BMJ Open

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038343
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2020
Complete List of Authors:	Ines, Felix; Sharp Mary Birch Hospital for Women and Newborns, Neonatal Research Institute Hutson, Shandee; Sharp Mary Birch Hospital for Women and Newborns Coughlin, Katherine; Sharp Mary Birch Hospital for Women and Newborns Hopper, Andrew; Loma Linda University Medical Center Banerji, Anamika; Loma Linda University Medical Center Finer, Neil; University of California San Diego Rich, Wade; Sharp Mary Birch Hospital for Women and Newborns Morales, Ana; Sharp Mary Birch Hospital for Women and Newborns Steen, Jane; Sharp Mary Birch Hospital for Women and Newborns Katheria, Anup; Sharp Mary Birch, Neonatology
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

Felix Ines, Shandee Hutson, Katherine Coughlin, Andrew Hopper, Anamika Banerji, Neil Finer, Wade Rich, Ana Morales, Jane Steen, Anup Katheria*

Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States.

Loma Linda University Medical Center, Loma Linda, CA, United States.

Corresponding author: Anup Katheria M.D., Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States. Email: Anup.Katheria@sharp.com

ABSTRACT

Introduction: Delivery room resuscitation of the very preterm infant has evolved dramatically over the past decades. Optimizing the care of these newborns now involves a variation of early continuous positive airway pressure (CPAP) and the avoidance of mechanical ventilation. A recent meta-analysis of non-invasive ventilation strategies demonstrated that Less invasive surfactant administration (LISA) had the lowest odd ratio (OR, 0.49; 95% CI 0.3-0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia (BPD) amongst non-invasive strategies compared to mechanical ventilation. Despite these results and studies showing it decreased the need for mechanical ventilation compared to CPAP, the use of the LISA method is still not widely accepted[4]. We will conduct a randomized, multicenter trial to test whether infants that receive caffeine and surfactant via the LISA method compared to early CPAP and positive pressure ventilation have a decreased need for mechanical ventilation in the first 72 hours of life.

Methods and Analysis:

After 5 minutes of life, consented infants that are assessed by a provider as clinically stable (i.e. HR >100 bpm) and spontaneously breathing on CPAP will be randomized by computer generated randomization cards placed in opaque envelopes. For infants not consented prior to birth, after 5 minutes of life and before 2 hours of life, postnatal consent may be obtained for any eligible infant admitted to the NICU and must be randomized and receive treatment prior to their two hours of age. Randomization will be stratified by gestational age (24-26+6 weeks and 27+0-29+6 weeks) and labeled as such on each envelope. Multiples will be randomized to the same treatment group for ease of consent and family considerations.

ETHICS AND DISSEMINATION:

IRB approval has been obtained by the Sharp Healthcare Ethics Board. The study will take over 5 years to conduct. This will include (3 months of startup, 2.5 years to enrollment subject goal. At 24 months CGA,

a neurodevelopmental outcome assessment using the standardized neurological and developmental [Bayley Scales of Infant Development (BSID), 4thed] will be performed and finally 3 months for data analysis and publication of results).

Results should be available by 2025. We will track and follow several exploratory outcomes and results presented at a major meeting and published in a major neonatal journal. This study is registered on www.ClinicalTrials.gov, number NCT#04209946.

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This is the first US study of LISA in extremely preterm infants
- This will be the first LISA trial to prescribe and mandate caffeine use with the LISA procedure
- Limitations include a small sample size and limited neonatal centers.

INTRODUCTION:

Delivery room resuscitation of the very preterm infant has evolved dramatically over the past decades. Optimizing the care of these newborns now involves a variation of early continuous positive airway pressure (CPAP) and the avoidance of mechanical ventilation. A recent meta-analysis of non-invasive ventilation strategies demonstrated that Less invasive surfactant administration (LISA) had the lowest odd ratio (OR, 0.49; 95% CI 0.3-0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia (BPD) amongst non-invasive strategies compared to mechanical ventilation.[1] Despite these results and studies showing it decreased the need for mechanical ventilation compared to CPAP,[2,3] the use of the LISA method is still not widely accepted[4]. We will conduct a randomized, multicenter trial to test whether infants that receive surfactant via the LISA method compared to early CPAP and positive pressure ventilation have a decreased need for mechanical ventilation in the first 72 hours of life. We will track and follow several exploratory outcomes and results presented at a major

meeting and published in a major neonatal journal. This study is registered on www.ClinicalTrials.gov, number NCT#04209946.

The study will take over 5 years to conduct. This will include (3 months of startup, 2.5 years to enrollment subject goal. At 24 months CGA, a neurodevelopmental outcome assessment using the standardized neurological and developmental [Bayley Scales of Infant Development (BSID), 4thed] will be performed and finally 3 months for data analysis and publication of results). This will be the first US led multicenter trial on Less Invasive Surfactant Administration in infants born under 30 weeks gestational age.

SPECIFIC AIMS:

To determine whether prophylactic administration of surfactant by the LISA method reduces the need for mechanical ventilation in the first 72 hours of life when compared to early CPAP alone.

Hypothesis 1:

Infants in the LISA group will have decreased need for mechanical ventilation compared to infants in the early CPAP group.

Primary Outcome:

Frequency of subjects requiring endotracheal intubation between the two groups (LISA vs CPAP) in the first 72 hours of life

Secondary Outcomes:

Duration of mechanical ventilation and/or CPAP

Requirement of supplemental oxygen at 36 weeks corrected age

Grade III and IV intraventricular hemorrhage

Neurodevelopment outcome at 24 months corrected gestational age

Need for repeat surfactant dosing

Incidence of intubation with NIMV as primary mode of non-invasive ventilation

Incidence of intubation with CPAP as primary mode of non-invasive ventilation

Exploratory outcomes:

Laryngoscopy attempt with the LISA procedure

Laryngoscopy attempt with the endotracheal intubation

Study Timeframe: From birth through 2 years of age.

Cost to Subjects: None

The secondary objective for this study is to assess neurodevelopmental outcome at 24 months corrected gestational age (CGA). The assessment tools to measure neurodevelopmental outcome will be the Bayley Scales of Infant and Toddler Development 4th ed. (BSID-4), a standardized neurologic exam, and neurosensory assessment of vision and hearing as reported by parents including:

- Neurodevelopmental Impairment (Mild/Moderate-Severe)
- Gross motor function: assessed by the Gross Motor Function Classification System
- Cerebral Palsy (mild, moderate, severe)
- Differences in 2 year developmental outcomes as assessed by Cognitive, Language & Motor Composite scores of Bayley Scales of Infant Development in infants born at 24-29+6 weeks

METHODS AND ANALYSIS:

The Caffeine and Less Invasive Surfactant Administration (CaLI) trial is a multicenter, randomized study done at 2 neonatal intensive care units with Level III designations in California, USA and is expected to be conducted between January 2020 and January 2025. Consented premature infants with gestational age from 24 weeks to 29 weeks plus 6 days will be enrolled within 2 hours of life. For infants not consented prior to birth, postnatal consent may be obtained after 5 minutes of life and before 2 hours of life for any

eligible infant admitted to the NICU. Subjects must be randomized and receive treatment prior to two hours of life.

Inclusion Criteria:

- Premature infants born at 24-29+6 weeks gestation
- Informed consent obtained (antenatal/postnatal)
- Infant is spontaneously breathing and maintains normal heart rate (HR>100 Bpm)

Exclusion Criteria:

- Declined consent
- Infants with known congenital anomalies
- Requiring intubation prior to randomization

All infants found to have anomalies post-randomization will be analyzed by intent to treat principle.

Randomization:

Only spontaneously breathing infants maintaining normal heart rate and saturations will be included. After 5 minutes of life, consented infants that are assessed by a provider as clinically stable (i.e. HR >100 bpm) and spontaneously breathing on CPAP will be randomized by computer generated randomization cards placed in opaque envelopes. For infants not consented prior to birth, after 5 minutes of life and before 2 hours of life, postnatal consent may be obtained for any eligible infant admitted to the NICU and must be randomized and receive treatment prior to their two hours of age. When the neonatal provider assesses the infant to be stable, a member of the research or neonatal team will pull a randomization card according to the infant's corrected gestational age. Once the treatment group is identified (LISA or CPAP), therapy will immediately commence. Randomization is stratified by gestational age (24-26+6 weeks and 27+0-29+6 weeks) and is labeled as such on each envelope. Multiples will be randomized to the same treatment group for ease of consent and family considerations.

Blinding:

The capacity to be blinded for this study is not feasible, since the providers caring for the patient are providing the intervention.

Study Design:

One hundred and fifty (150) premature infants born at GA of 24-29+6 weeks CGA will be enrolled at two centers. Infants will be allowed to transition and stabilize on CPAP (at 5-6 cm of water) and/or mask positive pressure ventilation (starting at PIP 20 and PEEP 5) in the delivery room. Once they are breathing spontaneously, have a stable heart rate (i.e. >100 Bpm), and assessed to be clinically stable by a neonatal provider, they will be randomized to either the LISA group or CPAP group.

Randomized infants in both groups will only be intubated if they meet strict failure criteria (see study design) to avoid bias in an un-blinded study. Any repeat dosing for surfactant will be based on clinical indication at the physicians' discretion by the conventional endotracheal approach. Both units routinely give caffeine immediately after birth.

LISA Group:

For infants randomized to LISA, we will have an orogastric tube placed into the stomach prior to laryngoscopy and the contents aspirated before and after the procedure to document any esophageal surfactant administration. Then a thin catheter (16G angiocatheter) will be measured and the depth of insertion will be marked with intubation tape. The thin catheter will then be placed in the trachea under direct visualization with a laryngoscope by a neonatal practitioner. After the catheter is placed, the laryngoscope will be removed and the infant's mouth will be closed. Surfactant (Curosurf 2.5 mL/kg, based on estimated fetal weight) will be slowly administered over 1-2 minutes (approximately in 3 aliquots) assuring synchronized instillation with infant's breathing pattern while on nasal CPAP. After instillation, the catheter will be immediately removed and nCPAP will continue. If apnea occurs during or

after the procedure, positive pressure ventilation will be given. All sites have agreed on using senior level physicians or practitioners that have prior experience with the LISA method.

CPAP Group:

Infants randomized to early CPAP will be managed according to unit practice for preterm infants on CPAP. Premature infants may require CPAP immediately after delivery if they elicit signs of labored breathing or unable to maintain oxygen saturations within neonatal resuscitation goals despite 100% oxygen supplementation. If randomized to the CPAP group, infant will continue on CPAP unless infant meets failure criteria and requires intubation.

Caffeine:

If randomized to LISA, caffeine will be given prior to the LISA procedure. In contrast, if randomized to CPAP, caffeine will be given soon after birth. If infants in the CPAP group meet intubation criteria, and the loading dose of caffeine has not been administered, to avoid any delay in intubation, Caffeine will be given no later than thirty minutes of intubation.

Randomized infants in both groups will only be intubated if they meet strict failure criteria (see study design) to avoid bias in an un-blinded study. Any repeat dosing for surfactant will be based on clinical indication at the physician discretion by the conventional endotracheal approach. Both units routinely give caffeine immediately after birth.

Intubation criteria once randomized:

As an un-blinded trial it is critical that both groups are standardized to avoid bias towards one arm for mechanical ventilation/treatment failure. Therefore, strict delivery room/ NICU criteria will be used.

Delivery room - Criteria for intubation will be as specified in the Neonatal Resuscitation Program guidelines [6] and will include: **1)** when chest compressions are needed; **2)** ineffective ventilation; **3)** prolonged PPV; or **4)** prolonged hypoxia. Infants intubated before randomization will be excluded to avoid any early selection bias.

NICU - Criteria for intubation/treatment failure will be recent guidelines for the management of RDS[7], including: 1) FiO_2 >0.40 required to maintain Sat >90% for 2 hour after randomization; 2) a pH of 7.15 or less OR a $paCO_2$ >65 mmHg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomization in the first 72 hours of life. To avoid the bias of withheld ventilation since the study is not masked, infants with these criteria will be regarded as treatment failures.

For pragmatic purpose sites will be able to use their standard approach for non-invasive ventilation (NCPAP at SMB and NIMV at LLU) as they have agreed to use each mode equally regardless of randomization. Subsequent analysis will include primary mode of non-invasive ventilation.

Statistics/Plans for Analysis:

We will describe / compare baseline demographics, clinical outcome variables between the two groups using univariate and appropriate bivariate analysis. We will use generalized linear models (GLM) (stratified by center and adjusting for a priori and posteriori variables) to evaluate clinical outcome variables. Appropriate repeated measures GLM models and correlation analysis will be performed to identify trends and relationships among the various hemodynamic parameters.

Statistical Analysis plan including sample size and power:

A chart review of the databases at Sharp Mary Birch has shown that approximately 49% of our infants 24-29+6 weeks' gestation were intubated and mechanically ventilated after 5 minutes of life but within the first 72 hours of life. Therefore, a very conservative sample size calculation indicates that in order to detect

a 22% absolute reduction (a reduction from 49% to 27%) we would need at least 150 subjects' enrolled (75 subjects in each arm) for an 80% power and a p-value of less than 0.05 for significance.

Data Collection:

Data will be collected and managed using REDCap electronic data capture tools hosted at Sharp Mary Birch Hospital for Women Newborns and managed by the lead site. All collected variables are listed in the CRF forms (see attached). Both Loma Linda University Medical Center and Sharp Mary Birch Hospital for Women & Newborns have extensive experience with REDCap data entry.

Human Subjects Protections:

The study interventions, Less Invasive Surfactant Administration (LISA) and Continuous Positive Airway Pressure (CPAP), are two different methods that we hope will support our specific aim in reducing mechanical ventilation within the first 72 hours of life for preterm infants. Both groups will receive the same surfactant, however, the LISA group will use a smaller catheter compared to an endotracheal tube to instill it into the trachea. The small catheter would allow infants to breath on their own while receiving surfactant and CPAP by nasal cannula compared to the endotracheal tube method that requires placing the infant on mechanical ventilation. The LISA method is currently used by our group, a number of hospitals in California and Florida but no US trials have been conducted to date. Only infants who are stable after 5 minutes of life (breathing on their own with normal oxygen and heart rate levels) would be included.

Prior to any research procedure, consent will be obtained by the primary investigator or a delegated sub-investigator or a research associate. The mother, or legally authorized representative must sign the informed consent document. Mother (or surrogate mother) must sign a HIPAA authorization providing access to her medical records for collection of maternal data. Either mother or father or legal guardian can sign a HIPAA authorization providing access to the child's medical records for data collection purposes. The subject's legally authorized representatives 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 electronic medical record and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute.

Pregnant women will be identified and screened from the labor and delivery floor or perinatal special care unit at each site. Parents will be approached and consented prior to delivery. In the delivery room, after the infant's five minutes of life, the research staff or neonatal delivery team will open the randomization envelope for the proper GA group. Multiples will be randomized to the same treatment group for ease of consent and family considerations. There is no crossover allowed between the LISA and CPAP groups, subjects should receive their randomized treatment. If the physician determines that the infant requires intubation or is determined to be unstable within five minutes of life, the infant will be intubated and excluded from the study.

Patient and public involvement:

We have collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. We have incorporated their suggestions and they enthusiastically support the study. One of the parents has agreed to be on the DSMB to monitor the trial for safety.

Risks:

Loss of confidentiality: All data will be safeguarded in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the principles and practices of strict confidentiality. Data will be maintained by numerical code rather than personal identifiers and computer-based files will be available

only to persons involved in the study through the use of access privileges and passwords. However, there is still a potential risk of loss of data and privacy.

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

Protection against Risk:

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

DATA AND SAFETY MONITORING PLAN

We have chosen an experience and well recognized data safety monitoring board (DSMB) with experience with respiratory trials. Drs. Brad Yoder and Wally Carlo have led and participated in a number of trials including High-Flow Nasal Cannula, High Frequency Ventilation, and surfactant. In addition, a former parent that has participated in research trials Kirsten Norman has agreed to serve on the DSMB. The DSMB will: 1) protect all study patients, 2) safeguard the interests of all study patients, 3) monitor the overall conduct of the trial, 4) advise the investigators in order to protect the integrity of the trial, and 5) supervise the conduct and analysis of all interim analyses. To this end, the DSMB will receive regular reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of predetermined early stopping rules. All SAEs, protocol deviations, non-serious adverse events (AEs), and unanticipated problems (UPs) will be reported to the Data Coordinating Center (DCC) and forwarded to the DSMB if indicated (see below); reports of adverse events and recruitment will be sent monthly; demographics will be included with the interim and final safety and efficacy analyses. Interim analyses determined by the DSMB and the project

statistician will be conducted, independently from the trial leadership and staff. The definitions and reporting process are as follows:

Serious Adverse Events defined as one or more of the following: decompensation during the administration of surfactant in either arm including the use of epinephrine in the delivery room and chest compressions, or death prior to discharge.

1. All SAEs will be reported within 72 hours of discovery of event, to the PI and the IRB at the Sharp Data center.
2. Any Unexpected AE or Serious Deviation will be reported within 7 days of discovery of event to the Sharp Data Center.

Not Serious Events

Unexpected events that are Not Serious are reported not more than 14 days after the PI first learns of the event. The DCC will forward all not-serious unexpected events to the DSMB, and PI. All other expected outcomes of prematurity, i.e. BPD, IVH grades 1-4, ROP, NEC will be collected in the electronic database and reviewed in interim reports, see attached CRF. We have appointed a DSMB to work closely with the PI and the IRB. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the investigators at the enrolling sites.

The study will be closely monitored for issues of data quality, study conduct, and adverse events. These analyses will be presented to the DSMB. Interim analyses will seek to identify results that are sufficiently extreme and precise to offset the goal of obtaining additional data that might lead to more precise, and perhaps less exaggerated and more convincing results, as well as information about differences in treatment effect by subgroups of patients. Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical practice. The superiority must be tested in the context of this

trial first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority.

