

THE SUSTAINED AERATION OF INFANT LUNGS (SAIL) STUDY

PROTOCOL

Sponsor	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH Grant Number	1-U01-HD072906-01A1
Protocol Number	Penn IRB# 819208
Clinical Trials.gov Number	NCT 02139800
Version Number & Date	Version 2.7 March 15, 2017

Protocol Summary

Study Title	The Sustained Aeration of Infant Lungs (SAIL) Study
Sponsor	National Institutes of Health (NIH), Eunice Kennedy Shriver National Institute of Child Health and Human Development
Population	Preterm infants born between 23-26 weeks gestational age
Primary Objective	To determine in preterm infants needing respiratory support at birth, which of two lung opening strategies – either a standard positive-end expiratory pressure /continuous positive airway pressure (PEEP/CPAP) of 5-7 cm H ₂ O in the delivery room as compared to early lung recruitment using Sustained Inflation (SI) in the delivery room, will result in a lower rate of the combined endpoint of death or bronchopulmonary dysplasia (BPD) at 36 weeks gestational age
Design and Sample Size	This prospective multi-national randomized controlled trial (RCT) is a two-arm parallel design of two alternative courses of treatment. 600 preterm infants – 300 control / 300 intervention
Inclusion Criteria	Infants who are born in participating NICUs (which do not use prophylactic surfactant) and who fulfill the following inclusion criteria are eligible for enrollment: (a) Gestational age (GA) at least 23 weeks but less than 27 completed weeks by best obstetrical estimate; (b) requiring resuscitation/respiratory intervention at birth – “apneic, labored breathing, gasping” (as defined in NRP 2011 AAP 6th Edition p. 45.)
Outcomes and Analytic Approach	The primary outcome to be used for efficacy evaluation is rate of death or BPD at 36 weeks gestation age. Analysis of the primary outcome will be intention-to-treat comparisons between treatment arms. Secondary outcomes include clinical measures collected from the first 10 days of life as well as neurodevelopment and respiratory outcomes at 22-26 months of corrected age in survivors. Secondary outcomes will be analyzed using similar procedures to the primary outcome comparisons between treatment arms.
Interim Analysis	2 interim analyses conducted when 1/3 and 2/3 participants complete primary outcome. An additional SAE safety analysis after 100 subjects complete.
Clinical Centers	21 multi-national sites (USA, Canada, Italy, Germany, Netherlands, Australia, Austria, Singapore, S. Korea)
Enrollment Period	2.5 years
Study Duration	5 years
ClinicalTrials.Gov Trial Link	http://www.ClinicalTrials.gov
Registration Number	NCT 02139800
Registration Title	www.sailtrial.org The Sustained Aeration of Infant Lungs (SAIL) Study

Modifications Made in Protocol Version 2.7 dated 20170315

Modification: Page 6: The version on the Investigator Agreement Page was changed to Version 2.7_20170315.

Modification: Page 14: The SAIL research network diagram was modified to reflect the addition of 7 new sites – Christiana Care, Wake Med Health, Loma Linda University, KK Women’s and Children’s Hospital, Mater Mother’s Hospital, Seoul National University, and Samsung Medical Center.

Modification: Page 15: The list of participating centers in Section 3.2 was modified to include the site names and site investigators.

LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ACS	Antenatal Corticosteroids
AE	Adverse events
ANCS	Antenatal Corticosteroid
BAC	Biostatistics Analysis Center
BPD	Bronchopulmonary Dysplasia
BPM	Beats per minute
BSID	Bayley Scale of Infant Development
BW	Birth weight
CAP	Caffeine for Apnea of Prematurity trial
CCC	Clinical Coordinating Center
cGA	Corrected Gestational Age
COI	Conflicts of Interest
COIN	Continuous Positive Airway Pressure or Intubation at Birth Trial
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRCU	Clinical Research Computing Unit
CXR	Chest x-ray
DCC	Data Coordinating Center
DR	Delivery room
DSMC	Data Safety Monitoring Committee
ELGAN	Extremely Low Gestational Age Newborns
ENaCs	Epithelial Sodium Channels
FiO ₂	Fraction of inspired oxygen
FRC	Functional Residual Capacity
FWA	Federal Wide Assurance
GA	Gestational age
GEE	Generalized estimating equation
GMFCS	Gross Motor Function Classification System
HR	Heart rate
HUP	Hospital of the University of Pennsylvania
IC	Informed consent
IDE	Investigational Device Exemption
ILCOR	International Liaison Committee on Resuscitation
IND	Investigational New Drug
IPPV	Intermittent positive pressure ventilation
IRB	Institutional review board
IT	Information technology
IQR	Interquartile range
IVH	Intraventricular hemorrhage

