (R01HD072929) evaluates the role of placental transfusion on cerebral oxygenation following asphyxia. He is also evaluating resuscitation with an intact cord in a term lamb model of asphyxia (R03HD060138) which serves as additional pilot data for this trial. He conducted several trials on placental transfusion including two NICHD-funded studies in preterm and term infants and is regarded as a leader in the field. Dr. Satyan is directly involved in the design and implementation of this trial. He will conduct any additional translational experiments as well as sharing data that may help improve the proposed pilot trial.

Dr. Robin Steinhorn is a Professor and Vice Dean for Children's Clinical Services at UC San Diego. She is a renowned expert in the pathophysiology of persistent pulmonary hypertension, investigating the basic mechanisms regulating vascular tone, and providing new evidence for therapies. RS will serve on the Steering Committee and provide guidance relative to the design, implementation, and analysis of the clinical trial. She will assist with ensuring the protocol design and implementation are successful and will also help with conducting the quarterly meetings.

Dr. Yvonne Gollin, Co-Investigator, is a SMB perinatologist, also collaborated and helped the team develop the ventilation during DCC strategy and served as an instructor to other obstetricians performing the procedure. Her participation will ensure adequate obstetrical involvement for study completion.

Dr. Debra Poeltler, Statistician, is a Senior Clinical Research and Quality Data Specialist and holds a PhD in Public Health with an emphasis in epidemiology and biostatistics. She has extensive experience in trial design and statistical analysis over the past 15 years. She will be responsible for overseeing proper collection of data into the REDCap system during the trial. She will also serve as the liaison with the Data Manager and Medical Monitor during the generation of monthly safety reports. The Statistician will be performing statistical analysis on the final dataset once the trial is completed.

References:

1. Rabe H, Wacker A, Hulskamp G, Homig-Franz I, Jorch G. Late cord clamping benefits extrauterine adaptation. Pediatric research. 1998;44:454.

2. Rabe H, Jewison A, Alvarez RF, Crook D, Stilton D, Bradley R, Holden D, Brighton Perinatal Study G. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. Obstetrics and gynecology. 2011;117(2 Pt 1):205-11. doi: 10.1097/AOG.0b013e3181fe46ff. PubMed PMID: 21252731.
3. Mercer JS, McGrath MM, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. Journal of perinatology : official journal of the California Perinatal Association. 2003;23(6):466-72. PubMed PMID: 13679933.
4. Nelle M, Fischer S, Conze S, Beedgen B, Brischke EM, Linderkamp O. Effects of later cord clamping on circulation in prematures (Abstract). Pediatric research. 1998;44:420.
5. Narenda A, Beckett CA, T., Kyle E, Coutis J, Turner T, Holland B, Wardrop C. Is it possible to promote placental transfusion at preterm delivery? Pediatric research. 1998;44:453.
6. Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CA. Umbilical cord clamping and preterm infants: a randomized trial. BMJ (Clinical research ed). 1993;306:172-5.
7. Ibrahim H, Krouskop R, Lewis D, Dhanireddy R. Placental transfusion: umbilical cord clamping and preterm infants. J Perinat. 2000;20:351-54.
8. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics. 2006;117(4):1235-42. PubMed PMID: 16585320.
9. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. S Afr Med J. 1988;73(2):104-6. PubMed PMID: 3340910.
10. Hofmeyr GJ, Gobetz L, Bex PJ, Van der Griendt M, Nikodem C, Skapinker R, Delahunt T. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. The Online journal of current clinical trials. 1993;Doc No 110:[2002 words; 26 paragraphs]. PubMed PMID: 8305996.
11. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. The Cochrane database of systematic reviews. 2004(4):CD003248. PubMed PMID: 15495045.
12. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, Simes J, Tarnow-Mordi W. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. American journal of obstetrics and gynecology. 2018;218(1):1-18. Epub 2017/11/04. doi: 10.1016/j.ajog.2017.10.231. PubMed PMID: 29097178.
13. Committee Opinion No.543: Timing of umbilical cord clamping after birth. Obstetrics and gynecology. 2012;120(6):1522-6. Epub 2012/11/22. doi: 10.1097/01.aog.0000423817.47165.48. PubMed PMID: 23168790.
14. WHO Guidelines Approved by the Guidelines Review Committee. Guidelines on Basic Newborn Resuscitation. Geneva: World Health Organization.; 2012.
15. Wyllie J, Perlman JM, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, Kim HS, Liley HG, Mildenhall L, Simon WM, Szyld E, Tamura M, Velaphi S. Part 7: Neonatal resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2015;95:e169-201. Epub 2015/10/20. doi: 10.1016/j.resuscitation.2015.07.045. PubMed PMID: 26477424.
16. Polglase GR, Dawson JA, Kluckow M, Gill AW, Davis PG, Te Pas AB, Crossley KJ, McDougall A, Wallace EM, Hooper SB. Ventilation onset prior to umbilical cord clamping (physiological-based cord clamping) improves systemic and cerebral oxygenation in preterm lambs. PloS one. 2015;10(2):e0117504. Epub 2015/02/18. doi: 10.1371/journal.pone.0117504. PubMed PMID: 25689406; PMCID: Pmc4331493.