Specific Drug Supply requirements:

The surfactant given to these infants is provided at no cost to the patients in both arms of the trial. The average dose of Curosurf is 2.5 mL/kg. Assuming an average weight of 1 kg (for 28 weeks as our mean gestational age) x 150 participants would be 375 mL of Curosurf.

Figure 1. Flowsheet of study procedure

Contributorship Statement: FI and AK developed the initial protocol and manuscript. SH, KC, AH, AB, NF, WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript.

COMPETING INTERESTS:

The authors declare that they have no competing interests.

Abbreviations (in alphabetical order)

BPD = Bronchopulmonary Dysplasia (supplemental O2 at 36 weeks CGA)

Bpm = beats per minute

BSID-4= Bayley Scales of Infant and Toddler Development 4th ed

CPAP = Continuous Positive Airway Pressure

LISA = Less Invasive Surfactant Administration

nCPAP = Nasal Continuous Positive Airway Pressure

NICU=Neonatal Intensive Care Unit

NIMV = Nasal Intermittent Minute Ventilation

PPV = positive pressure ventilation with bag & mask

RDS= Respiratory Distress Syndrome

FUNDING:

A grant for the CaLI trial has been obtained from Chiesi Farmaceutici, S.p.A

PRINCIPAL INVESTIGATOR

Anup Katheria MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Shandee Hutson MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Andrew Hopper, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Anamika Banerji, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Neil Finer MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Statistician

Debra Poeltler, PhD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

REFERENCES

1. Isayama T, Iwami H, McDonald S, Beyene J. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. Jama 2016;316:611-24.

2. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet 2011;378:1627-34.

3. Kribs A, Hartel C, Kattner E, et al. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. Klin Padiatr 2010;222:13-7.

4. Bhayat S, Kaur A, Premadeva I, Reynolds P, Gowda H. Survey of less Invasive Surfactant Administration in England, slow adoption and variable practice. Acta Paediatr 2019.

5. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. The New England journal of medicine 2010;362:1970-9.

6. Braner D, Denson S, Zaichkin J, American Heart Association., American Academy of Pediatrics. Committee on Fetus and Newborn. Textbook of neonatal resuscitation. Dallas, TX: American Heart Association; 2000.

7. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. Neonatology 2017;111:107-25.

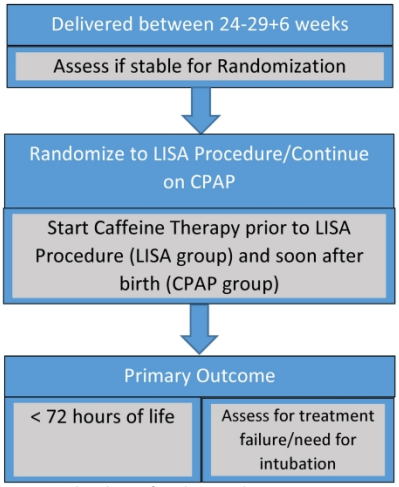


Figure 1. Flowsheet of study procedure

215x279mm (300 x 300 DPI)

BMJ Open

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038343.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Aug-2020
Complete List of Authors:	Ines, Felix; Sharp Mary Birch Hospital for Women and Newborns, Neonatal Research Institute Hutson, Shandee; Sharp Mary Birch Hospital for Women and Newborns Coughlin, Katherine; Sharp Mary Birch Hospital for Women and Newborns Hopper, Andrew; Loma Linda University Medical Center Banerji, Anamika; Loma Linda University Medical Center Uy, Cherry; University of California Irvine Finer, Neil; University of California San Diego Rich, Wade; Sharp Mary Birch Hospital for Women and Newborns Morales, Ana; Sharp Mary Birch Hospital for Women and Newborns Steen, Jane; Sharp Mary Birch Hospital for Women and Newborns Katheria, Anup; Sharp Mary Birch Hospital for Women and Newborns, Neonatology
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Paediatrics
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Felix Ines, Shandee Hutson, Katherine Coughlin, Andrew Hopper, Anamika Banerji, Cherry Uy, Neil Finer, Wade Rich, Ana Morales, Jane Steen, Anup Katheria*

Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States.

Loma Linda University Medical Center, Loma Linda, CA, United States.

University of California Irvine Medical Center, Irvine, CA, United States.

Corresponding author: Anup Katheria M.D., Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States. Email: Anup.Katheria@sharp.com

ABSTRACT

Introduction: A recent meta-analysis of non-invasive ventilation strategies demonstrated that Less Invasive Surfactant Administration (LISA) had the lowest odd ratio (OR, 0.49; 95% CI 0.3-0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia (BPD) amongst non-invasive ventilation strategies compared to invasive mechanical ventilation. Despite these results and studies showing it decreased the need for invasive mechanical ventilation compared to Continuous Positive Airway Pressure (CPAP), the use of the LISA method is not universally accepted, however, has found wide acceptance in Europe.

Methods and Analysis: Consented premature infants with gestational age from 24 weeks to 29 weeks plus 6 days will be enrolled within 2 hours of life. Caffeine will be administered prior to administration of surfactant in the LISA group or before 2 hours of life in the control arm.

Ethics and Dissemination: Ethics approval has been obtained. Results will be published and presented at the Pediatric Academic Societies meeting upon completion.

Clinical Trial Registration: www.Clinicaltrials.gov: NCT04209946

Protocol version 1.2P, 21Jul2020

STRENGTHS AND LIMITATIONS OF THIS TRIAL ARE:

- Limited to power for longer term outcomes such as BPD and neurodevelopmental impairment due its smaller size
- Pragmatic in design and does not include blinding
- The first to be prescriptive in the use of caffeine as a co-intervention for LISA administration to test its benefit
- This study will be the most recent in many years to re-study the use of prophylactic surfactant with the LISA method compared to expectant management with CPAP alone.

INTRODUCTION

Advances in the management of the extremely preterm neonates (24+0 weeks to 29+6 weeks) with neonatal respiratory distress syndrome (RDS) has evolved dramatically over the past decades. Interventions to improve outcome and minimize RDS begins with good prenatal care. However, premature delivery may be inevitable, therefore, delivery room management has become an integral part in optimizing the care of these newborns. Specifically, with lung protection in mind, management involves a variation of antenatal steroids, early continuous positive airway pressure (CPAP), early administration of caffeine, early administration of surfactant therapy and the avoidance of invasive mechanical ventilation. The adaptation of various management strategies of RDS continue to evolve due to sustained severe morbidity, including bronchopulmonary dysplasia.

Initial respiratory management includes, early initiation of continuous positive airway pressure (CPAP) and titration of FiO_2 [1], modifications in the administration of surfactant therapy using less invasive techniques, and the avoidance of mechanical ventilation [2]. Other strategies to optimize success of non-invasive support involves the use of caffeine therapy to serve as a respiratory stimulant. Dekker et al demonstrated that the administration of caffeine in the delivery room compared to upon admission to the NICU produced greater minute ventilation and tidal volumes in premature infants <30 weeks [3]. The less invasive surfactant administration (LISA) to spontaneously breathing preterm infants has been reported to reduce the duration of invasive mechanical ventilation and the incidence of bronchopulmonary dysplasia. [4] The combination of early caffeine and LISA has not been tested. Studies have showed a decrease in need for invasive mechanical ventilation compared to CPAP, [5] however, the LISA method is still not universally practiced, although widely adopted in Europe. [6]

We will conduct a randomized, multicenter trial to test whether infants that receive caffeine, early CPAP, and surfactant via the LISA method compared to infants that receive caffeine, early CPAP and positive pressure ventilation alone, have a decreased need for invasive mechanical ventilation in the first 72 hours of life.

METHODS AND ANALYSIS

The study will be conducted at 3 sites in the United States (Loma Linda University Medical Center, University of California, Irvine, and Sharp Mary Birch Hospital for Women & Newborns) over a 3 year period. Long term neurodevelopmental data will also be collected throughout 2 years of age. The following variables will be collected:

1. Frequency of subjects requiring endotracheal intubation between the two groups (LISA vs CPAP) in the first 72 hours of life
2. Duration of mechanical ventilation and/or CPAP
3. Requirement of supplemental oxygen at 36 weeks corrected age
4. Grade III and IV intraventricular hemorrhage
5. Spontaneous intestinal perforation
6. Retinopathy of prematurity requiring surgery
7. Need for repeat surfactant dosing

Pregnant women will be identified and screened from the labor and delivery floor or perinatal special care unit at each site. Parents will be approached and consented prior to delivery. For infants not consented prior to birth, after the first 5 minutes of life and before 2 hours of life, postnatal consent may be obtained for any eligible infant admitted to the NICU and must be randomized and receive treatment prior to their two hours of age. In the delivery room, after the infant's first five minutes of life, the research staff or neonatal delivery team will open the

randomization envelope for the proper gestational age (GA) group. Multiples will be randomized to the same treatment group for ease of consent and family considerations. There is no crossover allowed between the LISA and CPAP groups, subjects should receive their randomized treatment. If the physician determines that the infant requires intubation or is determined to be unstable within the first five minutes of life, the infant will be intubated and excluded from the study.

Inclusion Criteria:

- Premature infants born at 24-29+6 weeks gestational age
- Informed consent obtained (antenatal/postnatal)
- Infant is spontaneously breathing on CPAP of 5-8 cmH20 with an FiO2 of <.40 and maintains a normal heart rate (HR>100 Bpm)

Exclusion Criteria:

- Declined consent
- Infants with known congenital anomalies
- Requiring intubation prior to randomization

All infants found to have anomalies post-randomization will be analyzed by intent to treat principle.

Patient Allocation: Randomization cards are computer-generated by Sharp Mary Birch Hospital for Women & Newborns and will solely be known by the data manager. Each randomization card contains group assignment, real-time data information, and a randomization number, sealed in an opaque envelope with a label that indicates the envelope sequence number, site (facility) number, and stratification by gestational age. These envelopes will be logged by the data manager in a secured data file and then distributed to each research facility. We will enroll 180

preterm infants and will stratify by gestational age (24-26+6 weeks and 27+0-29+6 weeks), labeled as such on each opaque envelope.

Randomization:

In order to allow for initial stabilization on CPAP, infants will not be randomized until at least 5 minutes of life. If the providers have not intubated or plan to intubate the infant in the delivery room, consented infants that are assessed by a provider as clinically stable (i.e. HR >100 bpm) and spontaneously breathing on CPAP (5-8 cm H_2O) will be randomized. Stabilization of premature infants at delivery may include stimulation, positive pressure ventilation or CPAP. Multiples will be randomized to the same treatment group for ease of consent and family considerations.

Only spontaneously breathing infants on CPAP, maintaining normal heart rate and saturations will be included and randomized. When the neonatal provider assesses the infant to be stable on CPAP, a member of the research or neonatal team will pull a randomization card according to the infant's corrected gestational age. Once the treatment group is identified (LISA or CPAP), intervention will immediately commence.

LISA Group:

For infants randomized to LISA, an intravenous access will be established to administer caffeine. We will have an orogastric tube placed into the stomach prior to laryngoscopy and the contents aspirated before and after the procedure to document any esophageal surfactant administration. Thereafter, a thin catheter (16G angiocatheter) will be measured and the depth of insertion will be marked with intubation tape. The thin catheter will then be placed in the trachea under direct

or video-laryngoscopy by a neonatal practitioner. After the catheter is placed, the laryngoscope will be removed, the angiocatheter held securely in place, and the infant allowed to spontaneously breathe on CPAP. Surfactant (Curosurf 2.5 mL/kg, based on estimated fetal weight) will be slowly administered over 1-2 minutes (approximately in 3 aliquots) assuring synchronized instillation with infant's breathing pattern while on CPAP. After instillation, the catheter will be immediately removed and CPAP will continue. If apnea occurs during or after the procedure, positive pressure ventilation will be initiated. To improve adherence to protocol interventions, all sites have agreed on using senior level physicians or neonatal practitioners that have prior experience with the LISA method.

CPAP Group:

In adherence to protocol interventions, infants randomized to early CPAP will be managed according to sub-site unit practice for preterm infants on CPAP. Premature infants may require CPAP immediately after delivery if they elicit signs of labored breathing or unable to maintain oxygen saturations within neonatal resuscitation goals despite 100% oxygen supplementation. If randomized to the CPAP group, an intravenous access will be established to administer caffeine and the infant will continue on CPAP unless infant meets failure criteria and requires intubation.

Caffeine:

If randomized to LISA, caffeine will be given prior to the LISA procedure. In contrast, if randomized to CPAP, caffeine will be given soon after birth. If infants in the CPAP group meet intubation criteria, and the loading dose of caffeine has not been administered, to avoid any delay in intubation, Caffeine will be given no later than thirty minutes after intubation.

Blinding:

As a pragmatic design we realize that a separate research team would not always be able to be present for the randomization and intervention. Therefore, the clinical team caring for the infant will follow strict guidelines for intubation and management of infants to reduce any post-randomization bias (see below)

Intubation criteria:

As an un-blinded trial, it is critical that both groups are standardized to avoid bias towards one arm for mechanical ventilation/treatment failure. Therefore, strict delivery room/ NICU criteria will be used. Furthermore, infants cannot be randomized before 5 minutes of life to ensure that unstable infants that cannot be transitioned on CPAP would not be included. These would include infants that need intubation as specified in the Neonatal Resuscitation Program (NRP) guidelines [7] and such as: **1)** when chest compressions are needed; **2)** ineffective ventilation (inability to obtain good chest rise and fall despite implementation of the corrective ventilation steps: Mask adjustment; Reposition airway [try again]; Suction mouth and nose; Open mouth [try again]; Pressure increase [up to 40 cm H_20 pressure]; Airway alternative; (MRSOPA), as indicated by the NRP guidelines to obtain effective ventilation); **3)** prolonged PPV (infants requiring positive pressure ventilation for more than 2 minutes in order to maintain HR >100 BpM) ; or **4)** prolonged hypoxia (pre-ductal SpO2 is not met despite 100% oxygen supplements and resuscitation interventions). Randomization should be delayed until the providers are comfortable that none of these criteria are met in order to avoid any early selection bias.

After stabilization on CPAP infants can be randomized. Criteria for intubation/treatment failure will be recent guidelines for the management of RDS, [1] including: 1) CPAP level of 6-8 cmH20 and FiO_2 >0.40 required to maintain saturations 90%-95% for 2 hour after randomization; 2) a

pH of 7.15 or less or a $paCO_2$ >65 mmHg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomization and in the first 72 hours of life; 3) continued Apnea/Bradycardia/Desaturation events despite nasal intermittent minute ventilation (NIMV) mode of ventilation. To avoid the bias of withheld ventilation since the study is not masked, infants with these criteria will be regarded as treatment failures.

For pragmatic purpose sites will be able to use their standard approach for non-invasive ventilation as they have agreed to use each mode (NCPAP or NIMV) equally regardless of randomization. Subsequent analysis will include primary mode of non-invasive ventilation.

Participant Timeline: Figure 1. CaLI Participant Timeline (Supplemental File 1)

Study Overview Diagram: (Supplemental File 2)

Data Management and Collection:

Data will be managed using REDCap electronic data capture tools hosted and managed at Sharp Mary Birch Hospital for Women & Newborns. All collected variables are listed in the data report form, (DRF forms): CPAP arm Delivery Room Data Collection (supplemental file 3), LISA Data Collection (supplemental file 4), CaLI Intubation Data Collection (supplemental file 5). Loma Linda University Medical Center, University of California Irvine Medical Center, and Sharp Mary Birch Hospital for Women & Newborns have extensive experience with REDCap data entry.

Randomization cards are also utilized as data collection forms, with pertinent information completed and signed by care providers in real-time. To maintain integrity of the study data, site

Data Coordinators will enter data information into REDCap and verified by the primary site Data coordinator and Research Coordinator prior to locking the subject's electronic data fil

Data and safety monitoring plan:

An independent, well recognized, data safety monitoring board (DSMB) with experience with respiratory trials is chosen for this study. Drs. Brad Yoder and Wally Carlo have led and participated in a number of trials including: High-Flow Nasal Cannula, High Frequency Ventilation, and Surfactant. In addition, a former parent that has participated in research trials Kirsten Norman has agreed to serve on the DSMB. The DSMB will: 1) oversee the safety data on 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 monthly reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of predetermined early stopping rules. All SAEs, protocol deviations, non-serious adverse events (AEs), and unanticipated problems (UPs) will be reported to the Data Coordinating Center (DCC) and forwarded to the DSMB if indicated (see below). Reports of adverse events and recruitment will be sent monthly and demographics will be included with the interim and final safety and efficacy analyses. Interim analyses determined by the DSMB and the project statistician will be conducted independently from the trial leadership and staff. The definitions and reporting process are as follows:

Serious Adverse Events defined as one or more of the following: decompensation during the administration of surfactant in either arm including the use of epinephrine in the delivery room and chest compressions, or death prior to discharge.

1. All SAEs will be reported within 72 hours of discovery of event, to the PI and the site IRB.
2. Any Unexpected AE or Serious Deviation will be reported within 7 days of discovery of event to the Data Coordinating Center.

Non-Serious Events

Unexpected events that are Non-Serious are reported not more than 14 days after the PI first learns of the event. The DCC will forward all non-serious unexpected events to the DSMB, and main study PI. All other expected outcomes of prematurity, i.e. BPD, IVH grades 1-4, ROP, NEC, will be collected in the electronic database and reviewed in interim reports. We have appointed a DSMB to work closely with the main study PI. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the investigators at the enrolling sites.

The study will be closely monitored for issues of data quality, study conduct, and adverse events. These analyses will be presented to the DSMB. Interim analyses will seek to identify results that are sufficiently extreme and precise, this is to offset the goal of obtaining additional data that might lead to more precise and perhaps less exaggerated and more convincing results, as well as information about differences in treatment effect by subgroups of patients. Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical practice. The superiority must be tested in the context of this trial first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority.

