Title:	**Delayed Cord Clamping for Intubation and Gentle Ventilation in Infants with Congenital Diaphragmatic Hernia: A Pilot Feasibility Trial**
Short Title	Delayed Cord Clamping for CDH Pilot Trial
Drug or Device Name(s):	N/A
Regulatory Sponsor:	N/A
eIRB Number	17-014125
NCT Number	NCT03314233
Protocol Date:	September 5, 2018

Amendment 1 Date: January 3, 2018 Amendment 3 Date: April 11, 2018

Amendment 2 Date: February 2, 2018 Amendment 4 Date: June 19, 2018

Amendment 5 Date: September 5, 2018

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CDH	Congenital diaphragmatic hernia
CFDT	Center for fetal diagnosis and treatment
CHOP	Children's Hospital of Philadelphia
DCC	Delayed cord clamping
DING	Delayed cord clamping, Intubation, Gentle ventilation
DSMB	Data safety monitoring committee
SAE	Serious adverse event
SDU	Special delivery unit
UCC	Umbilical cord clamping

ABSTRACT

Context: Congenital diaphragmatic hernia (CDH) is a congenital anomaly associated with a high risk of mortality and need for life-saving interventions such as ECMO, nitric oxide, and vasopressor support. Although infants with CDH experience significant morbidity and mortality starting immediately after birth, high quality evidence informing delivery room resuscitation in this population is lacking. Infants with CDH are at risk for pulmonary hypoplasia and pulmonary hypertension and often experience hypoxemia and acidosis during neonatal transition. The standard approach to DR resuscitation is immediate umbilical cord clamping (UCC) followed by intubation and mechanical ventilation. Animal models suggest that achieving lung aeration prior to UCC results in improved pulmonary blood flow and cardiac function compared with immediate UCC before lung aeration is established. Trials of preterm infants demonstrated that initiating respiratory support prior to UCC is safe and feasible. Because infants with CDH are at high risk for pulmonary hypertension and systemic hypotension, they may benefit from the hemodynamic effects of lung aeration before UCC, namely increased pulmonary blood flow, decreased pulmonary vascular resistance, and improved cardiac output. To date, this approach has not been studied in infants with CDH.

Objective: To establish the safety and feasibility of delaying cord clamping until intubation and lung aeration has been achieved in infants with CDH.

Study Design: Unblinded single-arm pilot interventional trial. All eligible enrolled infants will receive the DING intervention (Delayed cord clamping for INtubation and Gentle ventilation).

Setting/Participants: This study will take place in the CHOP Special Delivery Unit (SDU).
Inclusion criteria: (1) Antenatal diagnosis of CDH; (2) Gestational age ≥ 36 weeks
Exclusion criteria: (1) Multiple gestation; (2) Other major congenital anomalies or aneuploidy; (3) Enrollment in FETO (Fetoscopic endoluminal tracheal occlusion) trial; (4) Palliative care planned or considered; (5) Maternal diagnosis of placenta previa, accreta, or abruption; (6) Maternal diagnosis of pre-eclampsia requiring Magnesium sulfate therapy at time of delivery (7) OB or Neonatal provider concerns for the clinical care of the mother or infant or study team not available.
Study Interventions and Measures:

- DING Intervention: Immediately after birth, the infant will be placed on a Lifestart trolley with an intact umbilical cord, intubated, and ventilated with the CHOP "gentle ventilation" protocol. UCC will occur after (1) colorimetric end-tidal CO_2 detection or (2) 3 minutes after delivery, whichever occurs first.
- Primary Outcome: Successful protocol completion (defined as infant successfully intubated prior to UCC).
- Secondary outcomes: Arterial pH and PaO_2 on first blood gas, Oxygenation index [OI] throughout first 24 hours of life [HOL], need for vasopressors (first 24

HOL), presence of severe pulmonary hypertension on first echocardiogram, need for ECMO and mortality during hospital discharge.

- Tertiary outcomes: Identification of salient themes in parent experiences of the DING intervention, Identification of factors during the intervention that mothers identify as stress inducing or alleviating.

PROTOCOL SYNOPSIS

Study Title	Delayed Cord Clamping for Intubation and Gentle Ventilation in Infants with Congenital Diaphragmatic Hernia: A Pilot Feasibility Trial
Funder	Departmental funds
Study Rationale	Infants with CDH are at risk for pulmonary hypoplasia and pulmonary hypertension and often experience hypoxemia and acidosis during neonatal transition. The standard approach to DR resuscitation is immediate UCC followed by intubation and mechanical ventilation. Animal models suggest that achieving lung aeration prior to UCC results in improved pulmonary blood flow and cardiac function compared with immediate UCC before lung aeration is established. Trials of preterm infants demonstrated that initiating respiratory support prior to UCC is safe and feasible. Because infants with CDH are at high risk for pulmonary hypertension and systemic hypotension, they may benefit from the hemodynamic effects of lung aeration before UCC, namely increased pulmonary blood flow, decreased pulmonary vascular resistance, and improved cardiac output. To date, this approach has not been studied in infants with CDH.
Study Aims	**Primary** To determine the safety and feasibility of performing delayed cord clamping for intubation and initiation of ventilation in infants with congenital diaphragmatic hernia. **Secondary** To characterize short-term hemodynamic and respiratory outcomes among infants with CDH who are treated with intubation and ventilation prior to UCC and to compare these outcomes with historical control infants with CDH who were treated with immediate UCC prior to intubation. The historical controls will be identified from IRB #3799. **Tertiary** To characterize maternal experiences and perspectives of delayed cord clamping until after intubation and lung aeration are established in the infant
Test Article(s)	The study intervention is the DING procedure: Immediately after birth, the infant will be placed on a Lifestart trolley with an intact umbilical cord, intubated, and ventilated with the CHOP “gentle ventilation” protocol. UCC will occur after (1) colorimetric end-tidal CO_2 detection or (2) 3 minutes after delivery, whichever occurs first.