MAP	Mean airway pressure
MRI	Magnetic resonance imaging
MR SOPA	Mask, readjustment, suction airway, open mouth, increase pressure, alternative airway
nCPAP	Nasal continuous positive airway pressure
NDI	Neurodevelopmental impairment
NICHHD	(Eunice Kennedy Shriver) National Institute of Child Health and Human Development
NICU	Neonatal intensive-care unit
NIH	National Institute of Health
NRP	Newborn (or Neonatal) Resuscitation Program
OHRP	Office for Human Research Protections
ORT	Oxygen Reduction Test
PaO ₂	Partial pressure of oxygen in blood
PCO ₂	Carbon Dioxide partial pressure
PDA	Patent ductus arteriosus
PEEP	Positive end-expiratory pressure
PIE	Pulmonary interstitial emphysema
PINT	The Premature Infants in Need of Transfusion Study
PIP	Peak inspiratory pressure
PMA	Postmenstrual age
PPV	Positive pressure ventilation
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
RT	Respiratory therapist
SAE	Serious Adverse Events
SAIL	Sustained Aeration of Infant Lungs
SD	Standard deviation
SGA	Small for gestational age
SI	Sustained inflation
SNAPPE	Score for Neonatal Acute Physiology Perinatal Extension
SpO ₂	Blood oxygen saturation
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial
TIPP	Trial of Indomethacin Prophylaxis in Preterm Infants
UAC	Umbilical artery catheter
UVC	Umbilical venous catheter

INVESTIGATOR AGREEMENT PAGE:

The Sustained Aeration of Infant Lungs (SAIL) Study (Version 2.7_20170315)

INVESTIGATOR (S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of subjects.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I will ensure that the requirements relating to obtaining HIPAA authorization following the federal mandate for disclosure of access to data and associated privacy protection will be met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
- I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments by providing them with copies of the protocol, any subsequent protocol amendments, and access to all information furnished by the sponsor.

Principal Investigator Signature

Date

Name (Please Print)

Institution

Once signed, this original shall be maintained in the Regulatory Binder at the clinical center, with a copy emailed or faxed to the DCC Project Manager (215-573-6262).

Contents

1. Introduction	9
1.1. Background	9
2. Study Objectives	12
2.1. Hypotheses	12
2.2. Specific Aims	12
3. Study Team	13
3.1. Research Leadership	13
3.2. Participating Clinical Sites	15
3.3. Data Coordinating Center (DCC)	15
3.4. NICHD Sponsorship	16
4. Trial Conduct	16
4.1. Identifying Potential Participants	16
4.2. Consent	16
4.3. Study Design	16
4.4. Study Population	16
4.4.1. Inclusion Criteria	16
4.4.2. Exclusion Criteria	17
4.4.3. Trial Withdrawals	17
4.4.4. Randomization Criteria and Methods	17
4.5. Intervention Maneuvers in Delivery Room	18
4.5.1. Control Arm Infants	21
4.5.2. Intervention Arm Infants	21
4.5.3. Data Collection for Non-eligible Infants	24
4.5.4. Training and Standardization of Research Intervention	24
4.6. Random Allocation in the Delivery Room	25
5. Study Data	26
5.1. Maintaining Adherence to Algorithms and Minimizing Protocol Deviations	29
5.1.1. Potential Confounders and Strategy to Limit Impact	30
6. Statistical Analysis	31
6.1. Statistical Plan	31
6.1.1. Sample Size Determination	31
6.1.2. Methods of Analysis	31
6.1.3. Analysis of Secondary Outcomes	33