Statistical Analysis Plan:

A chart review of the databases at Sharp Mary Birch has shown that approximately 49% of our infants 24-29+6 weeks' gestation were intubated and mechanically ventilated after 5 minutes of life but within the first 72 hours of life. Therefore, a very conservative sample size calculation indicates that in order to detect a 22% absolute reduction (a reduction from 49% to 27%) we would need at least 75 subjects in each arm for an 80% power and a p-value of less than 0.05 for significance. An adjustment of 1.12 derived from the NICHD Neonatal Research Network Generic Database, allowed for multiples to be randomized to the same treatment introducing a clustering effect. [8] In order to account for multiples and potential drop out of subjects we plan to consent 90 subjects in each arm (180 subjects total). A future detailed statistical analysis plan will be made available prior to completion of the trial.

Patient and Public Involvement:

We have collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. Based on their experiences and preferences, we have incorporated their suggestions and they enthusiastically support the study. One of the parents has agreed to be on the DSMB to monitor the trial for safety. Their involvement includes input on the consent form and perspective on the means of recruitment to the study.

ETHICS AND DISSEMINATION

Ethics approval has been obtained. Prior to any research procedure, consent will be obtained by the primary investigator or a delegated sub-investigator or a research associate. The mother, or legally authorized representative must sign the informed consent document. Mother (or surrogate mother) must sign a HIPAA authorization providing access to her medical records for collection of

maternal data. Either mother or father or legal guardian can sign a HIPAA authorization providing access to the child's medical record for data collection purposes. The subject's legally authorized representatives 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 electronic medical record and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute. Results will be published and presented at the Pediatric Academic Societies meeting upon completion. Any important protocol modifications will be communicated to sub-site lead investigators via secured email which will include automated confirmation of receipt and recorded audio/visual meetings.

Confidentiality:

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

Protection against Risk:

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 and DCC.

CONTRIBUTORSHIP STATEMENT

FI and AK developed the initial protocol and manuscript. SH, KC, AH, AB, CU, NF, WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript. KN represents a parent adviser and is involved in the conduct of the study by means of the DSMB.

REFERENCES:

1. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. *Neonatology* 2019;115(4):432-50. doi: 10.1159/000499361 [published Online First: 2019/04/12]
2. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]
3. Dekker J, Hooper SB, van Vonderen JJ, et al. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatric research* 2017;82(2):290-96. doi: 10.1038/pr.2017.45 [published Online First: 2017/03/14]
4. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
5. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. *JAMA : the journal of the American Medical Association* 2016;316(6):611-24. doi: 10.1001/jama.2016.10708 [published Online First: 2016/08/18]
6. Bhayat S, Kaur A, Premadeva I, et al. Survey of less Invasive Surfactant Administration in England, slow adoption and variable practice. *Acta paediatrica* 2020;109(3):505-10. doi: 10.1111/apa.14995 [published Online First: 2019/09/01]
7. Braner D, Denson S, Zaichkin J, et al. Textbook of neonatal resuscitation. Dallas, TX: American Heart Association 2000.
8. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]

FUNDING STATEMENT

A grant to support the CaLI trial has been obtained from Chiesi Farmaceutici, S.p.A and with this financial support, the primary study site maintains ultimate authority overall study activities.

Chiesi Grant #: CRTX-GR-717

COMPETING INTERESTS

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

APPENDIX

Figure 1. CaLI Participant Timeline

Supplementary Files: Data Report Forms (DRF)

Study Overview Diagram (Draft)

Abbreviations (in alphabetical order)

BPD = Bronchopulmonary Dysplasia (supplemental O2 at 36 weeks CGA)

Bpm = beats per minute

BSID-4= Bayley Scales of Infant and Toddler Development 4th ed

CPAP = Continuous Positive Airway Pressure

LISA = Less Invasive Surfactant Administration

NCPAP = Nasal Continuous Positive Airway Pressure

NICU=Neonatal Intensive Care Unit

NIMV = Nasal Intermittent Minute Ventilation

PPV = positive pressure ventilation with bag & mask

RDS= Respiratory Distress Syndrome

ROP= Retinopathy of Prematurity

SMBHWN= Sharp Mary Birch Hospital for Women & Newborns

LLU= Loma Linda University Medical Center

UCI= University of California Irvine Medical Center

PRINCIPAL INVESTIGATORS

Anup Katheria MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Shandee Hutson MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Andrew Hopper, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Anamika Banerji, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Cherry Uy MD, University of California Irvine, Irvine, CA, USA

Neil Finer MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Statistician

Debra Poeltler, PhD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

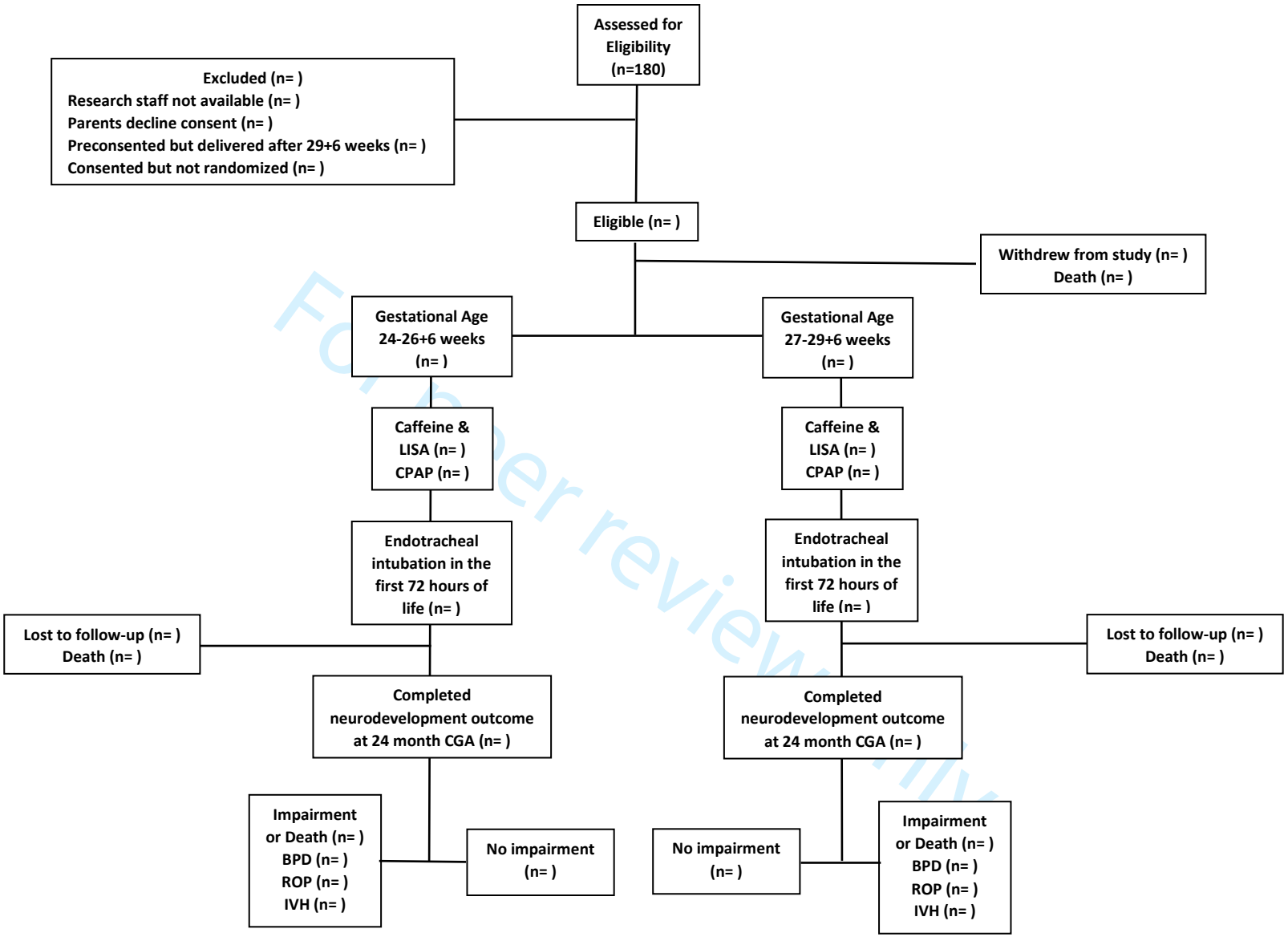
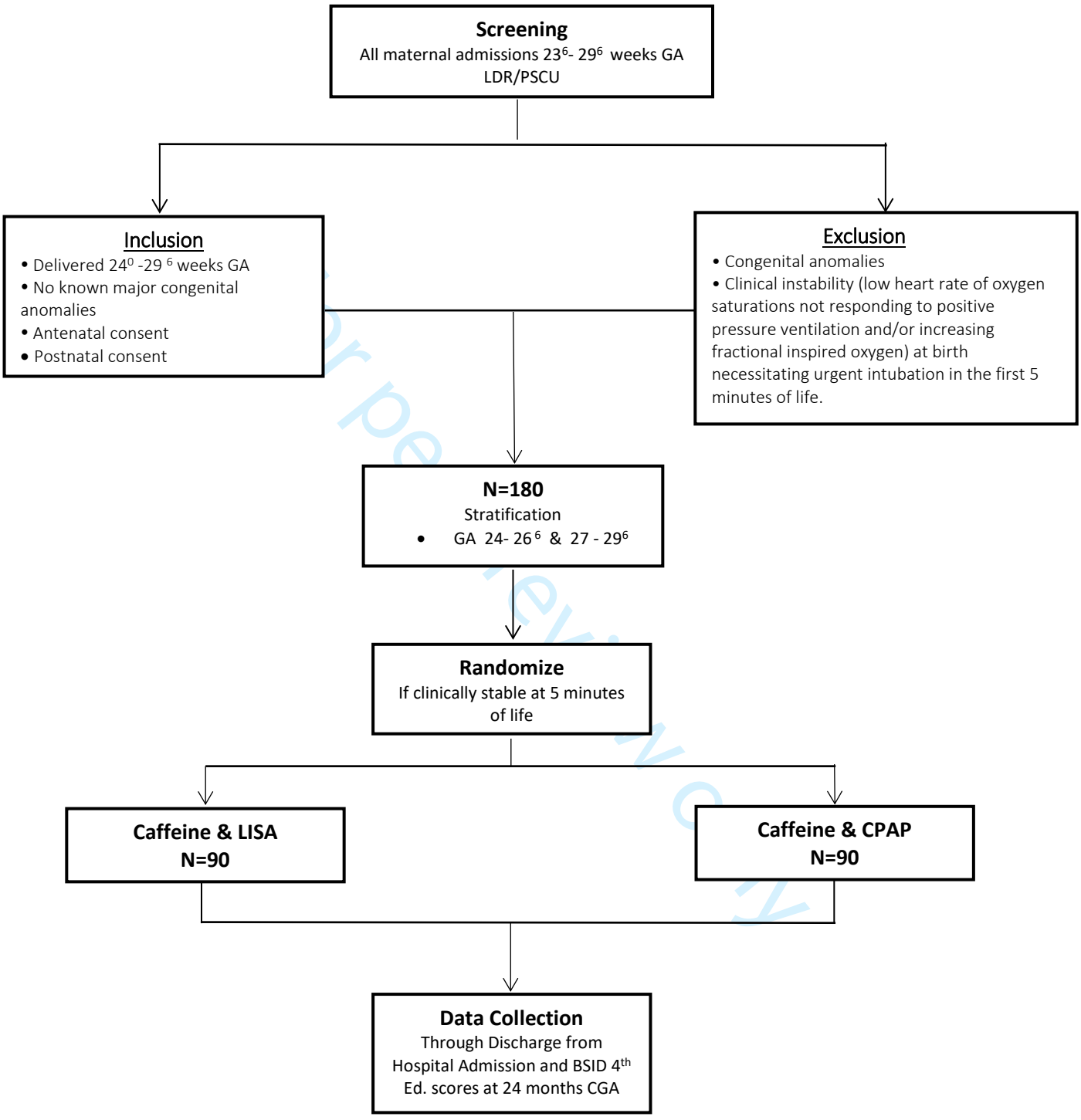


Figure 1 CaLI Participant Timeline

CaLI Study Overview Diagram



CALI Study Randomization Card

Treatment: *CPAP & Caffeine*

Subject ID: _____ **Site #: _____**

Date/time of Randomization: ____/____/_____ ____:____
MM / DD / YYYY HH : MM

Complete at time of randomization	
1. CPAP Level?	_____cmH2O
2. FiO2 requirement?	_____ %
3. Vitals: HR/SpO2	HR: _____Bpm SpO2 _____%
4. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
Notes/comments:	

If infant requires intubation within 72 hours of randomization, Please complete Intubation Card and call Neonatal Research at x6307

Affix patient label to back of this card

Completed By (Name): _____ Date: ___/____/_____

CALI Study Randomization Card

CALI Randomization Card

Treatment: *LISA & Caffeine*

Subject ID: _____ **Site #: _____**

Date/time of Randomization: ____/____/_____ _____:_____
MM / DD / YYYY HH : MM

PLEASE REFER ON BACK OF CARD FOR LISA PROCEDURAL CHECKLIST

FiO2:_____ CPAP:_____ SpO2:_____ HR:_____ at randomization

1. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
2. Start time of LISA *(from Laryngoscopy attempt)*	**Time:** ____:____ HH : MM
3. Duration of Laryngoscopy attempt? *(Time of insertion to removal)*	**1st** _____seconds **2nd** _____seconds **3rd** _____seconds
4. Successful placement of LISA catheter?	□ Yes □ No
5. Total surfactant administered (2.5 mL/kg)	_____ mLs
6. End time of LISA *(removal of angiocatheter)*	**Time:** ____:____ HH : MM
7. Surfactant aspirated from stomach or leaked from mouth (failure/regurgitation from trachea?	□ Yes □ No
8. Amount surfactant aspirated?	_____ mLs
9. Lowest HR during procedure?	_____ Bpm
10. Lowest SpO2 during procedure?	_____%
11. Interventions?	Notes:

Affix patient label to back of this card

Completed By (Name): _____ Date: ____/____/_____

CALI Study Randomization Card

CALI Randomization Card

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038343.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2020
Complete List of Authors:	Ines, Felix; Sharp Mary Birch Hospital for Women and Newborns, Neonatal Research Institute Hutson, Shandee; Sharp Mary Birch Hospital for Women and Newborns Coughlin, Katherine; Sharp Mary Birch Hospital for Women and Newborns Hopper, Andrew; Loma Linda University Medical Center Banerji, Anamika; Loma Linda University Medical Center Uy, Cherry; University of California Irvine Finer, Neil; University of California San Diego Rich, Wade; Sharp Mary Birch Hospital for Women and Newborns Morales, Ana; Sharp Mary Birch Hospital for Women and Newborns Steen, Jane; Sharp Mary Birch Hospital for Women and Newborns Katheria, Anup; Sharp Mary Birch Hospital for Women and Newborns, Neonatology
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Paediatrics
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Felix Ines, Shandee Hutson, Katherine Coughlin, Andrew Hopper, Anamika Banerji, Cherry Uy, Neil Finer, Wade Rich, Ana Morales, Jane Steen, Anup Katheria*

Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States.

Loma Linda University Medical Center, Loma Linda, CA, United States.

University of California Irvine Medical Center, Irvine, CA, United States.

Corresponding author: Anup Katheria M.D., Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States. Email: Anup.Katheria@sharp.com

ABSTRACT

Introduction: Respiratory Distress Syndrome (RDS) or surfactant deficiency occurs primarily in premature infants resulting in composite outcomes of death or bronchopulmonary dysplasia. Initial management strategies for preterm infants with RDS includes early initiation of continuous positive airway pressure (CPAP) and titration of FiO2, and may include the use of less invasive surfactant administration (LISA) to avoid the need for mechanical ventilation. The use of the LISA method in the United States is limited, but, is widespread in Europe and Australia. In order to optimize success of non-invasive support, the use of early caffeine therapy may be critical to the success of LISA. We will conduct a multicenter, randomized trial to test whether infants that receive caffeine, CPAP, and surfactant via the LISA method compared to infants that receive caffeine and CPAP alone, have a decreased need for invasive mechanical ventilation in the first 72 hours of life.

Methods and Analysis: Consented premature infants with gestational age from 24 weeks to 29 weeks plus 6 days will be enrolled within 2 hours of life. Caffeine will be administered soon after randomization in both arms and prior to surfactant in the LISA arm or before 2 hours of life in the control arm. A future detailed statistical analysis plan will be made available prior to completion of the trial.

Ethics and Dissemination: This protocol and the template informed consent form contained in Appendix II was reviewed and approved by the sponsor and the applicable Institutional Review Boards with respect to scientific content and compliance with applicable research and human subject regulations.

Results will be published and presented at the Pediatric Academic Societies meeting upon completion and study participants will be provided a copy of the results of the research article.

Clinical Trial Registration: www.Clinicaltrials.gov: NCT04209946

STRENGTHS AND LIMITATIONS OF THIS TRIAL ARE:

- Limited to power for longer term outcomes such as BPD and neurodevelopmental impairment due its smaller size
- Pragmatic in design and does not include blinding
- The first to be prescriptive in the use of caffeine as a co-intervention for LISA administration to test its benefit
- This study will be the most recent in many years to re-study the use of prophylactic surfactant with the LISA method compared to expectant management with CPAP alone.