Study Design	This is a single site single-arm open-label interventional trial.
Subject Population	The inclusion and exclusion criteria are identical for the DCC arm and the historical controls **Inclusion Criteria-** 1. Antenatal diagnosis of CDH, with care in the Center for Fetal Treatment 2. Gestational age ≥ 36 weeks at birth **Exclusion Criteria** 1. Multiple gestation 2. Major anomalies or aneuploidy 3. Enrolled in FETO trial (fetal endoluminal tracheal occlusion) 4. Palliative care planned or considered 5. Maternal diagnosis placenta previa, accreta, or abruption 6. Maternal diagnosis of pre-eclampsia requiring Magnesium sulfate therapy at time of delivery 7. OB or Neonatal provider concerns for the clinical care of the mother or infant, or study team not available.
Number Of Subjects	We will allocate 20 infant-mother dyads in this pilot feasibility trial and 20 infant-mother dyads for the historical controls.
Study Duration	Each subject's participation will last from birth until hospital discharge
Study Phases	This is an open-label single-arm interventional trial • Screening Phase will take place on an antenatal basis, during prenatal visits to the CHOP Center for Fetal Diagnosis and treatment or upon admission to the SDU. Mothers of potentially eligible infants will provide informed consent during the screening phase. • Study Treatment Phase: Prior to and during delivery, eligibility criteria will be reviewed. Eligible infants will receive the study intervention during the first 3 minutes of life. • Follow up Phase: Follow up will continue until hospital discharge.
Efficacy Evaluations	The primary endpoint will be successful completion of the DING intervention. Infants who are intubated and have ventilation initiated prior to UCC and prior to 3 minutes of life will be considered to have successfully completed the protocol.

	Secondary endpoints: Arterial pH and PaO_2 on first blood gas, Oxygenation index [OI] throughout first 24 hours of life [HOL], need for vasopressors (first 24 HOL), presence of severe pulmonary hypertension on first echocardiogram. Need for ECMO during hospitalization, mortality prior to discharge. Tertiary endpoints: Identification of salient themes in parent experiences of the DING intervention, Identification of factors during the intervention that mothers identify as stress inducing or alleviating.
Safety Evaluations	Safety evaluations will include: Neonatal evaluations: cord avulsion, need for chest compressions during resuscitation, hypothermia on first temperature in the SDU Maternal evaluations: post-partum hemorrhage, need for therapeutic uterotonics, estimated blood loss, contamination of sterile obstetrical field, wound infection
Statistical And Analytic Plan	Baseline characteristics, the primary, secondary, and tertiary endpoints, and safety evaluations will be summarized by standard descriptive summaries. Secondary outcomes will be compared with historical controls using bivariable analyses
Data and Safety Monitoring Plan	An independent data and safety monitoring board will review outcomes incrementally after allocation of every 5 subjects to ensure the study does not impose undue extra risk to treated subjects.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly associated with a high risk of mortality (29%) and need for life-saving interventions such as ECMO (33%), nitric oxide (62%), and vasopressor support (73%).[1] Although infants with CDH experience significant morbidity and mortality starting immediately after birth, high quality evidence informing delivery room resuscitation in this population is lacking.

Infants with CDH are at risk for pulmonary hypoplasia and pulmonary hypertension and often experience hypoxemia and acidosis during neonatal transition. The standard approach to DR resuscitation is immediate UCC followed by intubation and mechanical ventilation. The goals of this strategy are to immediately recruit and aerate the lung for gas exchange and oxygenation, while simultaneously avoiding gaseous distention of the thoracic gastrointestinal contents.

Animal models suggest that achieving lung aeration prior to UCC results in improved pulmonary blood flow and cardiac function compared with immediate UCC before lung aeration is established. Trials of preterm infants demonstrated that initiating respiratory support prior to UCC is safe and feasible. Because infants with CDH are at high risk for pulmonary hypertension and systemic hypotension, they may benefit from the hemodynamic effects of lung aeration before UCC, namely increased pulmonary blood flow, decreased pulmonary vascular resistance, and improved cardiac output.

We hypothesize that a sequence of intubation, gentle ventilation, and then umbilical cord clamping will result in improved cardiovascular transition after birth in infants with CDH. To date, this approach has not been studied in infants with CDH.

The DING trial will assess the feasibility and safety of this intervention in infants with CDH. The DING trial will also characterize short-term hemodynamic and respiratory outcomes among infants with CDH who are treated with intubation and ventilation prior to UCC and to compare these outcomes with historical control infants with CDH who were treated with immediate UCC prior to intubation

1.2 Name and Description of Investigational Intervention:

We will study the “DING” intervention: Delayed cord clamping for INtubation and Gentle ventilation.

In this intervention, the infant will undergo intubation and initial ventilation with an intact umbilical cord. Once lung aeration is established (as indicated by colorimetric CO_2 detection), the umbilical cord will be clamped, and the infant will be moved to the resuscitation suite for ongoing stabilization.

1.3 Relevant Literature and Data

1.3.1 Delayed Cord Clamping

1.3.1.1 Recommendations for Delayed Cord Clamping

Delayed cord clamping after birth is now recommended for infants who do not require resuscitation by multiple professional organizations (Table 1). Because the standard practice for infants with CDH is immediate intubation and ventilation, DCC is not performed in these infants, and the effects of DCC in this population remain unstudied.

Organization	Year	Recommendations
World Health Organization (WHO) [2]	2012	In term or preterm babies who do not require positive-pressure ventilation, the cord should not be clamped earlier than 1 minute after birth
Neonatal Resuscitation Program (NRP) [3]	2015	DCC (>30 seconds) for preterm and term infants who do not require resuscitation
American College Obstetrics and Gynecology (ACOG), endorsed by American Academy of Pediatrics (AAP) [4]	2017	Evidence supports DCC in vigorous term and preterm infants for at least 30-60 seconds after birth

Table 1: Professional Organizations: Recommendations for Delayed Cord Clamping

1.3.1.2 Physiologic Effects of Delayed Cord Clamping

Potential physiologic benefits from DCC result from both placental transfusion and improved cardiovascular transition at birth.