6.2.	Interim Analysis	33
7.	Trial Management	35
7.1.	Data Security	35
7.2.	Data Sharing	35
7.3.	Data Safety Monitoring Committee (DSMC)	36
7.3.1.	Composition and Function of the DSMC	36
8.	Research Ethics.....	38
8.1.	Consent Options	38
8.1.1.	Consent Approach and Consent Form for Families.....	39
8.2.	Risks of Study Participation	41
8.3.	Data Confidentiality.....	42
9.	Regulatory Oversight	43
9.1.	Conflict of Interest.....	45
9.2.	Collecting and Reporting Adverse Events	45
9.2.1.	Adverse Events (AE).....	45
9.2.2.	Serious Adverse Events (SAE)	45
9.2.3.	Clinical Events Defined	47
9.2.4.	Unanticipated Problems.....	47
9.2.5.	Adverse Event Management and Reporting	47
10.	Synopsis	48
11.	References	49

1. Introduction

This research study funded by the NICHD, is a Phase III randomized controlled trial (**RCT**), which aims to provide evidence for changing policy or standard of care. The context of this trial is an unacceptable rate of poor long-term outcomes of preterm infants born as Extremely Low Gestational Age Newborns (**ELGAN**) <1000 g birthweight (**BW**), but especially for those born between 23-26 weeks' gestational age (**GA**). Such infants are the most vulnerable and immature in all organ systems, including the lungs and the brain. These infants are at high risk of death and bronchopulmonary dysplasia (**BPD**) during their initial hospitalization, neurodevelopmental impairment (**NDI**) and pulmonary problems in infancy and childhood.

The SAIL trial focuses on facilitating the difficult transition of these most vulnerable infants from a liquid filled *in-utero* lung to an *ex-utero* air-filled lung. Sustained Inflation (SI) is a promising delivery room (DR) intervention, with evidence of short-term efficacy with minimal risk of additional harm beyond current standard accepted Newborn Resuscitation Programme (NRP) Guidelines. This protocol proposes a fully informed consenting procedure. We propose to evaluate the impact of a SI in the DR on the need for mechanical ventilation in the first week of life which would also impact mortality rates and the incidence and severity of BPD.

1.1. Background

Extreme prematurity makes the transition from intra-uterine life to extra-uterine life more difficult. During this transition - termed the 'Golden Hour' – the newborn must generate the critical opening pressure to aerate her/his lungs, remove the amniotic fluid and lung liquid to fill the lung with air to enable extra-uterine life. This requires an enormous physiological change and energy cost. Normally, high ambient oxygen, cord clamping, cold and other external stimuli will trigger breathing. However, the ELGAN infant has a compliant chest wall prone to collapse and weak respiratory muscles, and cannot cope with the high work of breathing. This work is increased in the presence of retained amniotic liquid. Most ELGANs are born by cesarean delivery, often without adequate labor. This retards the activation of the sodium channels (ENaCs), that switch the lung from a Na secreting to a sodium absorbing state, ensuring residual lung water.

We know that establishing uniform aeration also called an 'open lung' prevents lung injury.(1) Performing this well in the DR provides the best start to the critical first days of life. Yet the best manner to achieve this is poorly studied. In this trial we compare two alternative methods that have both received an AAP ILCOR-2010 endorsement. Positive-end expiratory pressure (PEEP) is now routinely used in the DR to establish and maintain functional residual capacity (FRC) and its use is well supported by data. There is some weak evidence that an alternative method, SI may help. Indeed in many parts of Europe the practice of SI has become a standard approach ([Appendix 1](#)) – Letters from Ulm Germany and Leiden Netherlands). However, a lack of high quality evidence and uncertainty about its safety make the current creep into more general practice, problematic.