17. Hooper SB, Te Pas AB, Lang J, van Vonderen JJ, Roehr CC, Kluckow M, Gill AW, Wallace EM, Polglase GR. Cardiovascular transition at birth: a physiological sequence. Pediatric research. 2015;77(5):608-14. Epub 2015/02/12. doi: 10.1038/pr.2015.21. PubMed PMID: 25671807.
18. 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.
19. Stenning FJ, Hooper SB, Kluckow M, Crossley KJ, Gill AW, Wallace EM, Te Pas AB, LaRosa D, Polglase GR. Transfusion or Timing: The Role of Blood Volume in Delayed Cord Clamping During the Cardiovascular Transition at Birth. Frontiers in pediatrics. 2019;7:405. Epub 2019/10/28. doi: 10.3389/fped.2019.00405. PubMed PMID: 31649907; PMCID: PMC6794342.
20. Katheria A, Reister F, Essers J, Mendler M, Hummler H, Subramaniam A, Carlo W, Tita A, Truong G, Davis-Nelson S, Schmolzer G, Chari R, Kaempf J, Tomlinson M, Yanowitz T, Beck S, Simhan H, Dempsey E, O'Donoghue K, Bhat S, Hoffman M, Faksh A, Arnell K, Rich W, Finer N, Vaucher Y, Khanna P, Meyers M, Varner M, Allman P, Szychowski J, Cutter G. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. JAMA : the journal of the American Medical Association. 2019;322(19):1877-86. Epub 2019/11/20. doi: 10.1001/jama.2019.16004. PubMed PMID: 31742630.
21. Katheria AC, Szychowski JM, Essers J, Mendler MR, Dempsey EM, Schmölzer GM, Arnell K, Rich WD, Hassen K, Allman P, Varner M, Cutter GR, Finer N. Early Cardiac and Cerebral Hemodynamics with Umbilical Cord Milking Compared with Delayed Cord Clamping in Infants Born Preterm. The Journal of pediatrics. 2020;223:51-6.e1. Epub 2020/06/03. doi: 10.1016/j.jpeds.2020.04.010. PubMed PMID: 32482392; PMCID: PMC7387184.
22. Katheria AC, Hassen K, Rich W, Poeltler D, Finer N. Resuscitation outcomes of infants that do not achieve a 5 min target SpO2 saturation. Journal of perinatology : official journal of the California Perinatal Association. 2019. Epub 2019/09/07. doi: 10.1038/s41372-019-0491-x. PubMed PMID: 31488904.
23. Oei JL, Finer NN, Saugstad OD, Wright IM, Rabi Y, Tarnow-Mordi W, Rich W, Kapadia V, Rook D, Smyth JP, Lui K, Vento M. Outcomes of oxygen saturation targeting during delivery room stabilisation of preterm infants. Archives of disease in childhood Fetal and neonatal edition. 2018;103(5):F446-f54. Epub 2017/10/11. doi: 10.1136/archdischild-2016-312366. PubMed PMID: 28988158; PMCID: PMC6490957.
24. 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;178:75-80.e3. Epub 2016/10/30. doi: 10.1016/j.jpeds.2016.07.053. PubMed PMID: 27574999; PMCID: Pmc5527831.
25. 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.
26. Duley L, Dorling J, Pushpa-Rajah A, Oddie SJ, Yoxall CW, Schoonakker B, Bradshaw L, Mitchell EJ, Fawke JA. Randomised trial of cord clamping and initial stabilisation at very preterm birth. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2017. doi: 10.1136/archdischild-2016-312567.
27. Dekker J, Martherus T, Lopriore E, Giera M, McGillick EV, Hutten J, van Leuteren RW, van Kaam AH, Hooper SB, te Pas AB. The Effect of Initial High vs. Low FiO2 on Breathing Effort in Preterm Infants at Birth: A Randomized Controlled Trial. Frontiers in pediatrics. 2019;7(504). doi: 10.3389/fped.2019.00504.

28. Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I, Roberts LJ, 2nd, Arduini A, Escobar JJ, Sastre J, Asensi MA. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics. 2009;124(3):e439-49. Epub 2009/08/08. doi: 10.1542/peds.2009-0434. PubMed PMID: 19661049.
29. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, Viña J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001;107(4):642-7. Epub 2001/05/23. doi: 10.1542/peds.107.4.642. PubMed PMID: 11335737.
30. 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.
31. Vento M, Aguar M, Escobar J, Arduini A, Escrig R, Brugada M, Izquierdo I, Asensi MA, Sastre J, Saenz P, Gimeno A. Antenatal steroids and antioxidant enzyme activity in preterm infants: influence of gender and timing. Antioxid Redox Signal. 2009;11(12):2945-55. Epub 2009/08/04. doi: 10.1089/ars.2009.2671. PubMed PMID: 19645572.