Placental Transfusion: DCC allows for ongoing redistribution of blood from the placenta to the fetus after birth, resulting in higher hemoglobin levels immediately after birth and improved iron stores throughout infancy.[5]

Cardiovascular Transition: There are potential hemodynamic benefits associated with DCC. Immediately after birth, lung aeration triggers a reduction in pulmonary vascular resistance and increase in pulmonary blood flow.[6,7] At the same time, clamping the umbilical cord and removing the low-resistance placental circuit results in increased systemic vascular resistance. These changes trigger the transition from the fetal to post-natal circulation.

However, clamping the umbilical cord prior to lung aeration may impair cardiac output due to a combination of decreased preload and increased afterload:[8]

- Decreased preload: In utero, umbilical venous blood is the major contributor to left ventricular preload. Once lung aeration occurs, the increased pulmonary blood flow results in adequate venous return to the left heart. However, if UCC occurs prior to lung aeration, umbilical venous blood flow is removed prior to the requisite increase in pulmonary blood flow, resulting in impaired preload.
- Increased afterload: UCC causes an increase in systemic peripheral resistance, which results in increased afterload.

Combined, these processes can result in up to 50% decrease in cardiac output.[9]

Most infants breathe independently after birth and do not require resuscitation. For these infants, DCC allows for lung aeration (from spontaneous respirations) to be established prior to UCC. Current recommendations for non-vigorous infants call for immediate UCC to facilitate initiation of resuscitation and positive pressure ventilation (Table 1). However, infants who do not independently aerate their lungs may benefit from initiating resuscitation to establish lung aeration prior to umbilical cord clamping. Thus, there is an active line of investigation to determine the impact of aerating the newborn lung prior to UCC among infants who require respiratory support for neonatal resuscitation.

1.3.2 Animal models

Bhatt et al studied the impact of establishing ventilation before umbilical cord clamping in preterm lambs.[10] Compared with UCC followed by ventilation, establishing ventilation prior to UCC resulted in fewer fluctuations in carotid arterial pressure, less bradycardia and improved pulmonary blood flow in the first minutes after cord clamping (Figure 1).

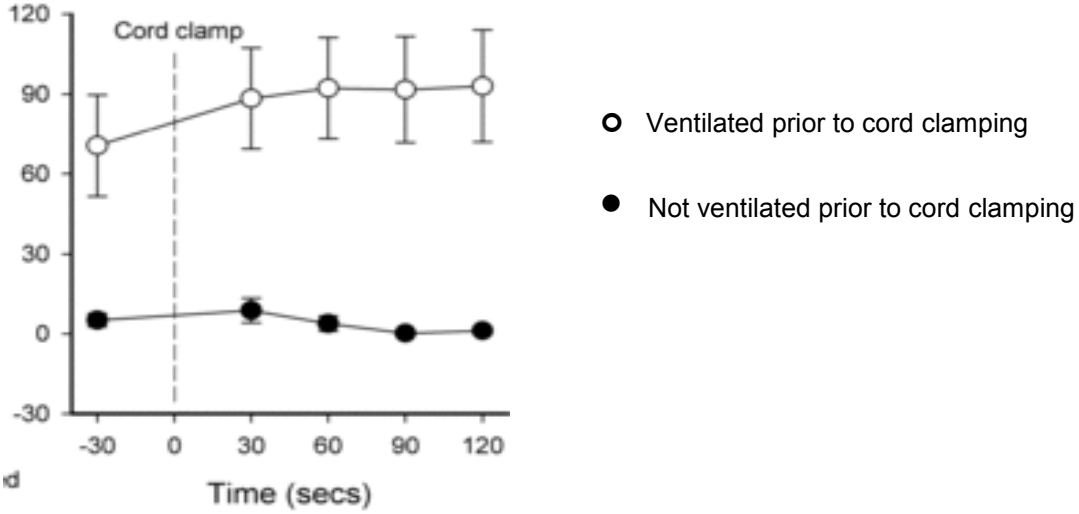

Figure 1: Pulmonary blood flow in first 2 minutes after cord clamping in preterm lambs.[10]

In addition, Polglase et al. studied the impact of ventilation prior to cord clamping on oxygenation and hemodynamics in preterm lambs.[11] Compared with lambs who were ventilated after UCC, lambs who were ventilated prior to UCC required significantly lower concentrations of inspired oxygen to maintain similar tissue oxygenation saturations after cord clamping.

1.3.3 Clinical trials in preterm infants

The available clinical evidence for of initiation of respiratory support during DCC comes from trials of preterm infants (**Table 2**). These trials vary in design but share the basic principle of initiating non-invasive respiratory support for preterm infants with an intact umbilical cord.

Trial	Design	Population	Intervention

Katheria, 2016 [12]	Single site RCT	N=150 infants GA: 23 0/7 – 31 $^{6/7}$ weeks 125 C-Section, 25 vaginal	60s DCC + respiratory support as needed vs. 60 s DCC +/- stimulation
Winter, 2016 [13]	Single site feasibility trial	N=29 infants GA: 24-32 $^{6/7}$ weeks 21 C-Section, 8 vaginal	Single Arm: 90s DCC plus respiratory support (CPAP or PPV)
Kattwinkel (ongoing)[14]	Multi-site RCT	Target n=940 infants GA: 23-28$^{6/7}$ weeks	120s DCC + CPAP or PPV vs. 30-60s DCC +/-stimulation
Pushpa-Raja (ongoing)[15]	Multi-site RCT	Target n=100 infant/mother pairs GA <32 weeks	120s DCC, with 'initial care' provided during DCC vs. UCC after 20s

Table 2: Trials of preterm infants undergoing resuscitation with an intact umbilical cord
Abbreviations: CPAP: continuous positive airway pressure; DCC: delayed cord clamping; GA: gestational age; PPV: positive pressure ventilation; RCT: randomized controlled trial

Of the combined 179 infants enrolled in the Katheria and Winter trials, 171 (96%) infants completed the assigned study protocol. Importantly, neither trial reported adverse events or safety concerns among infants who treated with respiratory support prior to UCC. Among the 8 infants who did not complete the full protocol in Katheria's trial, the umbilical cord was clamped early due to the obstetrical assessment that the infant was too unstable.