INTRODUCTION

Premature infants are commonly born with respiratory distress syndrome (RDS) or surfactant deficiency that may lead into respiratory failure. Advances in respiratory management includes, early initiation of continuous positive airway pressure (CPAP) and titration of FiO2, [1] modifications in the administration of surfactant therapy using less invasive techniques, and the avoidance of mechanical ventilation. [2] Other strategies to optimize success of non-invasive support involves the use of caffeine therapy to serve as a respiratory stimulant. Dekker et al demonstrated that the administration of caffeine in the delivery room compared to upon admission to the NICU produced greater minute ventilation and tidal volumes in premature infants <30 weeks. [3] The less invasive surfactant administration (LISA) to spontaneously

breathing preterm infants has been reported to reduce the need for mechanical ventilation. [4]A recent meta-analysis of non-invasive ventilation strategies demonstrated that Less Invasive Surfactant Administration (LISA) had the lowest odd ratio (OR, 0.49; 95% CI 0.3-0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia amongst non-invasive ventilation strategies compared to invasive mechanical ventilation. [5] The combination of early Caffeine and LISA has not been tested and despite these results and studies showing it decreased the need for invasive mechanical ventilation compared to Continuous Positive Airway Pressure, the use of the LISA method in the United States is limited, however, is widely adapted in Europe and Australia. [6]

METHODS AND ANALYSIS

The study is designed as a multicenter, un-blinded, randomized trial of preterm infants receiving Caffeine and Less Invasive Surfactant Administration compared to Caffeine and CPAP with a primary outcome of frequency of subject endotracheal intubation between the two groups (Caffeine and LISA vs Caffeine and CPAP) within the first 72 hours of life. The study will be conducted at 3 sites in the United States (Loma Linda University Medical Center, University of California, Irvine, and Sharp Mary Birch Hospital for Women & Newborns) over a 3 year period. The following variables will be collected:

1. Frequency of subjects requiring endotracheal intubation between the two groups (LISA vs CPAP) in the first 72 hours of life
2. Duration of mechanical ventilation and/or CPAP
3. Requirement of supplemental oxygen at 36 weeks corrected age
4. Grade III and IV intraventricular hemorrhage
5. Spontaneous intestinal perforation

6. Necrotizing Enterocolitis
7. Retinopathy of prematurity requiring surgery
8. Need for repeat surfactant dosing

Long term neurodevelopmental data will also be collected throughout 2 years of age.

Pregnant women will be identified and screened from the labor and delivery floor (LD) or perinatal special care unit (PSCU) at each site. Parents will be approached and consented prior to delivery. In the delivery room, after the infant's first five minutes of life, the research staff or neonatal delivery team will open the randomization envelope for the proper gestational age (GA) group. Multiples will be randomized to the same treatment group for ease of consent and family considerations. There is no crossover allowed between the LISA and CPAP groups, subjects should receive their randomized treatment. If the physician determines that the infant requires intubation or is determined to be unstable within the first five minutes of life, the infant will be intubated and excluded from the study.

Inclusion Criteria:

- Premature infants born at 24-29+6 weeks gestational age
- Informed consent obtained (antenatal/postnatal)
- Infant is spontaneously breathing on CPAP of 5-8 cmH20 with an FiO2 of <.40 and maintains a normal heart rate (HR>100 Bpm)

Exclusion Criteria:

- Declined consent
- Infants with known congenital anomalies
- Requiring intubation in the delivery room

All infants found to have anomalies post-randomization will be analyzed by intent to treat principle.

Patient Allocation: Randomization cards are computer-generated by Sharp Mary Birch Hospital for Women & Newborns and will solely be known by the data manager. Each randomization card contains group assignment, real-time data information, and a randomization number, sealed in an opaque envelope with a label that indicates the envelope sequence number, site (facility) number, and stratification by gestational age. These envelopes will be logged by the data manager in a secured data file and then distributed to each research facility. We will enroll 180 preterm infants and will stratify by gestational age (24-26+6 weeks and 27+0-29+6 weeks), labeled as such on each opaque envelope.

Randomization:

In order to allow for initial stabilization on CPAP, infants will not be randomized until at least 5 minutes of life. If the providers have not intubated or plan to intubate the infant in the delivery room, consented infants that are assessed by a provider as clinically stable (i.e. HR >100 bpm) and spontaneously breathing on CPAP (5-8 cm H_2O) will be randomized. Stabilization of premature infants at delivery may include stimulation, positive pressure ventilation or CPAP. Only spontaneously breathing infants on CPAP, maintaining normal heart rate and saturations will be included and randomized. When the neonatal provider assesses the infant to be stable on CPAP, a member of the research or neonatal team will pull a randomization card according to the infant's corrected gestational age. Once the treatment group is identified (Caffeine and LISA or Caffeine and CPAP), intervention will immediately commence.

LISA Group:

For infants randomized to LISA, an intravenous access will be established to administer caffeine. We will have an orogastric tube placed into the stomach prior to laryngoscopy and the contents aspirated before and after the procedure to document any esophageal surfactant administration. Thereafter, a thin catheter (16G angiocatheter) will be measured and the depth of insertion will be marked with intubation tape. The thin catheter will then be placed in the trachea under direct or video-laryngoscopy by a neonatal practitioner. After the catheter is placed, the laryngoscope will be removed, the angiocatheter held securely in place, and the infant allowed to spontaneously breathe on CPAP. Surfactant (Curosurf 2.5 mL/kg, based on estimated fetal weight) will be slowly administered over 1-2 minutes (approximately in 3 aliquots) assuring synchronized instillation with infant's breathing pattern while on CPAP. After instillation, the catheter will be immediately removed and CPAP will continue. If apnea occurs during or after the procedure, positive pressure ventilation will be initiated. To improve adherence to protocol interventions, all sites have agreed on using senior level physicians or neonatal practitioners that have prior experience with the LISA method.

Data collection in the LISA group is collected using the Caffeine and LISA Randomization card (Supplemental file 1)

CPAP Group:

In adherence to protocol interventions, infants randomized to early CPAP will be managed according to sub-site unit practice for preterm infants on CPAP. If randomized to the CPAP group, an intravenous access will be established to administer caffeine and the infant will continue on CPAP unless infant meets failure criteria and requires intubation.

Data collection in the CPAP group is collected using the Caffeine and CPAP Randomization card (Supplemental file 2)

Caffeine:

Caffeine will be given in both groups as soon as IV access is obtained. Since caffeine must be given prior to the LISA procedure we have required that it must be given as early as possible but 2 hours of birth. Similarly, if randomized to CPAP, caffeine will be given soon after birth. If infants in the CPAP group meet intubation criteria, and the loading dose of caffeine has not been administered, to avoid any delay in intubation, Caffeine will be given no later than thirty minutes after intubation.

The Caffeine preparation for this study is Caffeine Citrate with a loading dose of 20 mg/kg given via an intravenous access over 15-30 minutes. Time of Caffeine administration will be captured in subject's Electronic Medical Records (EMR).

Blinding:

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are strongly encouraged not to disclose the allocation status of the participant at the follow up assessments.

As a pragmatic design we realize that a separate research team would not always be able to be present for the randomization and intervention. Therefore, the clinical team caring for the infant will follow strict guidelines for intubation and management of infants to reduce any post-randomization bias (see below)

Intubation criteria:

As an un-blinded trial, it is critical that both groups are standardized to avoid bias towards one arm for mechanical ventilation/treatment failure. Therefore, strict delivery room/ NICU criteria will be used. Furthermore, infants cannot be randomized before 5 minutes of life to ensure that unstable infants that cannot be transitioned on CPAP would not be included. These would

include infants that need intubation as specified in the Neonatal Resuscitation Program (NRP) guidelines [7] and such as: **1)** when chest compressions are needed; **2)** ineffective ventilation (inability to obtain good chest rise and fall despite implementation of the corrective ventilation steps: Mask adjustment; Reposition airway [try again]; Suction mouth and nose; Open mouth [try again]; Pressure increase [up to 40 cm H_20 pressure]; Airway alternative; (MRSOPA), as indicated by the NRP guidelines to obtain effective ventilation); **3)** prolonged PPV (infants requiring positive pressure ventilation for more than 2 minutes in order to maintain HR >100 BpM) ; or **4)** prolonged hypoxia (pre-ductal SpO2 is not met despite 100% oxygen supplements and resuscitation interventions). Randomization should be delayed until the providers are comfortable that none of these criteria are met in order to avoid any early selection bias.

After stabilization on CPAP infants can be randomized. Criteria for intubation/treatment failure will be recent guidelines for the management of RDS, [1] including: 1) CPAP level of 6-8 cmH20 and FiO_2 >0.40 required to maintain saturations 90%-95% for 2 hour after randomization; 2) a pH of 7.15 or less or a $paCO_2$ >65 mmHg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomization and in the first 72 hours of life; 3) continued Apnea/Bradycardia/Desaturation events despite nasal intermittent minute ventilation (NIMV) mode of ventilation. To avoid the bias of withheld ventilation since the study is not masked, infants with these criteria will be regarded as treatment failures.

For pragmatic purpose sites will be able to use their standard approach for non-invasive ventilation as they have agreed to use each mode (NCPAP or NIMV) equally regardless of randomization. Subsequent analysis will include primary mode of non-invasive ventilation.

Data collection on intubation will be collected using the Intubation card (Supplemental file 3)

Participant Timeline: To indicate participant timeline between the Caffeine and LISA procedure vs the Caffeine and CPAP procedure, [Figure 1. CaLI Participant Timeline] (Supplemental File 4) is attached.

Patient and Public Involvement:

We have collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. Based on their experiences and preferences, we have incorporated their suggestions and they enthusiastically support the study. One of the parents has agreed to be on the DSMB to monitor the trial for safety. Their involvement includes input on the consent form and perspective on the means of recruitment to the study.

Study Overview Diagram: (Supplemental File 5)

Data Management and Collection:

Data will be managed using REDCap electronic data capture tools hosted and managed at Sharp Mary Birch Hospital for Women & Newborns. All collected variables are listed in the data report form, (DRF forms): LISA Data Collection (supplemental file 1), CPAP arm Delivery Room Data Collection (supplemental file 2), and CaLI Intubation Data Collection (supplemental file 3). Loma Linda University Medical Center, University of California Irvine Medical Center, and Sharp Mary Birch Hospital for Women & Newborns have extensive experience with REDCap data entry.

Randomization cards are also utilized as data collection forms, with pertinent information completed and signed by care providers in real-time. To maintain integrity of the study data, site

Data Coordinators will enter data information into REDCap and verified by the primary site Data coordinator and Research Coordinator prior to locking the subject's electronic data file.

Data and safety monitoring plan:

An independent, well recognized, data safety monitoring board (DSMB) with experience with respiratory trials is chosen for this study. Drs. Brad Yoder and Wally Carlo have led and participated in a number of trials including: High-Flow Nasal Cannula, High Frequency Ventilation, and Surfactant. In addition, a former parent that has participated in research trials Kirsten Norman has agreed to serve on the DSMB. The DSMB will: 1) oversee the safety data on 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 monthly reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of predetermined early stopping rules. All SAEs, protocol deviations, non-serious adverse events (AEs), and unanticipated problems (UPs) will be reported to the Data Coordinating Center (DCC) and forwarded to the DSMB if indicated (see below). Reports of adverse events and recruitment will be sent monthly and demographics will be included with the interim and final safety and efficacy analyses. Interim analyses determined by the DSMB and the project statistician will be conducted independently from the trial leadership and staff. The definitions and reporting process are as follows:

Serious Adverse Events defined as one or more of the following: decompensation during the administration of surfactant in either arm including the use of epinephrine in the delivery room and chest compressions, or death prior to discharge.

1. All SAEs will be reported within 72 hours of discovery of event, to the PI and the site IRB.
2. Any Unexpected AE or Serious Deviation will be reported within 7 days of discovery of event to the Data Coordinating Center.

Non-Serious Events

Unexpected events that are Non-Serious are reported not more than 14 days after the PI first learns of the event. The DCC will forward all non-serious unexpected events to the DSMB, and main study PI. All other expected outcomes of prematurity, i.e. BPD, IVH grades 1-4, ROP, NEC, will be collected in the electronic database and reviewed in interim reports. We have appointed a DSMB to work closely with the main study PI. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the investigators at the enrolling sites.

The study will be closely monitored for issues of data quality, study conduct, and adverse events. These analyses will be presented to the DSMB. Interim analyses will seek to identify results that are sufficiently extreme and precise, this is to offset the goal of obtaining additional data that might lead to more precise and perhaps less exaggerated and more convincing results, as well as information about differences in treatment effect by subgroups of patients. Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical practice. The superiority must be tested in the context of this trial first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority.

Statistical Analysis Plan:

A chart review of the databases at Sharp Mary Birch has shown that approximately 49% of our infants 24-29+6 weeks' gestation were intubated and mechanically ventilated after 5 minutes of life but within the first 72 hours of life. Therefore, a very conservative sample size calculation indicates that in order to detect a 22% absolute reduction (a reduction from 49% to 27%) we would need at least 75 subjects in each arm for an 80% power and a p-value of less than 0.05 for significance. An adjustment of 1.12 derived from the NICHD Neonatal Research Network Generic Database, allowed for multiples to be randomized to the same treatment introducing a clustering effect. [8] In order to account for multiples and potential drop out of subjects we plan to consent 90 subjects in each arm (180 subjects total). A future detailed statistical analysis plan will be made available prior to completion of the trial.

ETHICS AND DISSEMINATION

Ethics approval has been obtained. Prior to any research procedure, consent will be obtained by the primary investigator or a delegated sub-investigator or a research associate. The mother, or legally authorized representative must sign the informed consent document. Mother (or surrogate mother) must sign a HIPAA authorization providing access to her medical records for collection of maternal data. Either mother or father or legal guardian can sign a HIPAA authorization providing access to the child's medical record for data collection purposes. The subject's legally authorized representatives 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 electronic medical record and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute. Results will be

published and presented at the Pediatric Academic Societies meeting upon completion. Any important protocol modifications will be communicated to sub-site lead investigators via secured email which will include automated confirmation of receipt and recorded audio/visual meetings.

Confidentiality:

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

Protection against Risk:

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 and DCC.

APPENDIX II

Informed Consent Form

Abbreviations (in alphabetical order)

BPD = Bronchopulmonary Dysplasia (supplemental O2 at 36 weeks CGA)

Bpm = beats per minute

BSID-4= Bayley Scales of Infant and Toddler Development 4th ed

CPAP = Continuous Positive Airway Pressure

LISA = Less Invasive Surfactant Administration

NCPAP = Nasal Continuous Positive Airway Pressure

NICU=Neonatal Intensive Care Unit

NIMV = Nasal Intermittent Minute Ventilation

PPV = positive pressure ventilation with bag & mask

RDS= Respiratory Distress Syndrome

ROP= Retinopathy of Prematurity

SMBHWN= Sharp Mary Birch Hospital for Women & Newborns

LLU= Loma Linda University Medical Center

UCI= University of California Irvine Medical Center

PRINCIPAL INVESTIGATORS

Anup Katheria MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Shandee Hutson MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Andrew Hopper, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Anamika Banerji, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Cherry Uy MD, University of California Irvine, Irvine, CA, USA

Neil Finer MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Statistician

Debra Poeltler, PhD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

FUNDING STATEMENT

A grant to support the CaLI trial has been obtained from Chiesi Farmaceutici, S.p.A and with this financial support, the primary study site maintains ultimate authority overall study activities.

Chiesi Grant #: CRTX-GR-717

COMPETING INTERESTS

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

CONTRIBUTORSHIP STATEMENT

FI and AK developed the initial protocol and manuscript. SH, KC, AH, AB, CU, NF, WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript.

REFERENCES:

1. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. *Neonatology* 2019;115(4):432-50. doi: 10.1159/000499361 [published Online First: 2019/04/12]
2. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]
3. Dekker J, Hooper SB, van Vonderen JJ, et al. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatric research* 2017;82(2):290-96. doi: 10.1038/pr.2017.45 [published Online First: 2017/03/14]
4. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
5. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and

Meta-analysis. *JAMA : the journal of the American Medical Association* 2016;316(6):611-24. doi: 10.1001/jama.2016.10708 [published Online First: 2016/08/18]
6. Bhayat S, Kaur A, Premadeva I, et al. Survey of less Invasive Surfactant Administration in England, slow adoption and variable practice. *Acta paediatrica* 2020;109(3):505-10. doi: 10.1111/apa.14995 [published Online First: 2019/09/01]
7. Braner D, Denson S, Zaichkin J, et al. Textbook of neonatal resuscitation. Dallas, TX: American Heart Association 2000.
8. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]

CALI Study Randomization Card

CALI Randomization Card

Treatment: *LISA & Caffeine*

Subject ID: _____ **Site #:** _____

Date/time of Randomization: ____/____/_____ _____:_____
MM / DD / YYYY HH : MM

PLEASE REFER ON BACK OF CARD FOR LISA PROCEDURAL CHECKLIST

FiO2:_____ **CPAP:**_____ **SpO2:**_____ **HR:**_____ at randomization

1. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
2. Start time of LISA *(from Laryngoscopy attempt)*	**Time:** ____:____ HH : MM
3. Duration of Laryngoscopy attempt? *(Time of insertion to removal)*	**1st** _____seconds **2nd** _____seconds **3rd** _____seconds
4. Successful placement of LISA catheter?	□ Yes □ No
5. Total surfactant administered (2.5 mL/kg)	_____ mLs
6. End time of LISA *(removal of angiocatheter)*	**Time:** ____:____ HH : MM
7. Surfactant aspirated from stomach or leaked from mouth (failure/regurgitation from trachea?	□ Yes □ No
8. Amount surfactant aspirated?	_____ mLs
9. Lowest HR during procedure?	_____ Bpm
10. Lowest SpO2 during procedure?	_____%
11. Interventions?	Notes:

Affix patient label to back of this card

Completed By (Name): _____ **Date:** ____/____/_____

CALI Study Randomization Card

CALI Randomization Card

Supplies for LISA procedure:

- ○ 16g angiocatheter, measured and marked insertion length with tape or Sharpie, NEEDLE REMOVED
- ○ Laryngoscope size: ☐ 00 ☐ 0
- ○ Laryngoscope type: ☐ Video ☐ Conventional
- ○ Curosurf 2.5 mL/kg/dose in syringe
- ○ 8 FR feeding tube and compatible syringe
- ○ 2- 10 mL syringe
- ○ Blunt plastic needle
- ○ 7 inch IV small bore extension tubing

PROCEDURE:

- ○ At randomization infant will be on CPAP
- ○ Infant will be positioned in a "sniffing position"
- ○ An 8 FR orogastric (OG) tube will be placed and gastric contents aspirated. OG tube should remain in place during the LISA procedure
- ○ Ensure adequate CPAP and Vital Signs (VS) stable
- ○ Place IV for IV Caffeine loading dose
- ○ Obtain 16 gauge catheter and **remove needle**
- ○ Measure depth of catheter insertion using clean technique (6 + wt in Kg) mark with a small piece of intubation tape or sharpie
- ○ Provider visualizes vocal cords, inserts & stabilizes angiocatheter
- ○ RCP attaches 7 inch IV small bore extension tubing to angiocatheter
- ○ RCP attaches syringe with Curosurf to the extension tubing
- ○ RCP slowly administers Curosurf over 1-2 minutes (approximately in 3 aliquots) while infant is spontaneously breathing on CPAP
- ○ RCP will flush angiocath with 5 mLs of air to clear surfactant from angiocatheter
- ○ Provider will remove angiocatheter and infant will continue on CPAP therapy
- ○ Wean FiO2 as tolerated

If infant requires intubation within 72 hours, Please complete Intubation Card and call Neonatal Research at x6307

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Randomization Card. v1.0

(Supplemental File 1)

CALI Study Randomization Card

Treatment: *CPAP & Caffeine*

Subject ID: _____ **Site #: _____**

Date/time of Randomization: ____/____/_____ ____:____
MM / DD / YYYY HH : MM

Complete at time of randomization	
1. CPAP Level?	_____ cmH2O
2. FiO2 requirement?	_____ %
3. Vitals: HR/SpO2	HR: _____Bpm SpO2 _____%
4. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
Notes/comments:	

If infant requires intubation within 72 hours of randomization, Please complete Intubation Card and call Neonatal Research at x6307

Affix patient label to back of this card

Completed By (Name): _____ Date: ___/____/_____

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Randomization Card. v1.0

(Supplemental File 2)

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

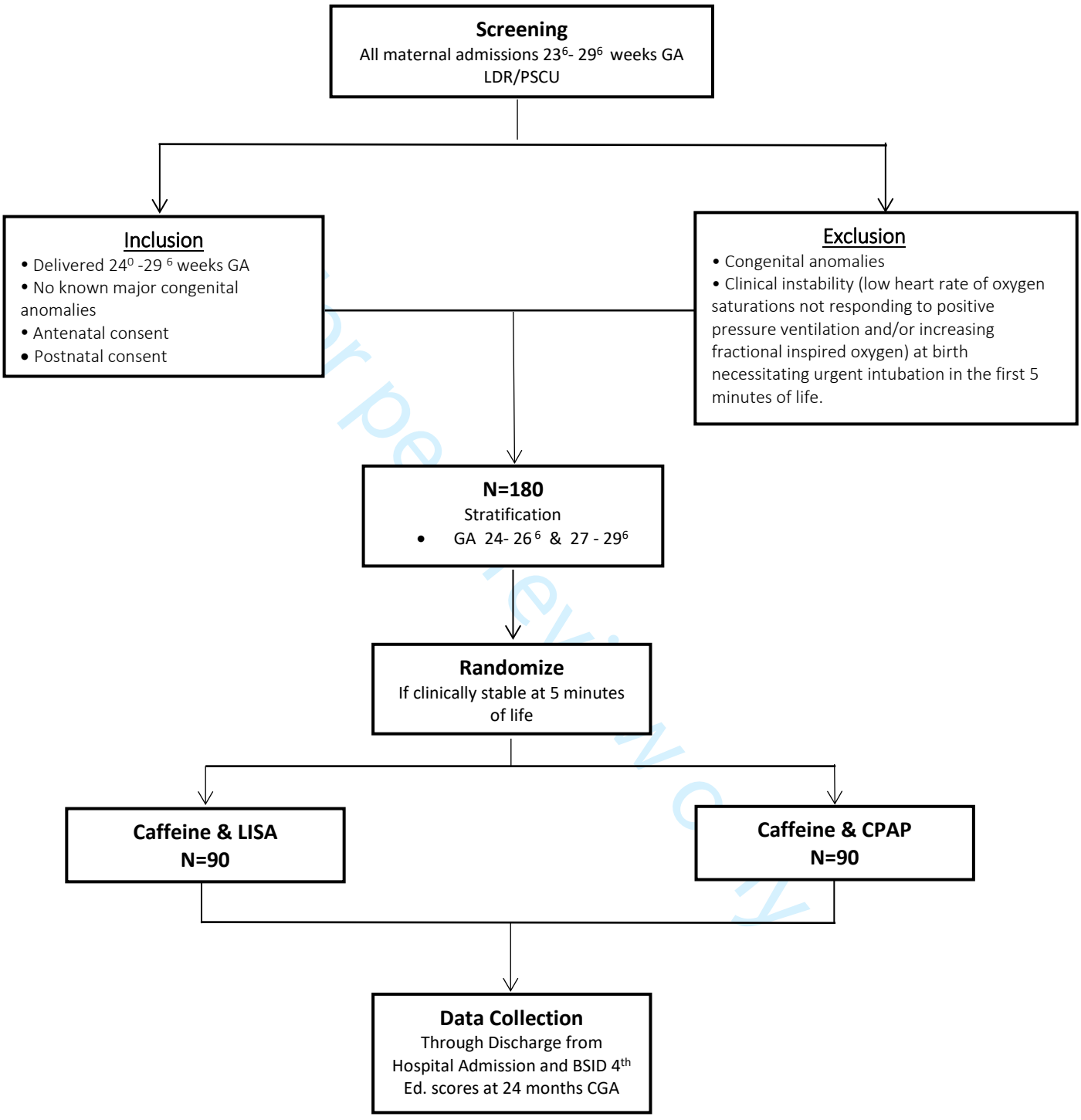
Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Intubation Card. v1.0

(Supplemental File 3)

CaLI Study Overview Diagram (Supplemental File 4)



SHARP Mary Birch Hospital for Women & Newborns

INFORMED CONSENT

A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

IRB #
1911902

Consent Date
06Aug2020 v1.2

Principal Investigator

Anup Katheria, MD
Neonatal Research Institute
SHARP Mary Birch Hospital for Women and Newborns
3003 Health Center Drive, San Diego, CA 92123

Research Grant

Chiesi Farmaceutici S.p.A.

If you are serving as a legally authorized representative, a guardian or are providing parental permission for a child in this study, the terms "you" and "your" refer to the person for whom you are providing consent or parental permission.

CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in an experimental procedure. Before you decide whether you want to participate in the experimental procedure, you have a right to:

1. Be informed of the nature and purpose of the experiment;

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

3. Be given a description of any discomforts and risks reasonably to be expected from your participation in the experiment;

4. Be given an explanation of any benefits reasonably to be expected from your participation in the experiment;

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to you, and their relative risks and benefits;

6. Be informed of the avenues of medical treatment, if any, available to you after the experimental procedure if complications arise;

7. Be given an opportunity to ask any questions concerning the medical experiment or the procedures involved;

8. Be instructed that consent to participate in the experimental procedure may be withdrawn at any time and that you may discontinue participation in the medical experiment without prejudice;

9. Be given a copy of this form and the signed and dated written consent form; and

10. Be given the opportunity to decide to consent or not to consent to the medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on your decision.

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

Signature of Parent or Legally Authorized Representative	Printed Name	Date

PARTICIPATION IN A RESEARCH STUDY

This is a research study. The purpose of a research study is to answer scientific questions. We are asking for your permission to have your baby participate in a research study so that we can learn new information that may help others in the future. Research is not the same as routine treatment or medical care.

Your participation is voluntary. You do not have to allow your baby to be in this study. You are free to say yes or no, or to allow your baby to drop out after joining. If you decide not to participate there is no penalty or loss of benefits. Whatever you decide, your baby's regular medical care will not change.

This process is known as the informed consent process. It is important that you read this consent form and ask the study doctor any questions you may have. Please take your time to make your choice. Discuss it with your friends and family.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

Your baby has been chosen because he/she may be born prematurely with immature lungs and a lack of natural lung surfactant, a fluid that coats the lungs and help them remain open. Due to this condition, your baby may not breathe well at birth or in the first days after birth and may benefit from receiving surfactant medicine or continuous airway pressure to help your baby's lungs remain open and improve oxygenation. Both Surfactant administration and continuous positive airway pressure (CPAP) are currently standard treatments for premature infants that need respiratory support after delivery.

Surfactant administration traditionally involves inserting a breathing tube in your baby's airway (intubation) and placing them on a breathing machine for respiratory support. Continuing on a breathing machine for a long period of time increases your baby's chance of developing bronchopulmonary dysplasia (BPD), a chronic lung disease of the neonate. Delivery room resuscitation of very premature infants has evolved dramatically over the past decades. Optimizing the care of these newborns now involves early continuous positive airway pressure (CPAP) and the avoidance of mechanical ventilation. However, mechanical ventilation is still often used when administering surfactant as the need arises.

The LISA method (Less Invasive Surfactant Administration) is another method that involves using a small catheter to administer surfactant directly into a baby's lungs. It also involves administering a precautionary dose of surfactant, compared to the traditional method which only administers doses of surfactant as needed using the breathing tube. A recent study in Europe showed that the Less Invasive Surfactant Administration (LISA) method had the lowest risk for the development of bronchopulmonary dysplasia (BPD) when compared to mechanical ventilation. Despite these results showing it decreased the need for mechanical ventilation compared to CPAP alone, there have been no studies done in the United States and the use of the LISA method is still not widely accepted.

We are conducting this study to find out if infants that receive surfactant by the LISA method (study method) compared to early CPAP and mechanical ventilation (standard method) require less intubation and less days on respiratory support.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 180 babies will take part in the study. We will enroll 120 babies at Sharp Mary Birch Hospital for Women & Newborns, 30 babies at Loma Linda University Medical Center, and 30 babies at University of California Irvine Medical Center.

HOW LONG WILL YOU BE IN THE STUDY?

Your baby will be in this study from birth through 2 years of age. We will also collect information about your baby from the 2-year follow-up visit described below.

WHAT IS INVOLVED IN THIS STUDY?

We are asking for your permission to have your baby be in a research study so that we can learn new information that may help other babies.

If you decide to let your baby take part in the current research study and your baby needs support with breathing, your baby will be given CPAP through the nose. If your baby's breathing remains stable, he/she will be randomized (meaning based on chance, like flipping a coin) to either continuing on CPAP or being given a medicine called surfactant. The surfactant medicine is a small volume of liquid that will be placed directly into your baby's lungs using a small catheter (a small flexible tube). This is called the LISA method. This medication helps keep your baby's lung inflated and improves oxygenation.

Your baby will have a 50/50 chance of being placed in either group (CPAP or LISA). After your baby is placed on CPAP or given surfactant, he/she will be carefully monitored.

In either case if your baby needs more help with breathing, your baby's doctor will decide the best way to help support your baby's breathing which may include placement of an endotracheal tube into your baby's airway.

In some cases, your baby may require additional surfactant, if they are not breathing well or continue to need increased support such as additional oxygen. If your baby is in the CPAP group and becomes unwell in this study, your baby's doctor may decide to provide an initial dose of surfactant, and maybe more doses, as needed. This would require insertion of a regular endotracheal breathing tube (if not already placed), which is the current standard practice for providing surfactant.

If your baby is in the LISA group and becomes unwell in this study, your baby's doctor may decide to provide additional doses of surfactant as needed. This will be done by insertion of a regular endotracheal tube.

The procedures of the study are described below. The decision for treatment will be made at the first 5 minutes after your baby's birth.

- The doctor will evaluate your baby's condition at birth. If your doctor determines that your baby needs immediate placement of an endotracheal tube to assist breathing, your baby will not be in the study. Babies who are intubated at birth will not be in the study.

- If your baby is stable and breathing on his/her own with CPAP, he/she will be randomized to either the LISA group with CPAP or CPAP alone. This is done by selecting an envelope which contains a card telling the team which treatment the baby will receive.

During the NICU hospitalization, your baby will be continuously monitored to check the health of your baby's heart, brain and lungs and overall condition. This is normally part of the standard care for preterm babies.

OUTPATIENT FOLLOW-UP

All premature babies are evaluated periodically (at 6 months, then once a year) as part of routine care at the Nemeth NICU Follow-up Clinic during the first 2 years of life. At these visits, the doctors and nurses who work at the clinic will check your baby's health and development. At every visit, they will ask questions about your living arrangements and your baby's medical condition. They will evaluate your baby's development using toys and items that are part of a developmental test. They will do a physical exam and check your baby's muscle strength and reflexes (neurologic exam).

WHAT IS THE RESEARCH PART OF OUTPATIENT FOLLOW-UP?

The research visit is between 22-26 months corrected age (2 years from your baby's original due date). At this visit, the doctors and nurses will do everything listed above that is routine for your infant given their prematurity. The results of the routine evaluation will be obtained as part of our data collection. We will use a study number, not your child's name to ensure confidentiality and anonymity of your medical information.

After that, your baby's involvement will be completed and there are no further study requirements for your baby.

WHAT ARE THE RISKS OF THE STUDY?

Both methods of administering surfactant either by the LISA method or the endotracheal tube are practiced in our NICU. The surfactant used in this trial is our current standard surfactant.

You should note:

- Infants randomized to the LISA group could receive an extra dose of surfactant when they otherwise might not have if they were not part of the study.
- Infants randomized to the CPAP group may receive mechanical ventilation that they otherwise might not have if they were not part of the study
- The catheter used in the LISA method is being used off-label, meaning it is used in a way that is different from the FDA's approved packaging label. It is used intratracheally (into the trachea) rather than intravenously (into the vein).

Risks of surfactant include:

- Low blood oxygen level
- Slow heart rate
- Low blood pressure

Risks of Intra-tracheal catheter:

- There may be risks that are unknown at this time

Risks of mechanical ventilation include:

- Volutrauma- over expansion of the lungs by delivery of too much gas
- Pneumothorax- is a collapsed lung
- Pneumonia- lung infection
- Development of Bronchopulmonary Dysplasia (BPD)- a chronic lung disease that affects premature infants

Based on the current literature to date, there are no increased risks with less invasive administration of surfactant with a small catheter (i.e. the LISA method) compared to endotracheal administration of surfactant in several large European trials. All risks with conducting this study are associated with prematurity including severe IVH, death, retinopathy of prematurity, chronic lung disease and other lung problems such as possible air leaks. There should be no more risks for babies in this study than are possible for any Extreme Low Birth Weight (ELBW) baby needing surfactant therapy. However, as with all research, there may be risks that are unknown at this time.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There may or may not be direct benefits to your baby for participating in this study. We hope the information we learn will help babies with respiratory distress syndrome in the future.

WHAT OTHER OPTIONS ARE THERE?

Your baby's alternative is to not participate in this study and receive treatment of Respiratory Distress Syndrome as prescribed by your personal physician. Your doctor will discuss these alternative treatments with you as well as their benefits and risks.

WILL YOU OR YOUR CHILD BE PAID TO BE IN THIS STUDY?

You and your child will not be paid to be in this study. No additional compensation is available for participation in this study.

WHAT ARE THE COSTS?

The study drug, Curosurf, will be provided for you at no cost by the study sponsor.

There are no additional costs to be in this study. You and/or your health plan/insurance company are responsible for the cost of your baby's hospitalization and standard clinical care provided. You will be responsible for co-pays and deductibles in the same way as outside of a clinical trial.

For more information about your costs, please discuss with the hospital's billing department, or call your health plan/insurance company to find out your financial responsibility for this trial.

RESEARCH-RELATED INJURY

If your baby gets sick or injured in this study, please tell your study doctor. Your baby will be treated or referred for medical treatment. You or your insurance will be responsible for the cost of treatment.

Sharp HealthCare will not provide any compensation for treatment of research related injury or illness.

PAYMENT TO STUDY SITE

CHIESI has provided a grant to Sharp Mary Birch Hospital for Women & Newborns to reimburse the study site for expenses related to the conduct of this study. This includes providing the Surfactant medication your baby may receive while in the study.

NEW INFORMATION

You will be told if any important new information is found during the course of this study that may affect your wanting to continue. If you decide to continue in the study, your study doctor may ask you to sign an updated consent form.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Organizations or individuals that may inspect and/or copy your medical and/or research records for quality assurance and data analysis include groups such as:

- Study Doctor and Research Staff at the Neonatal Research Institute
- Sharp HealthCare Institutional Review Board (IRB, a group of people who review the research to protect your rights)
- The Food & Drug Administration (FDA)

Your information will be coded and stored anonymously in a database with information about other people in this study. Access to this database is limited to the research staff.
Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

As part of this research study you will be asked to sign an additional document, Authorization to use Protected Health Information (PHI). This authorization will explain in further detail how your and your baby's PHI will be used and shared in the study, who will have access to it, what information will be obtained, and how long Sharp HealthCare will use your information. It will also explain what to do if you decide you no longer want to share your PHI, and your rights regarding your ability to see and copy your research information.

If the results of this study are published or presented at meetings, your identity will remain confidential.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Participating in this study is entirely voluntary. You may refuse to allow your baby to participate or withdraw your baby at any time without penalty or loss of benefits to which you or your baby are entitled. If you decide that you no longer want your baby to continue in this study, we encourage you to talk to the study doctor. Please contact Dr. Katheria to tell him you no longer want to participate:

Dr. Anup Katheria
(858) 939-4170
Anup.katheria@sharp.com

If you decide to remove your baby from the study, the study team may ask your permission to keep your baby's test results and information that has already been collected.

WHOM DO YOU CALL IF YOU HAVE ANY PROBLEMS, COMPLAINTS, CONCERNS, OR QUESTIONS?

If you have problems, complaints, concerns, or questions about this study, you may talk to your study doctor anytime.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	858-939-4170 Dr. Anup Katheria 858-939-6307 Neonatal Research Institute
If you get sick or hurt in this study	858-939-4170 Dr. Anup Katheria
Your rights as a research participant and: • Discuss problems, concerns, and questions • Obtain information	Sharp HealthCare Institutional Review Board 7930 Frost Street, Suite 300 San Diego, CA 92123 (858) 939-7195

WHERE CAN YOU GET MORE INFORMATION?