The underlying trial rationale is that augmenting PEEP by a SI will facilitate clearance of lung fluid and more effectively develop a stable FRC. The SAIL trial will promote evidence-based practice, by conducting a 600 patient prospective multi-center trial targeting clinically important outcomes. SAIL will randomize eligible infants to one of two methods of ensuring early DR lung aeration: the initial delivery of PEEP alone; or PEEP supplemented by SI. The combined primary outcome, BPD or death at 36 weeks, is well established, robust and clinically meaningful. Treatment assignment will be masked at the time of developmental follow-up and the outcome of BPD will be according to a blinded assessment of the Oxygen Reduction Test (ORT).¹ The SAIL trial addresses two unanswered, but important questions:

Firstly, “In preterms 23-26 weeks (GA) who require resuscitation and/or respiratory support in the DR, which of two alternative strategies to achieve lung aeration results in the lowest rate of death or BPD at 36 corrected weeks of age?”

Secondly, “In preterms 23-26 weeks (GA) who require resuscitation and/or respiratory support in the DR, what are the safety profiles of 2 currently used methods in the DR to achieve lung aeration?”

In addition to this primary outcome, we will describe several clinically relevant and/or physiologically relevant secondary outcomes, including: FiO₂, respiratory support, surfactant use, radiographic evidence of RDS, % of infants ever intubated, head ultrasound, duration of respiratory support; respiratory severity score (FIO₂ x mean airway pressure).

There are two defined ancillary studies that will be conducted within the trial. At one site (Ulm) we will have nirosopy brain recordings, and at several sites, we will obtain flow volume pressure records during and after SI in the DR.

- Thousands of babies per year die or develop BPD in the US. BPD is a costly chronic childhood illness. In a study of health care expenditure among children, BPD ranked second for total payments of \$2.4 billion annually (Appendix 2 - <http://www.lung.org/lung-disease/bronchopulmonary-dysplasia/>). Survivors with BPD often suffer serious pulmonary and/or neurodevelopmental sequelae. While extremely-low birth-weight (<1000 g at birth) infants are at high risk of death or BPD, the most vulnerable are those born between 23 and 26 weeks' GA. In this population, the rate of death or BPD was 68% in the recent SUPPORT trial.² Despite a significant amount of research designed to prevent BPD, there has been little improvement in the incidence or severity of the disease. Novel interventions are urgently needed.

The SUPPORT Trial evaluated both continuous positive airway pressure (CPAP) for infants breathing spontaneously, and PEEP during intermittent positive pressure ventilation in the DR. Both approaches help to establish and maintain FRC, which aerates the newborn lung. Several trials demonstrate that CPAP can be safely delivered in the DR, but do not reduce the incidence or severity of BPD.

These have been taken into account in the design of this trial. At the time of submission of the trial for peer-reviewed funding, the ILCOR-AAP 2010 statement (Appendix 3) stated:

“End-Expiratory Pressure: “There is no evidence to support or refute the use of CPAP in the delivery room in the term baby with respiratory distress.” (Page 1404 column 3). ILCOR states earlier in this section, that in preterm babies the situation is different:

“Although positive end–expiratory pressure (PEEP) has been shown to be beneficial and its use is routine during mechanical ventilation of neonates in intensive care units, there have been no studies specifically examining PEEP versus no PEEP when PPV is used during establishment of an FRC following birth. Nevertheless, PEEP is likely to be beneficial and should be used if suitable equipment is available (Class IIb, LOE C). PEEP can easily be given with a flow-inflating bag or T-piece resuscitator, mechanical ventilation (Class IIb, LOE B). The most appropriate choice may be guided by local expertise and preferences” (Page 1404 Column 2-3).

- After the meta-analysis contained in ([Appendix 4](#)) of pooled results of the three main trials evaluating CPAP vs other approaches for such small infants in the DR – it was clear the point estimate favors CPAP.
- As a result of these considerations, the standard of care at HUP ([Appendix 5](#)) has incorporated CPAP as the first line in the DR for these very small infants. In synopsis, this adopted the view that: ***“even for infants who eventually require intubation, there is no evidence of harm associated with starting CPAP in the delivery room.*”**

The approach of using PEEP-CPAP in the DR as an initial means of support has now been widely adopted in the US.³ It is now considered as the appropriate standard of care in the Hospital of Pennsylvania (HUP) NICU, and a recent quality improvement project targeted successful DR-CPAP intervention.