These preliminary data demonstrate that providing respiratory support with an intact umbilical cord is feasible and safe in preterm infants. However, a key difference in the current DING trial is that infants in the preterm trials were not intubated for resuscitation prior to UCC. A major logistical challenge to intubating infants with an intact cord relates to whether the umbilical cord is long enough to allow for appropriate positioning for intubation. Other authors have reported successful intubation prior to UCC in a limited number of preterm infants [16]. In addition, the full term umbilical cord is longer than the preterm umbilical cord (**Table 3**), which would allow more room to maneuver and position a full term infant for intubation.

In summary, pre-clinical evidence suggests that establishing lung aeration prior to UCC results in improved cardiovascular transition after birth. Further, performing resuscitation via non-invasive facemask with an intact umbilical cord is safe and feasible in preterm infants. A strategy of intubation and ventilation prior to UCC in infants with CDH has not been studied. This trial will determine the safety and feasibility of delayed cord clamping for intubation and gentle ventilation for full term infants with CDH.

Gestational Age	N	Umbilical cord length, cm mean (SD)
24-25 weeks	38	40.1 (10.1)
26-27 weeks	59	42.5 (11.3)
28-29 weeks	80	45.0 (9.7)
30-31 weeks	113	47.6 (11.3)
32-33 weeks	337	50.2 (12.1)
34-35 weeks	857	52.5 (11.2)
36-37 weeks	3,153	55.6 (12.6)
38-39 weeks	10,083	57.4 (12.6)
40-41 weeks	13,841	59.6 (12.6)

Table 3: Mean umbilical cord length (cm), according to gestational age, from Naeye et al.[17]

1.4 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain parental consent (unless a 'waiver of consent is granted) and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. A waiver of assent will be obtained since subjects are infants. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Aim

The primary objective of this study is to determine the safety and feasibility of the DING intervention (Delayed cord clamping for INtubation and Gentle ventilation) for full term infants with CDH.

2.2 Secondary Aim

The secondary objective is to characterize short-term hemodynamic and respiratory outcomes among full term infants with CDH who are treated with intubation and ventilation prior to UCC and to compare these outcomes with historical control infants with CDH who were treated with immediate UCC prior to intubation.

2.3 Tertiary Aim

To ascertain the mother's experience and perspectives of delayed cord clamping until after intubation and lung aeration are established in the infant.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is an open-label single-site single-arm interventional trial at the Children's Hospital of Philadelphia.

3.1.1 Screening Phase

Potential subjects will be screened on an antenatal basis in the CHOP Center for Fetal Diagnosis and Treatment (CFDT) and the SDU. We will identify and screen all women carrying a fetus at least 32 weeks gestation with a prenatal diagnosis of

CDH who plan to deliver in the CHP SDU. We will approach the parents during a prenatal visit at the CFDT or on an antenatal inpatient basis in the SDU to offer study participation and obtain informed consent. Given that the subjects are neonates, we will not obtain assent.
For fetuses with parental consent, we will then review the eligibility criteria again prior to and during delivery. Subjects with signed antenatal informed consent who meet all eligibility criteria will be allocated to the trial intervention at the time of birth.

3.1.2 Study Treatment Phase (start of the study intervention)

At the time of delivery, if the infant meets all eligibility criteria, the infant will be allocated to receive the DING intervention. The study treatment phase will last up to 3 minutes, after which point the infant will be moved to the SDU infant resuscitation suite and for ongoing standard-of-care clinical resuscitation.

3.1.3 Follow-up Phase

The follow-up phase will continue until hospital discharge. In this phase we will assess the infant's physiologic outcomes and the mother's perspectives of the DING intervention. Questionnaires will be administered to mothers who consent to participation in the DING trial from day 1 to 1 month post-partum. A study team member will also approach within 1 month of the infant's birth for an approximately 30 minute open-ended in-person interview.

3.2 Allocation to Treatment Groups and Blinding

This is an open-label single-arm interventional trial. All enrolled and eligible infants will be allocated to the DING study intervention.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Screening and informed consent will take place up to 8 weeks prior to birth.
Once subjects are considered eligible, the intervention will take no more than 3 minutes. The follow up phase will last until hospital discharge. For allocated infants, the duration of study participation is therefore from birth until discharge.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at the Children's Hospital of Philadelphia. Recruitment will stop when 20 infant-mother dyads are allocated to receive the study intervention.The total number of subjects is 40 infant-mother dyads, which includes the 20 historical controls.

3.4 Study Population

3.4.1 Inclusion Criteria

1. Antenatal diagnosis of CDH, with care in the Center for Fetal Treatment
2. Gestational age ≥ 36 weeks at birth

3.4.2 Exclusion Criteria

1. Multiple gestation
2. Major anomalies or aneuploidy
3. Enrolled in FETO (fetal endoluminal tracheal occlusion) trial
4. Palliative care planned or considered
5. Maternal diagnosis placenta previa, accreta, or abruption
6. Maternal diagnosis pre-eclampsia requiring Magnesium sulfate therapy at time of delivery
7. OB or Neonatal provider concerns for the clinical care of the mother or infant, or study team not available.