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you or other participants. At most, the web site will include a summary of the results. You can search the web site at any time. The registration identifier for this study is NCT#04209946.

STATEMENT OF CONSENT

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you carefully consider whether you agree to have your child take part in this study and how your and your child's information will be used.

You can change your mind later if you want to. You will be given a copy of this consent form including a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

You agree to participate in this research study.

Printed Name of Participant (Baby)

SIGNATURE OF PARENT OR LEGALLY AUTHORIZED REPRESENTATIVE **PRINTED NAME** **DATE**

AUTHORITY OF SIGNEE OR RELATIONSHIP TO PARTICIPANT

SIGNATURE OF PRINCIPAL INVESTIGATOR/DESIGNEE **PRINTED NAME** **DATE**

---------- **USE THE FOLLOWING ONLY IF APPLICABLE** ----------

If this consent form is read to the participant because the participant is unable to read the form, an impartial witness not affiliated with the research or study doctor must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant. The participant freely consented to be in the research study.

PRINTED NAME OF IMPARTIAL WITNESS

SIGNATURE OF IMPARTIAL WITNESS **DATE** **TIME**

NOTE: *This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling participants who do not speak English.*

Authorization to Use your Protected Health Information (PHI)

Study Title: A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

Investigator: Anup Katheria, MD
Neonatal Research Institute
Sharp Mary Birch Hospital for Women & Newborns

Research Grant: Chiesi Farmaceutici S.p.A

Protected Health Information, or PHI, is any personal health information through which you or your baby can be identified. We are asking for your permission to use your baby's PHI in this research study. The information we may use includes maternal (prenatal) data from your baby's record, your baby's present health information, information that can be used to contact you, and results of your and your baby's medical tests. Maternal data will be collected from your baby's medical record; your medical record will be accessed for study purposes. The specific items of information that will be used and disclosed include:

- Maternal (prenatal) information related to the health of your baby, including:
  - Information about mother's pregnancy
  - Fetal History
  - Pregnancy complications
  - Medications for mother
  - Delivery record
- Information from your baby's medical record, including:
  - Medications for baby
  - Results of lab tests
  - Blood gases
  - Respiratory management

- Vital signs
- Diagnoses

The following people will access and use your baby's PHI for the purpose of this research:

- Dr. Anup Katheria, Primary Investigator, Sharp Mary Birch Hospital for Women & Newborns
- Sharp Mary Birch Hospital Neonatologists
- Research Staff at Sharp Mary Birch Hospital for Women & Newborns

Who may see your PHI?

Certain offices and people other than the researchers may look at your medical charts and study records. There may be times when federal or state law requires the sharing of such records. This is very unlikely, but if sharing the information is ever required, Sharp Mary Birch Hospital for Women & Newborns will take steps allowable by law to protect the confidentiality of personal information. If this information is shared with outside reviewers for audit purposes, it may be further shared by them and may not be covered by the federal privacy laws.

Representatives that may review your study records:

- the Sharp HealthCare Institutional Review Board (IRB; a group of people that review the research to protect the rights of research participants)
- the US Food and Drug Administration

How long will the Neonatal Research Institute use your information, and what will it be used for?

- Your and your baby's PHI may be used and shared until December 31, 2044.

The groups above will use your health information:

- To complete this research
- To evaluate the results of the study
- To check that the study is being done properly

What if you change your mind and want to withdraw your authorization for the use and disclosure of your PHI for this study?

You must write to the study doctor and tell him that you no longer want to share your child's information at: Anup Katheria, MD. Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, 3003 Health Center Drive, San Diego, CA 92123.

- Your baby will no longer be a part of the research study because the study doctor, and the research staff will not be able to use any new information about your baby.
- The research team can continue to use any of the PHI that was already collected.
- You and your baby will still get the same medical care that you have always had from Sharp Mary Birch Hospital for Women & Newborns.

Do you have the right to see and receive a copy of your research information?

You can see your research information if:

- It is also being used for your and your baby's current treatment, or
- At the end of the study.

****

Authorization:

If you agree to share your and your baby's PHI, you must sign this form below. If you do not sign this form, you and your baby will not be able to participate in this research study. You will be given a copy of this form.

_____

Printed Names of Mother and Baby

_____

Signature of Mother or Legally Authorized Representative | Printed Name | Date

_____

Signature of Father | Printed Name | Date

_____

Authority of Signee or Relationship to Participant

Figure 1. CaLI Study Patient Timeline

Assessment	On admission prior to study treatment	0	5'	15'	30'	1-h	2-h	6-h	12-h	24-h	2-d	3-d	Day 28	36-WK PMA	Discharge home	24-m BSID
Inclusion/Exclusion Criteria	×															
Parental Informed Consent	×															
Apgar Score	×	×	×													
Demographic data (weight)	×		×										×	×	×	×
Oxygen Saturation (SpO2)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Vital Sign (HR)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Fraction of Inspired Oxygen (FiO2)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
CPAP Level	×	←													→	
Caffeine Therapy	×	←													→	
Bronchopulmonary Dysplasia (BPD)													×	×	×	
Severe Adverse Events (SAEs)	×	←													→	
Bayley Scales of Infant Development (BSID)																×

Parental Informed Consent will be obtained prior to birth. Vital signs will be obtained at randomization and during surfactant administration. SAEs are surfactant administration procedure-related and or death prior to discharge.

× *indicates continuous monitoring* ←→ *indicates possible discontinuation during hospital admission*

Sharp Mary Birch Hospital for Women & Newborns (version 21OCT2020)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038343.R3
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2020
Complete List of Authors:	Ines, Felix; Sharp Mary Birch Hospital for Women and Newborns, Neonatal Research Institute Hutson, Shandee; Sharp Mary Birch Hospital for Women and Newborns Coughlin, Katherine; Sharp Mary Birch Hospital for Women and Newborns Hopper, Andrew; Loma Linda University Medical Center Banerji, Anamika; Loma Linda University Medical Center Uy, Cherry; University of California Irvine Finer, Neil; University of California San Diego Rich, Wade; Sharp Mary Birch Hospital for Women and Newborns Morales, Ana; Sharp Mary Birch Hospital for Women and Newborns Steen, Jane; Sharp Mary Birch Hospital for Women and Newborns Katheria, Anup; Sharp Mary Birch Hospital for Women and Newborns, Neonatology
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Paediatrics
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine)

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Multicenter, Randomized Trial of Preterm Infants receiving Caffeine and Less Invasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial): Study Protocol

Felix Ines, Shandee Hutson, Katherine Coughlin, Andrew Hopper, Anamika Banerji, Cherry Uy, Neil Finer, Wade Rich, Ana Morales, Jane Steen, Anup Katheria*

Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States.

Loma Linda University Medical Center, Loma Linda, CA, United States.

University of California Irvine Medical Center, Irvine, CA, United States.

Corresponding author: Anup Katheria M.D., Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States. Email: Anup.Katheria@sharp.com

ABSTRACT

Introduction: Respiratory Distress Syndrome (RDS) or surfactant deficiency occurs primarily in premature infants resulting in composite outcomes of death or bronchopulmonary dysplasia. Initial management strategies for preterm infants with RDS includes early initiation of continuous positive airway pressure (CPAP) and titration of FiO2, and may include the use of less invasive surfactant administration (LISA) to avoid the need for mechanical ventilation. In order to optimize success of non-invasive support, the use of early caffeine therapy may be critical to the success of LISA. The objective of our trial is to evaluate whether of infants that receive early caffeine, CPAP, and surfactant via the LISA method compared to infants that receive caffeine and CPAP alone, have a decreased need for invasive mechanical ventilation in the first 72 hours of life.

Methods and analysis: CaLI is an unblinded multicenter, randomized controlled, trial of 180 preterm infants (24+0 – 29+6 weeks CGA). Criteria for intubation/treatment failure will be recent guidelines for the management of RDS, including: 1) CPAP level of 6-8 cmH20 and FiO_2 >0.40 required to maintain saturations 90%-95% for 2 hours after randomization; 2) a pH of 7.15 or less or a $paCO_2$ >65 mmHg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomization and in the first 72 hours of life; 3) continued Apnea/Bradycardia/Desaturation events despite nasal intermittent minute ventilation (NIMV) mode of ventilation.

Infants w will be randomized by 1 hour of life and Caffeine/Lisa treatments by by 2 hours of life. Caffeine will be administered soon after randomization in both arms, prior to surfactant in the LISA arm and before 2 hours of life in the control arm.

Ethics and Dissemination: Chiesi Farmaceutici, S.p.A is the sponsor of CaLI. Ethical approval has been obtained. Results will be submitted for publication in peer reviewed journals.

Clinical Trial Registration: www.Clinicaltrials.gov: NCT04209946

STRENGTHS AND LIMITATIONS OF THIS TRIAL ARE:

- Limited power for longer term outcomes such as BPD and neurodevelopmental impairment due its smaller size
- CaLI is not a double blind trial due to the complexity of blinding treatments in the delivery room with different modes of administration and the need to initial the trial very rapidly after birth.
- The trial is the first to be prescriptive in the use of caffeine as a co-intervention for LISA administration to test its benefit
- This study will be the most recent in many years to re-study the use of early surfactant with the LISA method compared to expectant management with CPAP alone.

INTRODUCTION

Premature infants are commonly born with respiratory distress syndrome (RDS) or surfactant deficiency that may lead into respiratory failure. Advances in respiratory management includes, early initiation of continuous positive airway pressure (CPAP) and titration of FiO2, [1] modifications in the administration of surfactant therapy using less invasive techniques, and the avoidance of mechanical ventilation. [2] Other strategies to optimize success of non-invasive support involves the use of caffeine therapy to serve as a respiratory stimulant. Dekker et al

demonstrated that the administration of caffeine in the delivery room compared to upon admission to the NICU produced greater minute ventilation and tidal volumes in premature infants <30 weeks. [3] The less invasive surfactant administration (LISA) to spontaneously breathing preterm infants has been reported to reduce the need for mechanical ventilation. [4]A recent meta-analysis of non-invasive ventilation strategies demonstrated that Less Invasive Surfactant Administration (LISA) had the lowest odd ratio (OR, 0.49; 95% CI 0.3-0.79) for the development of the composite outcome of death or bronchopulmonary dysplasia amongst non-invasive ventilation strategies compared to invasive mechanical ventilation. [5] The combination of early Caffeine and LISA has not been tested and despite these results and studies showing it decreased the need for invasive mechanical ventilation compared to Continuous Positive Airway Pressure, the use of the LISA method in the United States and countries such as England. [6 7].

METHODS AND ANALYSIS

The study is designed as a multicenter, un-blinded, randomized trial of preterm infants receiving Caffeine and Less Invasive Surfactant Administration compared to Caffeine and CPAP with a primary outcome of frequency of subject endotracheal intubation between the two groups (Caffeine and LISA vs Caffeine and CPAP) within the first 72 hours of life. The study will be conducted at 3 sites in the United States (Loma Linda University Medical Center, University of California, Irvine, and Sharp Mary Birch Hospital for Women & Newborns) over a 3 year period. The following variables will be collected:

1. Frequency of subjects requiring endotracheal intubation between the two groups (LISA vs CPAP) in the first 72 hours of life
2. Duration of mechanical ventilation and/or CPAP
3. Requirement of supplemental oxygen at 36 weeks corrected age

4. Grade III and IV intraventricular hemorrhage
5. Spontaneous intestinal perforation
6. Necrotizing Enterocolitis
7. Retinopathy of prematurity requiring surgery
8. Need for repeat surfactant dosing
9. Long term neurodevelopmental data through 2 years of age.

Pregnant women will be identified and screened from the labor and delivery floor (LD) or perinatal special care unit (PSCU) at each site. Parents will be approached and consented prior to delivery. In the delivery room, after the infant's first five minutes of life, the research staff or neonatal delivery team will open the randomization envelope for the proper gestational age (GA) group. Multiples will be randomized to the same treatment group for ease of consent and family considerations. There is no crossover allowed between the LISA and CPAP groups, subjects should receive their randomized treatment. If the physician determines that the infant requires intubation or is determined to be unstable within the first five minutes of life, the infant will be intubated and excluded from the study.

Inclusion Criteria:

- Premature infants born at 24-29+6 weeks gestational age
- Informed consent obtained (antenatal)
- Infant is spontaneously breathing on CPAP of 5-8 cmH20 with an FiO2 of <.40 and maintains a normal heart rate (HR>100 Bpm)

Exclusion Criteria:

- Declined consent
- Infants with known congenital anomalies

- Requiring intubation in the delivery room

All infants found to have anomalies post-randomization will be analyzed by intent to treat principle.

Patient Allocation: Randomization cards are computer-generated by Sharp Mary Birch Hospital for Women & Newborns and will solely be known by the data manager. Each randomization card contains group assignment, real-time data information, and a randomization number, sealed in an opaque envelope with a label that indicates the envelope sequence number, site (facility) number, and stratification by gestational age. These envelopes will be logged by the data manager in a secured data file and then distributed to each research facility. We will enroll 180 preterm infants and will stratify by gestational age (24-26+6 weeks and 27+0-29+6 weeks), labeled as such on each opaque envelope.

Randomization:

In order to allow for initial stabilization on CPAP, infants will be randomized by 1 hour of life. If the providers have not intubated or plan to intubate the infant in the delivery room, consented infants that are assessed by a provider as clinically stable (i.e. HR >100 bpm) and spontaneously breathing on CPAP (5-8 cm H_2O) will be randomized. Stabilization of premature infants at delivery may include stimulation, positive pressure ventilation or CPAP. Only spontaneously breathing infants on CPAP, maintaining normal heart rate and saturations will be included and randomized. When the neonatal provider assesses the infant to be stable on CPAP, a member of the research or neonatal team will pull a randomization card according to the infant's corrected gestational age. Once the treatment group is identified (Caffeine and LISA or Caffeine and CPAP), intervention will immediately commence.

LISA Group:

For infants randomized to LISA, an intravenous access will be established to administer caffeine. We will have an orogastric tube placed into the stomach prior to laryngoscopy and the contents aspirated before and after the procedure to document any esophageal surfactant administration. Thereafter, a thin catheter (16G angiocatheter) will be measured and the depth of insertion will be marked with intubation tape. The thin catheter will then be placed in the trachea under direct or video-laryngoscopy by a neonatal practitioner. After the catheter is placed, the laryngoscope will be removed, the angiocatheter held securely in place, and the infant allowed to spontaneously breathe on CPAP. Surfactant (Curosurf 2.5 mL/kg, based on estimated fetal weight) will be slowly administered over 1-2 minutes (approximately in 3 aliquots) assuring synchronized instillation with infant's breathing pattern while on CPAP. After instillation, the catheter will be immediately removed and CPAP will continue. If apnea occurs during or after the procedure, positive pressure ventilation will be initiated. To improve adherence to protocol interventions, all sites have agreed on using senior level physicians or neonatal practitioners that have prior experience with the LISA method.

Data collection in the LISA group is collected using the Caffeine and LISA Randomization card. (Supplemental file 1)

CPAP Group:

In adherence to protocol interventions, infants randomized to early CPAP will be managed according to sub-site unit practice for preterm infants on CPAP. If randomized to the CPAP group, an intravenous access will be established to administer caffeine and the infant will continue on CPAP unless infant meets failure criteria and requires intubation.

Data collection in the CPAP group is collected using the Caffeine and CPAP Randomization card (Supplemental file 2)

Caffeine:

Caffeine will be given in both groups as soon as IV access is obtained. Since caffeine must be given prior to the LISA procedure it must be given as early as possible but 2 hours of birth. Similarly, if randomized to CPAP, caffeine will be given soon after birth. If infants in the CPAP group meet intubation criteria, and the loading dose of caffeine has not been administered, to avoid any delay in intubation, caffeine will be given no later than thirty minutes after intubation.

The caffeine preparation for this study is caffeine citrate with a loading dose of 20 mg/kg given via an intravenous access over 15-30 minutes. Time of caffeine administration will be captured in subject's Electronic Medical Records (EMR).

Blinding:

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are strongly encouraged not to disclose the allocation status of the participant at the follow up assessments.

As a pragmatic design we realize that a separate research team would not always be able to be present for the randomization and intervention. Therefore, the clinical team caring for the infant will follow strict guidelines for intubation and management of infants to reduce any post-randomization bias (see below)

Intubation criteria:

As an un-blinded trial, it is critical that both groups are standardized to avoid bias towards one arm for mechanical ventilation/treatment failure. Therefore, strict delivery room/ NICU criteria

will be used. Furthermore, infants cannot be randomized before 5 minutes of life to ensure that unstable infants that cannot be transitioned on CPAP would not be included. These would include infants that need intubation as specified in the Neonatal Resuscitation Program (NRP) guidelines and such as: **1)** when chest compressions are needed; **2)** ineffective ventilation (inability to obtain good chest rise and fall despite implementation of the corrective ventilation steps: Mask adjustment; Reposition airway [try again]; Suction mouth and nose; Open mouth [try again]; Pressure increase [up to 40 cm H_20 pressure]; Airway alternative; (MRSOPA), as indicated by the NRP guidelines to obtain effective ventilation); **3)** prolonged PPV (infants requiring positive pressure ventilation for more than 2 minutes in order to maintain HR >100 BpM) ; or **4)** prolonged hypoxia (pre-ductal SpO2 is not met despite 100% oxygen supplements and resuscitation interventions). Randomization should be delayed until the providers are comfortable that none of these criteria are met in order to avoid any early selection bias.

After stabilization on CPAP infants can be randomized. Criteria for intubation/treatment failure will be recent guidelines for the management of RDS, [1] including: 1) CPAP level of 6-8 cmH20 and FiO_2 >0.40 required to maintain saturations 90%-95% for 2 hour after randomization; 2) a pH of 7.15 or less or a $paCO_2$ >65 mmHg on any (2) blood gases (arterial/capillary/or venous) at least 2 hours after randomization and in the first 72 hours of life; 3) continued Apnea/Bradycardia/Desaturation events despite nasal intermittent minute ventilation (NIMV) mode of ventilation. To avoid the bias of withheld ventilation since the study is not masked, infants with these criteria will be regarded as treatment failures.