Finally to emphasize that our approach does not depart from current standards of care, three very recent statements of the Committee on Fetus Newborn of the American Academy of Pediatrics (AAP) point out:

1. Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Strong Recommendation)([Appendix 6](#))

This message is reinforced in another recent statement:

2. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with surfactant is delayed or not given (Level of Evidence: 1).
3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy (Level of Evidence: 1).([Appendix 7](#))

Therefore the use of CPAP in the DR for these infants should be considered a standard of care in North America and other developed parts of the world.

We propose however, that a new approach to actively recruit lung capacity in the DR would reduce the need for mechanical ventilation and further decrease morbidity and mortality in the most vulnerable preterms. While the NRP guidelines are accepted as the standard routine resuscitation of premature infants, the NRP does not have a specific algorithm for extremely premature infants. The NRP algorithm

for term infants is adapted for the premature infant population. The SAIL study is in a unique position to offer a possible algorithm specifically designed for the ELGAN population. The NRP Committee has been extremely supportive of this trial and wishes to see such a study performed to help guide its future advice.

2. Study Objectives

2.1. Hypotheses

(i) Early lung recruitment with SI superimposed upon standard PEEP/CPAP in the DR will reduce the need for mechanical ventilation in the first seven days of life, and reduce need for surfactant use; and (ii) A policy of DR SI on standard PEEP/CPAP recruitment will confer better outcomes at 36 weeks post-menstrual age (PMA) than standard PEEP/CPAP.

We will test these hypotheses in a multi-site randomized trial with the following specific aims:

2.2. Specific Aims

- 1) To determine in 600 infants born at 23-26 weeks GA requiring respiratory support at birth, which of two lung opening strategies – either a standard PEEP/CPAP of 5-7 cm H₂O in the DR, compared to early lung recruitment using SI in the DR, results in a lower rate of the combined endpoint of death or BPD (using a standardized oxygen reduction test) at 36 weeks PMA.
- 2) To compare the rates of other important secondary outcomes such as:
 - a. Detailed outcomes of potential importance in the first 10 days of life:
 - i. Heart rate in the DR
 - ii. Detailed status on departure from the DR
 - iii. Use of inotropes on arrival in NICU
 - iv. Chest X-ray reports showing pneumothorax or new chest drains in the first 48 hours of life;
 - v. Need for new chest drains after NICU admission
 - vi. Duration of any chest drain in-situ post-DR
 - vii. Oxygen profile over first 24 hours post DR using hourly FiO₂ records
 - viii. Oxygen profile with highest FiO₂ up to 48 hours
 - ix. Head US and/or MRI findings of intraventricular hemorrhage by all grades but especially focusing on grades 3 and 4 by 48 hour and by day 10, if clinically available
 - x. CXR appearance between days 7-10, if clinically obtained
 - b. Components of the primary outcome (i.e. death by 36 weeks PMA or BPD at 36 weeks PMA)
 - c. Need for intubation in DR or by 24 hours of age
 - d. Pressure-volume characteristics in the DR (at several but not all sites)
 - e. Death or need for positive pressure ventilation at 7 days
 - f. Highest FiO₂ and Area under the curve FiO₂ for first week of life

- g. Survival to discharge home without BPD, retinopathy of prematurity (grades 3 & 4), or significant brain abnormalities on head ultrasound
- h. Pneumothorax and pulmonary interstitial emphysema (PIE)
- i. Duration of respiratory support (ventilation, CPAP, supplemental oxygen)
- j. Retinopathy of prematurity (ROP) stage 3 or greater requiring treatment
- k. Death before discharge
- l. Use of postnatal steroids for treatment of BPD
- m. Length of hospital stay
- n. Neurodevelopmental and respiratory outcome at 22-26 months corrected GA