The inclusion and exclusion criteria are the same for the interventional arm and the historical controls. Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

- We will screen for potential subjects during antenatal visits in the CFDT and on an antenatal basis for women admitted to the SDU. The screening visit includes:
- Medical Record Review
- Informed Consent
- The historical controls will be identified from IRB # 3799 and will be selected as the most recent historical control, matched for gestational age and CDH severity markers to allocated subjects in the interventional arm.

4.2 Study Treatment Phase

4.2.1 Visit 1: Delivery visit

The delivery visit occurs when mothers of fetuses with informed consent present for delivery. The delivery visit includes:

- Medical Record Review
- Study intervention
- Video Recording of Resuscitation

4.2.2 Matched Historical Controls

Medical record review will include the specified secondary clinical outcomes for control infants.

4.3 Follow-up Phase

The follow up phase will occur for until hospital discharge and includes

- Medical Record Review

In the follow up phase, we will also ascertain the maternal experience and perspectives of participating in the DING intervention through:

- Maternal questionnaire administration
- Semi-structured maternal interview

Maternal perspectives will be ascertained through a questionnaire administered to the mother within the first month post-partum. The DING questionnaire will be provided to mothers while they are visiting their infants in the NICU. At that point, mothers can opt in to participate in a semi-structured interview to further explore their experience and views in a qualitative fashion. The interview will take place within the first month of delivery.

4.4 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. The Investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons.
It will be documented whether or not each subject completes the clinical study.
If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.4.1 Early Termination Study Visit

All study procedures will occur during the birth hospitalization, on an inpatient basis. There is no specific early termination study visit for subjects who withdraw from the study.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Identification of eligible subjects

A study team member will search for patients meeting inclusion and exclusion criteria by **reviewing, but <u>not obtaining or recording</u>,** data from the Epic electronic health record to determine if patients are potentially eligible. Patients who are preliminarily identified as possibly eligible will be placed on a screening log that is locked in a file cabinet in a locked research office. The historical controls will come from IRB # 3799.

5.2 Screening and Monitoring Evaluations

5.2.1 Medical Record Review – for both interventional arm and historical controls

We will abstract the following variables from the maternal and infant chart:

- Baseline characteristics
    - Prenatal ultrasound findings
    - Gestational age at prenatal diagnosis
    - Date of birth
    - Time of birth
    - Mode of delivery
    - Gestational age
    - Birth weight
    - Sex
    - Race
    - Ethnicity
- Type and timing of resuscitation interventions in the delivery suite and SDU:
    - Intubation
        - Number of attempts
        - Time of successful intubation
        - Tracheal intubated adverse events, using NEAR4Neos operational definitions
    - Interval between birth and UCC (for interventional arm only)
    - Chest compressions performed
    - Medications and fluids administered
    - Supplemental FiO_2
    - Ventilator settings
    - Vital signs during resuscitation (temperature, heart rate, respiratory rate, blood pressure, pulse oximetry)
- Cardiorespiratory Interventions and diagnostic tests in first 7 days of life
    - Vital signs (heart rate, pulse oximetry, blood pressure)
    - Supplemental FiO_2
    - Ventilator settings
    - Vasopressors (type and dose)
    - Laboratory tests (blood gasses, complete blood count, bilirubin level)
    - Echocardiogram findings
- Clinical outcomes during hospitalization
    - ECMO cannulation (occurrence and day of life)
    - Mortality (occurrence, day of life, and cause)
- Maternal chart review (outcomes will be ascertained in first 7 days after delivery, or until discharge- whichever period is shorter – for interventional arm only)
    - Estimated blood loss at delivery (all deliveries)
    - Need for therapeutic uterotonics (all deliveries)
    - First post-partum hemoglobin (all deliveries)

- OR time (for Cesarean deliveries)
- Contamination of sterile field (for Cesarean deliveries)
- Surgical wound infection (for Cesarean deliveries)

5.2.2 Video Recording

Video recording is clinical standard of care for post-delivery resuscitation in the SDU. These clinically obtained videos will be reviewed as additional source documentation to confirm the sequence and timing of resuscitative interventions performed after the DING intervention.
In addition, we will mount a CHOP-owned portable video camera to the LifeStart trolley to record the DING intervention as it is performed.

5.2.3 Laboratory Evaluations

No specific laboratory evaluations will be obtained specifically for this study. We will abstract data from the following laboratory tests, which are obtained as part of standard clinical care:

- Arterial blood gasses obtained in SDU and in the first 24 hours of life
- Hemoglobin from admission CBC
- Peak bilirubin level in first week of life

5.3 Efficacy Evaluations

The primary outcome is successful completion of the DING intervention. After each infant is allocated to the intervention, the study team will review the resuscitation video and the medical record and will discuss the intervention with the resuscitation team. The manual of operations will be iteratively refined based on these findings. The following measures related to protocol feasibility will be documented:

- Infant successfully positioned on the table
- Successful intubation prior to cord clamping
  - If not: why not
- Number of intubation attempts
- Duration of time between birth and cord clamping

5.4 Safety Evaluation

Subject safety will be monitored through medical record review and debriefing the clinical staff. We will monitor for the following;

- Neonatal outcomes:
  - Cord avulsion
  - Need for chest compressions during resuscitation
  - Hypothermia (first documented temperature in the SDU <36.0)
- Maternal outcomes:
  - Any potential contamination of sterile obstetrical field
  - Surgical wound infection
  - Post-partum hemorrhage
  - Estimated blood loss

    - Need for therapeutic uterotonics
- Any additional concerns from Obstetrical or Neonatal staff

5.5 Evaluation of Maternal Perspectives:

All interviews will be audio-recorded.
Questionnaires will include questions pertaining to the following topics:

- How well-prepared for the intervention mothers felt
- Whether they felt staff gave good explanations during the intervention
- Whether they understood the interventions taking place
- Whether they felt the intervention was traumatic or stressful, increased worry, provided reassurance
- Whether they would want to be in close proximity again should they be presented with a similar situation

Interview questions will address the following topics:

- How the experience in the delivery room could have been improved
- If there are things that could have been explained ahead of time that would have resulted in an improved experience
- How parents felt while their babies were being intubated
- The impact of having additional providers in the delivery room

STATISTICAL CONSIDERATIONS

5.6 Primary Endpoint

The primary endpoint will be successful completion of the DING intervention for those subjects allocated to the interventional arm of the study. Infants who are intubated and have ventilation initiated prior to UCC and prior to 3 minutes of life will be considered to have successfully completed the protocol

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5.7 Secondary Endpoints

Secondary endpoints include arterial pH and PaO_2 on first blood gas, oxygenation index [OI] throughout first 24 hours of life [HOL], need for vasopressors (first 24 HOL), presence of severe pulmonary hypertension on first echocardiogram, need for ECMO and mortality during hospitalization for both the subject allocated to the interventional arm and the historical controls.