For pragmatic purpose sites will be able to use their standard approach for non-invasive ventilation as they have agreed to use each mode (NCPAP or NIMV) equally regardless of randomization. Subsequent analysis will include primary mode of non-invasive ventilation.

Data collection on intubation will be collected using the Intubation card (Supplemental file 3)

Participant Timeline: To indicate participant timeline between the Caffeine and LISA procedure vs the Caffeine and CPAP procedure, [CaLI Study Overview Diagram] (Supplementary Appendix I) is attached.

Patient and Public Involvement:

We have collaborated with parents by presenting this study to the Sharp Mary Birch Parent Advisory Board. Based on their experiences and preferences, we have incorporated their suggestions and they enthusiastically support the study. One of the parents has agreed to be on the DSMB to monitor the trial for safety. Their involvement includes input on the consent form and perspective on the means of recruitment to the study.

Study Overview Diagram: (Supplemental File 4)

Data Management and Collection:

Data will be managed using REDCap electronic data capture tools hosted and managed at Sharp Mary Birch Hospital for Women & Newborns. All collected variables are listed in the data report form, (DRF forms): LISA Data Collection (supplemental file 1), CPAP arm Delivery Room Data Collection (supplemental file 2), and CaLI Intubation Data Collection (supplemental file 3). Loma Linda University Medical Center, University of California Irvine Medical Center, and Sharp Mary Birch Hospital for Women & Newborns have extensive experience with REDCap data entry.

Randomization cards are also utilized as data collection forms, with pertinent information completed and signed by care providers in real-time. To maintain integrity of the study data, site Data Coordinators will enter data information into REDCap and verified by the primary site Data coordinator and Research Coordinator prior to locking the subject's electronic data file.

Data and safety monitoring plan:

An independent, well recognized, data safety monitoring board (DSMB) with experience with respiratory trials is chosen for this study. Drs. Brad Yoder and Wally Carlo have led and participated in a number of trials including: High-Flow Nasal Cannula, High Frequency Ventilation, and Surfactant. In addition, a former parent that has participated in research trials Kirsten Norman has agreed to serve on the DSMB. The DSMB will: 1) oversee the safety data on 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 monthly reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of predetermined early stopping rules. All SAEs, protocol deviations, non-serious adverse events (AEs), and unanticipated problems (UPs) will be reported to the Data Coordinating Center (DCC) and forwarded to the DSMB if indicated (see below). Reports of adverse events and recruitment will be sent monthly and demographics will be included with the interim and final safety and efficacy analyses. Interim analyses determined by the DSMB and the project statistician will be conducted independently from the trial leadership and staff. The definitions and reporting process are as follows:

Serious Adverse Events defined as one or more of the following: decompensation during the administration of surfactant in either arm including the use of epinephrine in the delivery room and chest compressions, or death prior to discharge.

1. All SAEs will be reported within 72 hours of discovery of event, to the PI and the site IRB.
2. Any Unexpected AE or Serious Deviation will be reported within 7 days of discovery of event to the Data Coordinating Center.

Non-Serious Events

Unexpected events that are Non-Serious are reported not more than 14 days after the PI first learns of the event. The DCC will forward all non-serious unexpected events to the DSMB, and main study PI. All other expected outcomes of prematurity, i.e. BPD, IVH grades 1-4, ROP, NEC, will be collected in the electronic database and reviewed in interim reports. We have appointed a DSMB to work closely with the main study PI. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the investigators at the enrolling sites.

The study will be closely monitored for issues of data quality, study conduct, and adverse events. These analyses will be presented to the DSMB. Interim analyses will seek to identify results that are sufficiently extreme and precise, this is to offset the goal of obtaining additional data that might lead to more precise and perhaps less exaggerated and more convincing results, as well as information about differences in treatment effect by subgroups of patients. Determinations on stopping must reflect ethical considerations of the impact of interim results on clinical equipoise as well as considerations on the potential impact (or lack of impact) of interim results on clinical

practice. The superiority must be tested in the context of this trial first and then superiority assessed, unless the DSMB is ethically motivated to stop the trial for superiority.

Statistical Analysis Plan:

A chart review of the databases at Sharp Mary Birch has shown that approximately 49% of our infants 24-29+6 weeks' gestation were intubated and mechanically ventilated after 5 minutes of life but within the first 72 hours of life. Therefore, a very conservative sample size calculation indicates that in order to detect a 22% absolute reduction (a reduction from 49% to 27%) we would need at least 75 subjects in each arm for an 80% power and a p-value of less than 0.05 for significance. An adjustment of 1.12 derived from the NICHD Neonatal Research Network Generic Database, allowed for multiples to be randomized to the same treatment introducing a clustering effect. [8] In order to account for multiples and potential drop out of subjects we plan to consent 90 subjects in each arm (180 subjects total). A future detailed statistical analysis plan will be made available prior to completion of the trial.

ETHICS AND DISSEMINATION

Ethics approval has been obtained. Prior to any research procedure, consent will be obtained by the primary investigator or a delegated sub-investigator or a research associate. The mother, or legally authorized representative must sign the informed consent document. Mother (or surrogate mother) must sign a HIPAA authorization providing access to her medical records for collection of maternal data. Either mother or father or legal guardian can sign a HIPAA authorization providing access to the child's medical record for data collection purposes. The subject's legally authorized representatives 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 electronic medical record and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute. Results will be published and presented at the Pediatric Academic Societies meeting upon completion. Any important protocol modifications will be communicated to sub-site lead investigators via secured email which will include automated confirmation of receipt and recorded audio/visual meetings.

Confidentiality:

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

Protection against Risk:

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 and DCC.

APPENDIX II

Informed Consent Form (Supplementary Appendix II)

Abbreviations (in alphabetical order)

BPD = Bronchopulmonary Dysplasia (supplemental O2 at 36 weeks CGA)

Bpm = beats per minute

BSID-4= Bayley Scales of Infant and Toddler Development 4th ed

CPAP = Continuous Positive Airway Pressure

LISA = Less Invasive Surfactant Administration

NCPAP = Nasal Continuous Positive Airway Pressure

NICU=Neonatal Intensive Care Unit

NIMV = Nasal Intermittent Minute Ventilation

PPV = positive pressure ventilation with bag & mask

RDS= Respiratory Distress Syndrome

ROP= Retinopathy of Prematurity

SMBHWN= Sharp Mary Birch Hospital for Women & Newborns

LLU= Loma Linda University Medical Center

UCI= University of California Irvine Medical Center

PRINCIPAL INVESTIGATORS

Anup Katheria MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Shandee Hutson MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Andrew Hopper, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Anamika Banerji, MD, Loma Linda University Medical Center, Loma Linda, CA, USA

Cherry Uy MD, University of California Irvine, Irvine, CA, USA

Neil Finer MD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

Statistician

Debra Poeltler, PhD, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, USA

FUNDING STATEMENT

A grant to support the CaLI trial has been obtained from Chiesi Farmaceutici, S.p.A and with this financial support, the primary study site maintains ultimate authority overall study activities.

Chiesi Grant #: CRTX-GR-717

COMPETING INTERESTS

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

CONTRIBUTORSHIP STATEMENT

FI and AK developed the initial protocol and manuscript. SH, KC, AH, AB, CU, NF, WR helped revise the manuscript and protocol. AM and JS helped develop the dataset and variables for the manuscript.

REFERENCES:

1. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. *Neonatology* 2019;115(4):432-50. doi: 10.1159/000499361 [published Online First: 2019/04/12]
2. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]

3. Dekker J, Hooper SB, van Vonderen JJ, et al. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatric research* 2017;82(2):290-96. doi: 10.1038/pr.2017.45 [published Online First: 2017/03/14]
4. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
5. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. *JAMA : the journal of the American Medical Association* 2016;316(6):611-24. doi: 10.1001/jama.2016.10708 [published Online First: 2016/08/18]
6. Kurepa D, Perveen S, Lipener Y, et al. The use of less invasive surfactant administration (LISA) in the United States with review of the literature. *Journal of perinatology : official journal of the California Perinatal Association* 2019;39(3):426-32. doi: 10.1038/s41372-018-0302-9 [published Online First: 2019/01/13]
7. Bhayat S, Kaur A, Premadeva I, et al. Survey of less Invasive Surfactant Administration in England, slow adoption and variable practice. *Acta Paediatrica* 2020;109(3):505-10. doi: https://doi.org/10.1111/apa.14995
8. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]

CALI Study Randomization Card

CALI Randomization Card

Treatment: *LISA & Caffeine*

Subject ID: _____ **Site #:** _____

Date/time of Randomization: ____/____/_____ _____:_____
MM / DD / YYYY HH : MM

PLEASE REFER ON BACK OF CARD FOR LISA PROCEDURAL CHECKLIST

FiO2:_____ **CPAP:**_____ **SpO2:**_____ **HR:**_____ at randomization

1. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
2. Start time of LISA *(from Laryngoscopy attempt)*	**Time:** ____:____ HH : MM
3. Duration of Laryngoscopy attempt? *(Time of insertion to removal)*	**1st** _____seconds **2nd** _____seconds **3rd** _____seconds
4. Successful placement of LISA catheter?	□ Yes □ No
5. Total surfactant administered (2.5 mL/kg)	_____ mLs
6. End time of LISA *(removal of angiocatheter)*	**Time:** ____:____ HH : MM
7. Surfactant aspirated from stomach or leaked from mouth (failure/regurgitation from trachea?	□ Yes □ No
8. Amount surfactant aspirated?	_____ mLs
9. Lowest HR during procedure?	_____ Bpm
10. Lowest SpO2 during procedure?	_____%
11. Interventions?	Notes:

Affix patient label to back of this card

Completed By (Name): _____ **Date:** ____/____/_____

CALI Study Randomization Card

CALI Randomization Card

Supplies for LISA procedure:

- ○ 16g angiocatheter, measured and marked insertion length with tape or Sharpie, NEEDLE REMOVED
- ○ Laryngoscope size: ☐ 00 ☐ 0
- ○ Laryngoscope type: ☐ Video ☐ Conventional
- ○ Curosurf 2.5 mL/kg/dose in syringe
- ○ 8 FR feeding tube and compatible syringe
- ○ 2- 10 mL syringe
- ○ Blunt plastic needle
- ○ 7 inch IV small bore extension tubing

PROCEDURE:

- ○ At randomization infant will be on CPAP
- ○ Infant will be positioned in a "sniffing position"
- ○ An 8 FR orogastric (OG) tube will be placed and gastric contents aspirated. OG tube should remain in place during the LISA procedure
- ○ Ensure adequate CPAP and Vital Signs (VS) stable
- ○ Place IV for IV Caffeine loading dose
- ○ Obtain 16 gauge catheter and **remove needle**
- ○ Measure depth of catheter insertion using clean technique (6 + wt in Kg) mark with a small piece of intubation tape or sharpie
- ○ Provider visualizes vocal cords, inserts & stabilizes angiocatheter
- ○ RCP attaches 7 inch IV small bore extension tubing to angiocatheter
- ○ RCP attaches syringe with Curosurf to the extension tubing
- ○ RCP slowly administers Curosurf over 1-2 minutes (approximately in 3 aliquots) while infant is spontaneously breathing on CPAP
- ○ RCP will flush angiocath with 5 mLs of air to clear surfactant from angiocatheter
- ○ Provider will remove angiocatheter and infant will continue on CPAP therapy
- ○ Wean FiO2 as tolerated

If infant requires intubation within 72 hours, Please complete Intubation Card and call Neonatal Research at x6307

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Randomization Card. v1.0

(Supplemental File 1)

CALI Study Randomization Card

Treatment: *CPAP & Caffeine*

Subject ID: _____ **Site #: _____**

Date/time of Randomization: ____/____/_____ ____:____
MM / DD / YYYY HH : MM

Complete at time of randomization	
1. CPAP Level?	_____ cmH2O
2. FiO2 requirement?	_____ %
3. Vitals: HR/SpO2	HR: _____Bpm SpO2 _____%
4. Caffeine Therapy started in LDR/Resuscitation Rm?	□ Yes □ No
Notes/comments:	

If infant requires intubation within 72 hours of randomization, Please complete Intubation Card and call Neonatal Research at x6307

Affix patient label to back of this card

Completed By (Name): _____ Date: ___/____/_____

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Randomization Card. v1.0

(Supplemental File 2)

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

CaLI STUDY

Use only if intubating within ***72 HOURS***

Date/Time of 72 hours after randomization: ___/___/_____ ____:____
MM/ DD/ YYYY HH : MM

Subject ID: _____ **Site #:** _____

Treatment assignment: ☐ ***Caffeine & CPAP*** ☐ ***Caffeine & LISA***

PLEASE COMPLETE & CALL Neonatal Research at X6307	
1. Date/Time of Intubation	___/___/_____ ____:____ **MM/ DD/ YYYY HH : MM**
2. Duration of Laryngoscopy? (*Time of insertion to removal*)	1st _____seconds 2nd _____seconds 3rd _____seconds
3. Was Intubation successful?	☐ Yes ☐ No
4. Lowest HR during procedure?	_____ Bpm
5. Lowest SpO2 during procedure?	_____ %
6. Reason Patient Intubated *(check all that apply)*	☐ Requiring FiO2 > .40 for more than 2 hours to maintain SpO2 >90% ☐ Any 2 blood gases 2 hours after randomization: (pH 7.15 or less **OR** paCO2 > 65 mmHg) ☐ MD decision ☐ Apnea ☐ Surfactant administration ☐ Other: _____

Affix patient label to back of this card

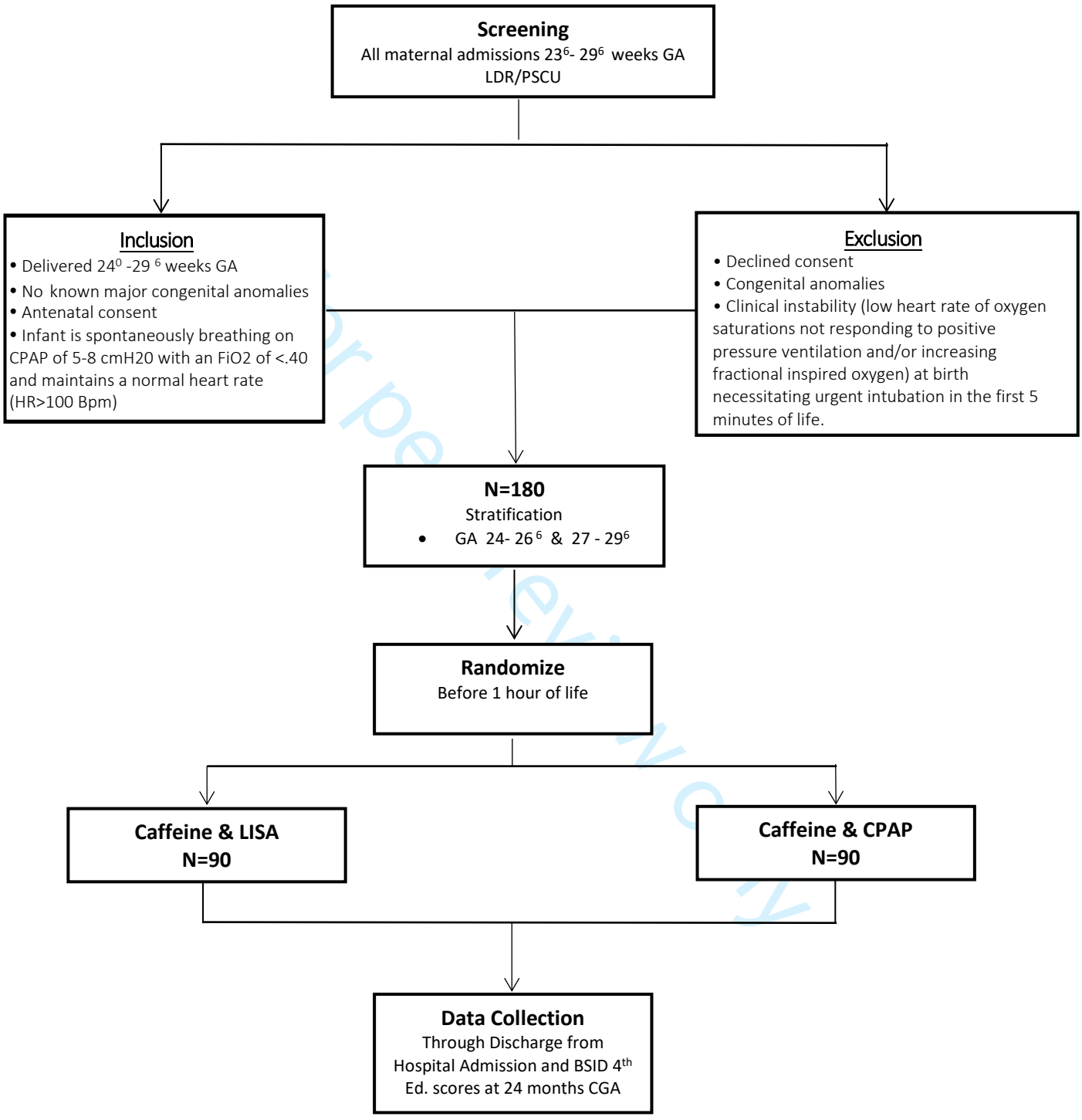
Completed By

Printed Name: _____**Initials:** _____**Date:** ____/____/_____

Sharp Mary Birch Hospital for Women & Newborns. (2020). CaLI Study Intubation Card. v1.0

(Supplemental File 3)

CaLI Study Overview Diagram (Supplemental File 4)



Sharp Mary Birch Hospital for Women & Newborns 2020, Legend: BSID-Bayley Scales of Infant Development, CPAP- Continuous Positive Airway Pressure, GA-Gestational Age, LDR- Labor and Delivery Room, LISA- Less Invasive Surfactant Administration, PSCU- Perinatal Special Care Unit

Figure 1. CaLI Study Patient Timeline

Assessment	On admission prior to study treatment	0	5'	15'	30'	1-h	2-h	6-h	12-h	24-h	2-d	3-d	Day 28	36-WK PMA	Discharge home	24-m BSID
Inclusion/Exclusion Criteria	×															
Parental Informed Consent	×															
Apgar Score	×	×	×													
Demographic data (weight)	×		×										×	×	×	×
Oxygen Saturation (SpO2)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Vital Sign (HR)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Fraction of Inspired Oxygen (FiO2)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
CPAP Level	×	←													→	
Caffeine Therapy	×	←													→	
Bronchopulmonary Dysplasia (BPD)													×	×	×	
Severe Adverse Events (SAEs)	×	←													→	
Bayley Scales of Infant Development (BSID)																×

Parental Informed Consent will be obtained prior to birth. Vital signs will be obtained at randomization and during surfactant administration. SAEs are surfactant administration procedure-related and or death prior to discharge.