3. Study Team

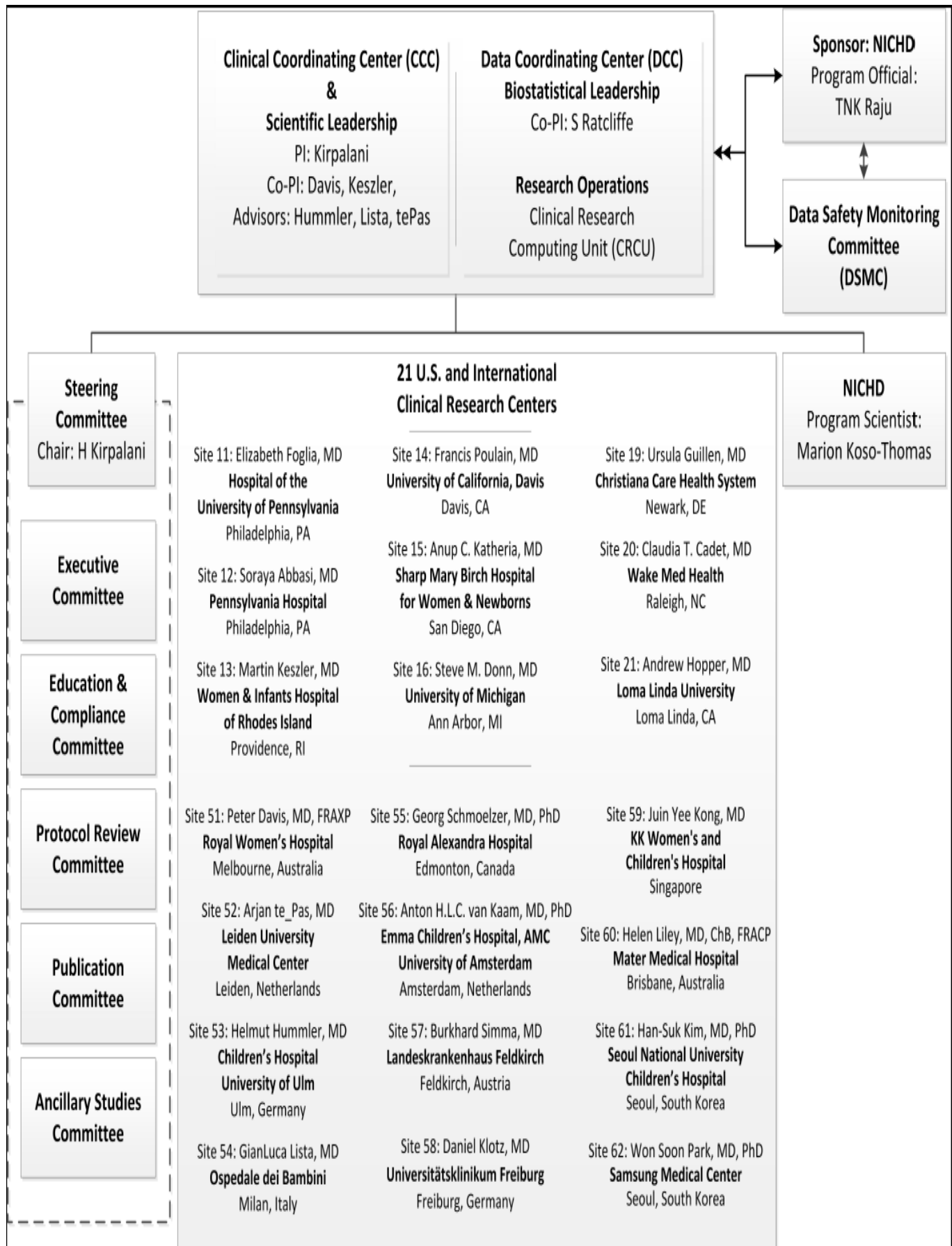
3.1. Research Leadership

This research group is an experienced, productive team led by five clinical Co-PIs (HK, MK, PD, AtP, HH) and one biostatistical Co-PI (SR), who are all experienced clinical trialists, and methodologists or biostatisticians. All six have participated in or led multi-center or multi-national studies.