5.8 Tertiary Endpoints:

Identification of salient themes in parent experiences of the DING intervention, Identification of factors during the intervention that mothers identify as stress inducing or alleviating.

5.9 Statistical Methods

5.9.1 Baseline Data

Baseline characteristics, the primary, secondary, and tertiary endpoints, and safety evaluations will be summarized by standard descriptive summaries.

5.9.2 Primary Analysis

The primary analysis will be based on an intention to treat approach. All infants who meet all eligibility criteria at the time of birth and are allocated to the intervention are considered evaluable. The proportion of evaluable infants who successfully complete the DING intervention will be reported as the primary outcome.

5.9.3 Secondary Outcomes

We will compare secondary clinical outcomes between evaluable DING participants and evaluable historical controls who are enrolled in the Pulmonary Hypoplasia Program (PHP) registry (IRB#06-003779).
Controls will be identified from the CHOP Pulmonary Hypoplasia Program registry, which contains detailed information about infants with CDH treated at CHOP. For each DING participant, we will select the most recent historical control, matched for gestational age and CDH severity markers. Matched historical controls will be considered evaluable if they meet all inclusion and exclusion criteria and their medical record is complete for comparison.
We will ascertain the specified secondary clinical outcomes for control infants. The data for the controls will come from the PHP registry (IRB # 3799).

We will compare the short-term outcomes between groups, using Student's t test or Wilcoxon rank sum test for continuous variables and chi square or Fisher's exact test for dichotomous variables.

5.9.4 Safety Analysis

All subjects who have been allocated to the DING intervention will be included in the safety analysis. The frequencies of AEs will be summarized. SAEs (if any) will be described in detail.

5.9.5 Qualitative Analysis of Maternal Perspectives

We will use qualitative methods to identify thematic maternal responses to the DING intervention. Summary statistics will be used to describe parental responses to the questionnaire items. In an exploratory analysis, we will also compare responses between mothers who choose to have a screen in place during the DING intervention and those who do not if there are sufficient respondents in each group to do so, using bivariate analyses. Because of our small sample size, it is unlikely

that we will be able to draw firm conclusions from such comparisons but we may be able to identify trends. Recordings of the interviews will be sent to the ADA transcription services for transcription. Transcripts will be coded and analyzed by CHOP study team members. These codes will be defined and entered into the project data dictionary and will ultimately applied to all transcripts. We will then explore for thematic responses in the open ended interviews. We will investigate for common themes related to parent descriptions of modifiable factors that mothers identify as impacting their experiences, again working to identify, describe, and analyze key themes.

5.10 Sample Size and Power

We will enroll 25 mother-infant dyads in this pilot feasibility trial in order to obtain 20 evaluable subjects. The DING intervention has not been previously studied in infants with CDH, so the objective of this trial is to determine the feasibility of this intervention. A sample size of 20, consistent with other delivery room feasibility trials,[13,18] was selected to permit adequate assessment of feasibility. In addition, review and comparison of secondary outcomes will inform power analyses for a subsequent RCT of clinical outcomes. Since this is a pilot study, we do not anticipate finding statistically significant differences, though clinically significant differences may be observed. Instead, the analytic aims are to obtain estimates needed for designing future randomized trials of the DING intervention.

Approximately 40-50 infants with CDH are born in the SDU per year, ensuring the recruitment goal is feasible.

5.11 Interim Analysis

An independent data and safety monitoring board (DSMB), comprising a clinical epidemiologist and two clinical content experts, will review specified safety events incrementally after allocation of every 5 subjects to ensure the study does not impose undue extra risk on infants with CDH.

As this is a single-arm trial, there are no early stopping rules for efficacy.

Figure 2: Demonstration of DING intervention during vaginal delivery, using Lifestart Trolley

6 STUDY INTERVENTION

6.1 Description

All eligible infants will be allocated to receive the DING intervention. Immediately after birth, the infant will be placed on a LifeStart trolley with an intact umbilical cord, intubated, and ventilated according to the CHOP clinical “Gentle ventilation” protocol. UCC will occur after (1) colorimetric end-tidal CO2

detection or (2) 3 minutes after delivery, whichever occurs first.
DCC has been variably defined in studies, using a time-based approach (ranging from 1-5 minutes) or physiologic approach (ie: cessation of cord pulsation, or placental descent). [5] An upper limit of 3-minutes prior to UCC was selected through discussion with the clinical team, as this interval would to allow sufficient time for the neonatal team to establish lung aeration prior to placental separation, while also avoiding a delay in transferring the infant to the infant stabilization suite. A retrospective review of intubations performed at CHOP demonstrated a 62% first-attempt success rate for attending neonatologists, and over 85% of attending neonatologists were successful within the first 2 intubation attempts.[19] Thus, we anticipate that 3 minutes is a sufficient time period for most DING trial participants to be successfully intubated prior to UCC.
The Lifestart trolley is a small resuscitation trolley specifically designed to facilitate neonatal resuscitation with an intact umbilical cord. The trolley includes a warmer mattress and has FDA 510K clearance (See attachment). The CHOP Medical Device Committee approved the Lifestart trolley for use in this DING trial. The trolley will be positioned next to the mother covered in a sterile drape prior to the delivery. The senior neonatal clinician (who will perform the intubation and is a member of the study team), the neonatal nurse, and the neonatal respiratory therapist will all attend the infant during the DING intervention.
Immediate cord clamping will be performed for any of the following:

- Inadequate umbilical cord length or inability to adequately position infant on the trolley for intubation
- If the neonatologist or obstetrician has any concerns about the infant or mother's safety or the team's ability to perform clinical interventions

Team coordination:
The DING intervention requires complex coordination of providers across many disciplines. We have performed multidisciplinary simulations (including neonatology, obstetrics, nursing, respiratory therapy) to determine the optimal placement of providers and equipment to perform the DING intervention while ensuring mother and infant safety. Study team neonatologists will perform DING study procedures. (**Figure 2**).

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. Given the short duration of the study intervention, we will monitor adverse events that occur in the SDU setting and in the ensuing 24 hours (the Follow Up phase).
Because of the disease severity and protocol-driven clinical interventions for the study population, we will not classify the following events (which are typical and expected in the CDH population in the first 24 hours of life) as SAEs: mechanical ventilation, inotropic medications, or iNO.

7.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

7.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

7.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse experience that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

7.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

7.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

7.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8 STUDY ADMINISTRATION

8.1 Treatment Assignment Methods

8.1.1 Randomization

This is a non-randomized trial.

8.1.2 Blinding

This is an unblinded trial.

8.2 Data Collection and Management

All data management will be consistent with CHOP Policy A-3-6: Acceptable Use of Technology Resources:

1. Confidentiality. Coded data will be collected on data collection forms. A master list containing any identifying PHI and subject ID number will be kept separate from the data forms. Subjects will be identified in the study database by study ID only. The master list will be kept in in a locked office.

2. Security. A copy of the password protected master code will be kept in a password-protected file on the PI's office computer, which is kept in a locked office. Coded data collected on the data forms will be entered as a limited dataset into the Redcap database, a password protected secure internet-based database. User's rights to the dataset will be limited to the study PI and study coordinator. The hard copy of the data collection forms will be kept in a locked file cabinet, separate from the master file.
3. Anonymization, de-identification or destruction. The master file linking subjects' PHI to subject ID numbers will be destroyed according to CHOP's A-3-9 policy for Human Subjects Research which states 10 years earlier from age 18 or death; or longer period required by sponsor.
4. Video recordings: Recordings will be maintained in a password-protected file on the study PI's password-protected office computer, which is kept in a locked office or CHOP secure server. Video recordings will be destroyed as soon as data analysis is complete.
5. Audio files: Audio recordings will be kept in a locked cabinet in a locked office. Interviews will be recorded with a hand held recorder and audio files will be uploaded to the secure ADA transcription website, and/or the ADA call-in service will be used for direct recording and transcription. Audio recordings will be stored on a password protected computer prior to being transferred via the secure website. To the best of our ability, names, titles, conditions, and any possible identifying information of participants will not be recorded. In order to minimize recording of identifiable information, the participant will be told to refrain from using names or any other identifiable information before the recorded interview takes place. ADA maintains strict confidentiality when working with research studies and their participants and will remove any identifiable information, should participants reference anything identifiable, from the transcript. Transcripts will be reviewed after received from ADA and scrubbed for any possible remaining identifying information before they are uploaded to qualitative software for analysis. There will be no linkage of participants to their quotes in the final manuscript, thus obscuring the identity of individuals. All interview-related materials, including audio, transcripts, study information, documentation, and any other materials received by or created for the interview portion of the project, are safely sand securely kept and maintained while under the possession of the study team and ADA Transcription. ADA transcription guarantees that all audio files and transcripts for this study will be completely deleted two weeks after payment for transcripts are received. All study-related information and documentation held by ADA is then deleted within three weeks of payment. This includes hard drives, backup drives, and any all device copies that may exist. The study team will maintain a copy of the de-identified interviews in accordance with CHOP policy.

8.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the

Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.
No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset.

8.4 Regulatory and Ethical Considerations

8.4.1 Data and Safety Monitoring Plan

After each DING intervention is attempted, the Principal Investigator will review medical record and video recordings and debrief the clinical staff to ascertain potential safety and feasibility concerns. The Principal Investigator will provide oversight for emerging safety information.
In addition, a Data Safety Monitoring Board (DSMB), comprising two clinical content experts and a neonatal clinical trialist, will review specified safety events incrementally after allocation of every 5 subjects to ensure the study does not impose undue extra risk on infants with CDH.

8.4.2 Risk Assessment

This trial poses a minor increase above minimal risk for this population. While the trial intervention includes an invasive procedure (endotracheal intubation), this is standard of care for all infants with CDH. The intervention in this trial relates to the timing of actions standardly performed in infants with CDH after delivery, from the standard (clamp the umbilical cord, intubation, and gentle ventilation) to novel treatment (intubation, gentle ventilation, clamp the umbilical cord).
Risks from the study intervention:

1. Positioning the infant on the Lifestart trolley for intubation could put tension on the umbilical cord, leading to cord avulsion and bleeding. To minimize this risk, we have performed multi-disciplinary simulations in both the labor rooms and the obstetrical operating room to define the provider's roles and identify provider positions around the Lifestart trolley (**Figure 2**). In addition, the umbilical cord will be clamped immediately if the neonatologist or obstetrician has any concerns about the patient's safety or the team's ability to perform clinical interventions.
2. There is the potential for the infant to become cold from exposure during the procedure. We will use a warmer mattress on the LifeStart trolley to minimize this risk. In addition, the intervention will last 3 minutes maximum, reducing the potential opportunity for cold stress. Once the infant is moved to the infant stabilization suite, we will monitor his/her temperature and apply ambient heat for thermoregulation.
3. For mothers delivering via Cesarean section, there is the potential for contamination of the surgical field from the neonatal equipment. To minimize this risk, we will drape the Lifestart trolley in surgical covers and drapes, we will use sterile equipment when possible (such as suction catheters), and all

neonatal providers who will be in close proximity to the surgical field for the study intervention will be in sterile surgical attire.