× *indicates continuous monitoring* ←→ *indicates possible discontinuation during hospital admission*

Sharp Mary Birch Hospital for Women & Newborns (version 21OCT2020)

SHARP Mary Birch Hospital for Women & Newborns

INFORMED CONSENT

A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

IRB #
1911902

Consent Date
06Aug2020 v1.2

Principal Investigator

Anup Katheria, MD
Neonatal Research Institute
SHARP Mary Birch Hospital for Women and Newborns
3003 Health Center Drive, San Diego, CA 92123

Research Grant

Chiesi Farmaceutici S.p.A.

If you are serving as a legally authorized representative, a guardian or are providing parental permission for a child in this study, the terms "you" and "your" refer to the person for whom you are providing consent or parental permission.

CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in an experimental procedure. Before you decide whether you want to participate in the experimental procedure, you have a right to:

1. Be informed of the nature and purpose of the experiment;

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

3. Be given a description of any discomforts and risks reasonably to be expected from your participation in the experiment;

4. Be given an explanation of any benefits reasonably to be expected from your participation in the experiment;

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to you, and their relative risks and benefits;

6. Be informed of the avenues of medical treatment, if any, available to you after the experimental procedure if complications arise;

7. Be given an opportunity to ask any questions concerning the medical experiment or the procedures involved;

8. Be instructed that consent to participate in the experimental procedure may be withdrawn at any time and that you may discontinue participation in the medical experiment without prejudice;

9. Be given a copy of this form and the signed and dated written consent form; and

10. Be given the opportunity to decide to consent or not to consent to the medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on your decision.

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

Signature of Parent or Legally Authorized Representative	Printed Name	Date

PARTICIPATION IN A RESEARCH STUDY

This is a research study. The purpose of a research study is to answer scientific questions. We are asking for your permission to have your baby participate in a research study so that we can learn new information that may help others in the future. Research is not the same as routine treatment or medical care.

Your participation is voluntary. You do not have to allow your baby to be in this study. You are free to say yes or no, or to allow your baby to drop out after joining. If you decide not to participate there is no penalty or loss of benefits. Whatever you decide, your baby's regular medical care will not change.

This process is known as the informed consent process. It is important that you read this consent form and ask the study doctor any questions you may have. Please take your time to make your choice. Discuss it with your friends and family.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

Your baby has been chosen because he/she may be born prematurely with immature lungs and a lack of natural lung surfactant, a fluid that coats the lungs and help them remain open. Due to this condition, your baby may not breathe well at birth or in the first days after birth and may benefit from receiving surfactant medicine or continuous airway pressure to help your baby's lungs remain open and improve oxygenation. Both Surfactant administration and continuous positive airway pressure (CPAP) are currently standard treatments for premature infants that need respiratory support after delivery.

Surfactant administration traditionally involves inserting a breathing tube in your baby's airway (intubation) and placing them on a breathing machine for respiratory support. Continuing on a breathing machine for a long period of time increases your baby's chance of developing bronchopulmonary dysplasia (BPD), a chronic lung disease of the neonate. Delivery room resuscitation of very premature infants has evolved dramatically over the past decades. Optimizing the care of these newborns now involves early continuous positive airway pressure (CPAP) and the avoidance of mechanical ventilation. However, mechanical ventilation is still often used when administering surfactant as the need arises.

The LISA method (Less Invasive Surfactant Administration) is another method that involves using a small catheter to administer surfactant directly into a baby's lungs. It also involves administering a precautionary dose of surfactant, compared to the traditional method which only administers doses of surfactant as needed using the breathing tube. A recent study in Europe showed that the Less Invasive Surfactant Administration (LISA) method had the lowest risk for the development of bronchopulmonary dysplasia (BPD) when compared to mechanical ventilation. Despite these results showing it decreased the need for mechanical ventilation compared to CPAP alone, there have been no studies done in the United States and the use of the LISA method is still not widely accepted.

We are conducting this study to find out if infants that receive surfactant by the LISA method (study method) compared to early CPAP and mechanical ventilation (standard method) require less intubation and less days on respiratory support.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 180 babies will take part in the study. We will enroll 120 babies at Sharp Mary Birch Hospital for Women & Newborns, 30 babies at Loma Linda University Medical Center, and 30 babies at University of California Irvine Medical Center.

HOW LONG WILL YOU BE IN THE STUDY?

Your baby will be in this study from birth through 2 years of age. We will also collect information about your baby from the 2-year follow-up visit described below.

WHAT IS INVOLVED IN THIS STUDY?

We are asking for your permission to have your baby be in a research study so that we can learn new information that may help other babies.

If you decide to let your baby take part in the current research study and your baby needs support with breathing, your baby will be given CPAP through the nose. If your baby's breathing remains stable, he/she will be randomized (meaning based on chance, like flipping a coin) to either continuing on CPAP or being given a medicine called surfactant. The surfactant medicine is a small volume of liquid that will be placed directly into your baby's lungs using a small catheter (a small flexible tube). This is called the LISA method. This medication helps keep your baby's lung inflated and improves oxygenation.

Your baby will have a 50/50 chance of being placed in either group (CPAP or LISA). After your baby is placed on CPAP or given surfactant, he/she will be carefully monitored.

In either case if your baby needs more help with breathing, your baby's doctor will decide the best way to help support your baby's breathing which may include placement of an endotracheal tube into your baby's airway.

In some cases, your baby may require additional surfactant, if they are not breathing well or continue to need increased support such as additional oxygen. If your baby is in the CPAP group and becomes unwell in this study, your baby's doctor may decide to provide an initial dose of surfactant, and maybe more doses, as needed. This would require insertion of a regular endotracheal breathing tube (if not already placed), which is the current standard practice for providing surfactant.

If your baby is in the LISA group and becomes unwell in this study, your baby's doctor may decide to provide additional doses of surfactant as needed. This will be done by insertion of a regular endotracheal tube.

The procedures of the study are described below. The decision for treatment will be made at the first 5 minutes after your baby's birth.

- The doctor will evaluate your baby's condition at birth. If your doctor determines that your baby needs immediate placement of an endotracheal tube to assist breathing, your baby will not be in the study. Babies who are intubated at birth will not be in the study.

- If your baby is stable and breathing on his/her own with CPAP, he/she will be randomized to either the LISA group with CPAP or CPAP alone. This is done by selecting an envelope which contains a card telling the team which treatment the baby will receive.

During the NICU hospitalization, your baby will be continuously monitored to check the health of your baby's heart, brain and lungs and overall condition. This is normally part of the standard care for preterm babies.

OUTPATIENT FOLLOW-UP

All premature babies are evaluated periodically (at 6 months, then once a year) as part of routine care at the Nemeth NICU Follow-up Clinic during the first 2 years of life. At these visits, the doctors and nurses who work at the clinic will check your baby's health and development. At every visit, they will ask questions about your living arrangements and your baby's medical condition. They will evaluate your baby's development using toys and items that are part of a developmental test. They will do a physical exam and check your baby's muscle strength and reflexes (neurologic exam).

WHAT IS THE RESEARCH PART OF OUTPATIENT FOLLOW-UP?

The research visit is between 22-26 months corrected age (2 years from your baby's original due date). At this visit, the doctors and nurses will do everything listed above that is routine for your infant given their prematurity. The results of the routine evaluation will be obtained as part of our data collection. We will use a study number, not your child's name to ensure confidentiality and anonymity of your medical information.

After that, your baby's involvement will be completed and there are no further study requirements for your baby.

WHAT ARE THE RISKS OF THE STUDY?

Both methods of administering surfactant either by the LISA method or the endotracheal tube are practiced in our NICU. The surfactant used in this trial is our current standard surfactant.

You should note:

- Infants randomized to the LISA group could receive an extra dose of surfactant when they otherwise might not have if they were not part of the study.
- Infants randomized to the CPAP group may receive mechanical ventilation that they otherwise might not have if they were not part of the study
- The catheter used in the LISA method is being used off-label, meaning it is used in a way that is different from the FDA's approved packaging label. It is used intratracheally (into the trachea) rather than intravenously (into the vein).

Risks of surfactant include:

- Low blood oxygen level
- Slow heart rate
- Low blood pressure

Risks of Intra-tracheal catheter:

- There may be risks that are unknown at this time

Risks of mechanical ventilation include:

- Volutrauma- over expansion of the lungs by delivery of too much gas
- Pneumothorax- is a collapsed lung
- Pneumonia- lung infection
- Development of Bronchopulmonary Dysplasia (BPD)- a chronic lung disease that affects premature infants

Based on the current literature to date, there are no increased risks with less invasive administration of surfactant with a small catheter (i.e. the LISA method) compared to endotracheal administration of surfactant in several large European trials. All risks with conducting this study are associated with prematurity including severe IVH, death, retinopathy of prematurity, chronic lung disease and other lung problems such as possible air leaks. There should be no more risks for babies in this study than are possible for any Extreme Low Birth Weight (ELBW) baby needing surfactant therapy. However, as with all research, there may be risks that are unknown at this time.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There may or may not be direct benefits to your baby for participating in this study. We hope the information we learn will help babies with respiratory distress syndrome in the future.

WHAT OTHER OPTIONS ARE THERE?

Your baby's alternative is to not participate in this study and receive treatment of Respiratory Distress Syndrome as prescribed by your personal physician. Your doctor will discuss these alternative treatments with you as well as their benefits and risks.

WILL YOU OR YOUR CHILD BE PAID TO BE IN THIS STUDY?

You and your child will not be paid to be in this study. No additional compensation is available for participation in this study.

WHAT ARE THE COSTS?

The study drug, Curosurf, will be provided for you at no cost by the study sponsor.

There are no additional costs to be in this study. You and/or your health plan/insurance company are responsible for the cost of your baby's hospitalization and standard clinical care provided. You will be responsible for co-pays and deductibles in the same way as outside of a clinical trial.

For more information about your costs, please discuss with the hospital's billing department, or call your health plan/insurance company to find out your financial responsibility for this trial.

RESEARCH-RELATED INJURY

If your baby gets sick or injured in this study, please tell your study doctor. Your baby will be treated or referred for medical treatment. You or your insurance will be responsible for the cost of treatment.

Sharp HealthCare will not provide any compensation for treatment of research related injury or illness.

PAYMENT TO STUDY SITE

CHIESI has provided a grant to Sharp Mary Birch Hospital for Women & Newborns to reimburse the study site for expenses related to the conduct of this study. This includes providing the Surfactant medication your baby may receive while in the study.

NEW INFORMATION

You will be told if any important new information is found during the course of this study that may affect your wanting to continue. If you decide to continue in the study, your study doctor may ask you to sign an updated consent form.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Organizations or individuals that may inspect and/or copy your medical and/or research records for quality assurance and data analysis include groups such as:

- Study Doctor and Research Staff at the Neonatal Research Institute
- Sharp HealthCare Institutional Review Board (IRB, a group of people who review the research to protect your rights)
- The Food & Drug Administration (FDA)

Your information will be coded and stored anonymously in a database with information about other people in this study. Access to this database is limited to the research staff.
Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

As part of this research study you will be asked to sign an additional document, Authorization to use Protected Health Information (PHI). This authorization will explain in further detail how your and your baby's PHI will be used and shared in the study, who will have access to it, what information will be obtained, and how long Sharp HealthCare will use your information. It will also explain what to do if you decide you no longer want to share your PHI, and your rights regarding your ability to see and copy your research information.

If the results of this study are published or presented at meetings, your identity will remain confidential.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Participating in this study is entirely voluntary. You may refuse to allow your baby to participate or withdraw your baby at any time without penalty or loss of benefits to which you or your baby are entitled. If you decide that you no longer want your baby to continue in this study, we encourage you to talk to the study doctor. Please contact Dr. Katheria to tell him you no longer want to participate:

Dr. Anup Katheria
(858) 939-4170
Anup.katheria@sharp.com

If you decide to remove your baby from the study, the study team may ask your permission to keep your baby's test results and information that has already been collected.

WHOM DO YOU CALL IF YOU HAVE ANY PROBLEMS, COMPLAINTS, CONCERNS, OR QUESTIONS?

If you have problems, complaints, concerns, or questions about this study, you may talk to your study doctor anytime.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	858-939-4170 Dr. Anup Katheria 858-939-6307 Neonatal Research Institute
If you get sick or hurt in this study	858-939-4170 Dr. Anup Katheria
Your rights as a research participant and: • Discuss problems, concerns, and questions • Obtain information	Sharp HealthCare Institutional Review Board 7930 Frost Street, Suite 300 San Diego, CA 92123 (858) 939-7195

WHERE CAN YOU GET MORE INFORMATION?

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you or other participants. At most, the web site will include a summary of the results. You can search the web site at any time. The registration identifier for this study is NCT#04209946.

STATEMENT OF CONSENT

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you carefully consider whether you agree to have your child take part in this study and how your and your child's information will be used.

You can change your mind later if you want to. You will be given a copy of this consent form including a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

You agree to participate in this research study.

Printed Name of Participant (Baby)

SIGNATURE OF PARENT OR LEGALLY AUTHORIZED REPRESENTATIVE **PRINTED NAME** **DATE**

AUTHORITY OF SIGNEE OR RELATIONSHIP TO PARTICIPANT

SIGNATURE OF PRINCIPAL INVESTIGATOR/DESIGNEE **PRINTED NAME** **DATE**

---------- **USE THE FOLLOWING ONLY IF APPLICABLE** ----------

If this consent form is read to the participant because the participant is unable to read the form, an impartial witness not affiliated with the research or study doctor must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant. The participant freely consented to be in the research study.

PRINTED NAME OF IMPARTIAL WITNESS

SIGNATURE OF IMPARTIAL WITNESS **DATE** **TIME**

NOTE: *This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling participants who do not speak English.*

Authorization to Use your Protected Health Information (PHI)

Study Title: A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

Investigator: Anup Katheria, MD
Neonatal Research Institute
Sharp Mary Birch Hospital for Women & Newborns

Research Grant: Chiesi Farmaceutici S.p.A

Protected Health Information, or PHI, is any personal health information through which you or your baby can be identified. We are asking for your permission to use your baby's PHI in this research study. The information we may use includes maternal (prenatal) data from your baby's record, your baby's present health information, information that can be used to contact you, and results of your and your baby's medical tests. Maternal data will be collected from your baby's medical record; your medical record will be accessed for study purposes. The specific items of information that will be used and disclosed include:

- Maternal (prenatal) information related to the health of your baby, including:
  - Information about mother's pregnancy
  - Fetal History
  - Pregnancy complications
  - Medications for mother
  - Delivery record
- Information from your baby's medical record, including:
  - Medications for baby
  - Results of lab tests
  - Blood gases
  - Respiratory management

- Vital signs
- Diagnoses

The following people will access and use your baby's PHI for the purpose of this research:

- Dr. Anup Katheria, Primary Investigator, Sharp Mary Birch Hospital for Women & Newborns
- Sharp Mary Birch Hospital Neonatologists
- Research Staff at Sharp Mary Birch Hospital for Women & Newborns

Who may see your PHI?

Certain offices and people other than the researchers may look at your medical charts and study records. There may be times when federal or state law requires the sharing of such records. This is very unlikely, but if sharing the information is ever required, Sharp Mary Birch Hospital for Women & Newborns will take steps allowable by law to protect the confidentiality of personal information. If this information is shared with outside reviewers for audit purposes, it may be further shared by them and may not be covered by the federal privacy laws.

Representatives that may review your study records:

- the Sharp HealthCare Institutional Review Board (IRB; a group of people that review the research to protect the rights of research participants)
- the US Food and Drug Administration

How long will the Neonatal Research Institute use your information, and what will it be used for?

- Your and your baby's PHI may be used and shared until December 31, 2044.

The groups above will use your health information:

- To complete this research
- To evaluate the results of the study
- To check that the study is being done properly

What if you change your mind and want to withdraw your authorization for the use and disclosure of your PHI for this study?

You must write to the study doctor and tell him that you no longer want to share your child's information at: Anup Katheria, MD. Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, 3003 Health Center Drive, San Diego, CA 92123.

- Your baby will no longer be a part of the research study because the study doctor, and the research staff will not be able to use any new information about your baby.
- The research team can continue to use any of the PHI that was already collected.
- You and your baby will still get the same medical care that you have always had from Sharp Mary Birch Hospital for Women & Newborns.

Do you have the right to see and receive a copy of your research information?

You can see your research information if:

- It is also being used for your and your baby's current treatment, or
- At the end of the study.

****

Authorization:

If you agree to share your and your baby's PHI, you must sign this form below. If you do not sign this form, you and your baby will not be able to participate in this research study. You will be given a copy of this form.

_____

Printed Names of Mother and Baby

_____

Signature of Mother or Legally Authorized Representative | Printed Name | Date

_____

Signature of Father | Printed Name | Date

_____

Authority of Signee or Relationship to Participant

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.