The Co-PIs will form an Executive Committee that will meet by telephone conference monthly and face-to-face as need dictates, but at a minimum bi-annually at international meetings. We have shown this is feasible in the design of this study and through a combination of telephone discussions and very frequent and detailed emails, have established an open, concrete discussion. The Multiple PD/PI Leadership Plan details how we will address any potential problems.

The NICHD Scientist participates in discussions with the investigators during phases of protocol development and analyses of results; oversees the overall progress of the study, the pace of subject recruitment, and reviews DSMC reports to take appropriate actions.

SAIL STUDY RESEARCH NETWORK



3.2. Participating Clinical Sites

The following investigators from diverse United States and international clinical centers will participate in the trial.

Investigator	Clinical Center	Location
Elizabeth Foglia, MD, MSE.	Hospital of the University of Pennsylvania	Philadelphia, PA
Soraya Abbasi, MD	Pennsylvania Hospital	Philadelphia, PA
Martin Keszler, MD	Women & Infants Hospital of Rhode Island	Providence, RI
Francis Poulain, MD	University of California, Davis	Davis, CA
Anup C. Katheria, MD	Sharp Mary Birch Hospital for Women & Newborns	San Diego, CA
Steve M. Donn, MD	University of Michigan	Ann Arbor, MI
Ursula Guillen, MD, MSE.	Christiana Care Health System	Newark, DE
Claudia T. Cadet, MD	WakeMed Health	Raleigh, NC
Andrew Hopper, MD	Loma Linda University	Loma Linda, CA
Peter Davis, MD, FRAXP	Royal Women's Hospital	Melbourne, Australia
Arjan te_Pas, MD	Leiden University Medical Center	Leiden, Netherlands
Helmut Hummler, MD	Children's Hospital, University of Ulm	Ulm, Germany
GianLuca Lista, MD	Ospedale dei Bambini	Milan, Italy
Georg Schmoelzer, MD, PhD	Royal Alexandra Hospital	Edmonton, Canada
Anton H.L.C. van Kaam, MD, PhD	Emma Children's Hospital, AMC University of Amsterdam	Amsterdam, Netherlands
Burkhard Simma, MD	Landeskrankenhaus, Feldkirch, Austria	Feldkirch, Austria
Daniel Klotz, MD	Universitätsklinikum Freiburg	Freiburg, Germany
Juin Yee Kong, MD	KK Women's and Children's Hospital	Singapore
Helen Liley, MB, ChB, FRACP	Mater Mother's Hospital	Brisbane, Australia
Han-Suk Kim, MD, PhD	Seoul National University Children's Hospital	Seoul, South Korea
Won Soon Park, MD, PhD	Samsung Medical Center	Seoul, South Korea

3.3. Data Coordinating Center (DCC)

Data from all clinical participating sites will be centrally managed by the Data Coordinating Center (DCC) housed at the University of Pennsylvania, Philadelphia, PA. The DCC will be directed by Dr. Ratcliffe. The DCC is comprised of four parts: Biostatistics, Project Management, Data Management and Information Systems. The DCC will provide statistical collaboration, data management and information technology support for the development and conduct of the trial. The DCC is responsible for regulatory oversight and coordination of protocol modifications at the participating clinical sites. DCC Personnel are shown in the table below.

DCC Team	Expertise	Role
Sarah Ratcliffe	Biostatistics	Co-PI / DCC director / Faculty Biostatistician
Russ Localio	Biostatistics	Co-I / Faculty Biostatistician
Sherry Han	Biostatistics	Sr. Statistician (BAC)
Min Du	Biostatistics	Programmer (BAC)
Clinical Research Computing Unit	Research Operations Service Center	Project Management, Data Management, Research Technology

3.4. NICHD Sponsorship

The NICHD has funded this study based on its scientific importance, the opinion by the study section, and the approval from the NICHD National Advisory Council.

4. Trial Conduct

4.1. Identifying Potential Participants

Research coordinators will evaluate maternal admissions to the Labor and Delivery Unit at the clinical site to preliminarily assess eligibility based on estimated gestational age and maternal labor status.