4. Witnessing the neonatologist intubate the infant in close proximity may cause emotional distress for the parents. We will discuss their preferences before birth and offer the use of privacy screens if they do not want the intubation to be visible.

Risks From Delayed Cord Clamping (DCC):

DCC after birth is now widely recommended as standard care by multiple professional bodies (Table 1). The safety of this practice for full term newborns and their mothers is well established.[5] The definition of DCC varies significantly across published trials, ranging from 1-5 minutes after birth.

- Infant Risks: DCC is associated with an increased risk of hyperbilirubinemia requiring phototherapy. All infants in the DING trial will be monitored for hyperbilirubinemia and treated with phototherapy, according to the American Academy of Pediatrics recommendations. DCC is not associated with increased risk for other studied infant morbidities.
- Maternal Risk: DCC is not associated with increased risk of severe post-partum hemorrhage, any post-partum hemorrhage, or other any of the other maternal morbidities that have been studied.[5]

Risks from Maternal Questionnaire/Interview

Witnessing a neonatologist intubate their baby at close proximity may cause mothers emotional distress. Asking mothers about this potentially distressing experience may put them at risk of further distress. We may uncover evidence of this distress or of other mental health disorders as a result of this study. Dr. Joanna Cole is a clinical psychologist and manager of psychosocial services in the Special Delivery Unit. Dr. Cole is a member of the DING study team and will be available to arrange for any necessary follow-up in the event of significant parental stress or the uncovering of such disorders.

The main risk from audio-recording of the interviews is breach of confidentiality. This risk is minimal and investigators will take steps to minimize breach of confidentiality (see related section). Some people may feel uncomfortable having the interview recorded. Participants may skip any question or stop the interview at any time.

Risks from Data collection for Historical Controls

There could be a risk of privacy, however only coded data will be collected. All measures will be taken to minimize this risk.

8.4.3 Potential Benefits of Trial Participation

Potential direct benefits include the potential physiologic benefit from the DING intervention. Indirect benefits include contribution of knowledge for future infants with CDH. There are no potential benefits to infants in the historical controls.

8.4.4 Risk-Benefit Assessment

Given the potential direct benefit to subjects, the indirect benefit to future patients, and the minor increase in risk above baseline, it is reasonable to proceed with the study.

8.5 Recruitment Strategy

Parents will be recruited on an antenatal basis, either in the CFDT outpatient setting or in the SDU inpatient setting. We will identify women carrying a fetus with a prenatal diagnoses with CDH who are at ≥32 weeks gestation. If the potential subject is eligible for co-enrollment in additional studies designed with antenatal consent process, we will coordinate with those study teams to ensure a cohesive approach to the parents.

- CFDT: We will work with the CFDT staff to identify potentially eligible women on the outpatient schedule. These women meet with a neonatologist for a consult during their scheduled antepartum visits between 33-35 weeks gestation. After gaining permission from the neonatologist who performed the consult, a member of the research team will approach the potential subject's parents in person.
- SDU inpatient: If a potential subject's parents were not approached in the CFDT setting or did not make a decision in the CFDT setting, a member of the study team will offer study participation in the inpatient SDU setting. All admissions to the SDU are sent out to the NICU clinical team in real time via ASCOM system message. The study team will coordinate with the clinical team to be alerted when women carrying a fetus with CDH are admitted to the SDU. A study team member will offer study participation to the parents at that time, as long as the mother is not in the active phase of labor.

In both environments, the study team will leave written information for the subject's guardian to review before obtaining informed consent. No direct advertising directed at potential participants will be used. However, we will be including brief information on the DING trial on the CFDT website.

Approximately 40-50 infants with CDH are referred to the CFDT and born in the SDU per year, ensuring the recruitment goal is feasible.

8.6 Informed Consent/Assent and HIPAA Authorization

A member of the study team (investigators or coordinator) will obtain informed consent and HIPAA Authorization using a combined consent-authorization document. As the study subjects are newborns, assent will not be obtained.

- CFDT: The study team member will approach the potential parents in a private consultation room in the outpatient CFDT office suite. The study team member will describe the study and review the informed consent document. The team member will review all risks and benefits of study participation, will confirm that the parents understand the nature of the study, and will answer all study related questions.
- SDU: The study team member will approach the potential parents in a private inpatient room in the SDU. The study team member will describe the study and review the informed consent document. The team member will review all risks and benefits of study participation, will confirm that the parents understand the nature of the study, and will answer all study related questions.

No member of the study team will pressure the parent or guardian to enroll the subject. There is no limit on the time allotted to make the decision, with the caveat that potential subjects may no longer be eligible if parents have not made a decision prior to delivery.
Prior to the start of any study-related procedure, a signed and dated informed consent and HIPAA authorization must be obtained and documented in the study binder. Once it has been determined that the infant meets all inclusion criteria and no exclusion criteria, the infant will be considered allocatable.

A waiver of consent/parental permission, assent, and HIPAA authorization is requested for control subjects from study #3779 as they have already provided consent for future research.

8.6.1 Waiver of Assent

We request a waiver of assent, as all subjects are newborns who do not have the capability to provide assent.

8.7 Payment to Subjects/Families

Subjects and their families will not receive any payment for study participation.

8.7.1 Gifts

No gifts or tokens of appreciation will be given to subjects or families.

9 PUBLICATION

Once all 40 subjects (20 in the interventional arm and 20 in the historical controls) have been evaluated and the data analysis is complete, the aggregate results will be prepared and submitted for publication in a peer-reviewed journal. No identifiable data will be included in the manuscript for publication.

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