4.2. Consent

A waiver or deferred consent approach was initially proposed but with IRB recommendations, a full antenatal consent procedure has been adopted. These are fully described in Section 8, 'Research Ethics'.

4.3. Study Design

This prospective multi-site, multi-national randomized intention-to-treat, trial will randomize 600 infants into one of two arms:

Group 1: Standard of care – DR PEEP/CPAP 5-7 cm H₂O, or PPV and NRP compliant practice in the DR.

Group 2: DR SI and standard PEEP-CPAP of 5-7 cm H₂O, and NRP compliant practice in the DR.

Although un-blinded intervention is necessary, bias is controlled by blinded outcome assessment of BPD at 36 weeks, neurodevelopment and an objective outcome of death. This blinded 36 week PMA assessment will be performed by clinicians (nurses, RTs, physicians) who did not look after that infant. Parents will not be blinded to the intervention and will be informed of the allocation after the infant has been admitted to the neonatal intensive unit.

4.4. Study Population

4.4.1. Inclusion Criteria

Infants who are born in participating NICUs (which do not use prophylactic surfactant) and who fulfill the following inclusion criteria are eligible for enrollment: (a) Gestational age (GA) at least 23 weeks but less than 27 completed weeks by best obstetrical estimate; (b) requiring resuscitation/respiratory intervention at birth – “apneic, labored breathing, gasping” (as defined in NRP 2011 AAP 6th Edition p. 45.)⁴

The window for determining eligibility is up to 30 seconds. The decision making process in determining if an infant is eligible is to be done simultaneously while performing the initial steps, such as:

- 1) Placing the infant on the resuscitation trolley;
- 2) Suction airway, open airway and proceed with CPAP;
- 3) Wrap the infant in saran wrap/neo wrap for temperature stability;
- 4) Assessment of heart rate and respiratory effort ; and
- 5) Placement of the pulse oximeter probe.

All 5 initial steps take place at the same time by various members of the DR team. This is consistent with the NRP guidelines which allows up to 30 seconds to accomplish the initial steps and determine the need for PPV. This has been independently verified in several sites (Leiden; Ulm; Edmonton; and Hospital University Pennsylvania in repeated simulations).

4.4.2. Exclusion Criteria

- a. Considered non-viable by the attending neonatologist
- b. Refusal of antenatal informed consent
- c. Known major anomalies, pulmonary hypoplasia
- d. Mothers who are unable to consent for their medical care and who do not have a surrogate guardian will not be approached for consent.

4.4.3. Trial Withdrawals

It is anticipated that there will be a small number of infants who, because of acute clinical deterioration are treated according to the preference of their medical team rather than by study protocol. However, their outcomes will be measured and analyzed according to original allocation by intention-to-treat principles.

4.4.4. Randomization Criteria and Methods

Consent:

As the lead site, the Hospital of University of Pennsylvania (HUP) will provide the template for a study wide consent approach. This template asks that each site approach the IRB with request for antenatal consent. We recognize that at some sites an approach will be made (or have already has been made) in requesting their respective IRBs for deferred or waiver of consent for their particular institution.

This protocol assumes the approach for antenatal consent as per the recommendations of the University of Pennsylvania's IRB. In those sites where antenatal consent is being sought, parents of potentially eligible infants from 23 +⁰ to 26 +⁶ GA who may conform to the inclusion and exclusion criteria will be approached by the clinical study team (either a research coordinator or the site investigator) in the antenatal period in order to offer study participation.

Randomization:

A randomization schema will be developed centrally by the DCC at the University of Pennsylvania, and implemented at each clinical site using color-coded opaque sealed envelopes to ensure allocation concealment and proper and efficient randomization. Envelopes will be packaged and shipped to each study site.

A permuted block randomization procedure will be used to formulate assignment lists in order to assure close to equal numbers of subjects in each treatment group. Randomly permuted blocks with unequal blocks of varying sizes, and allocation ratio within each block of 1, will be used. The block sizes will be determined by site in order to ensure balance between treatment arms in sites with potentially small, or large, subject enrollment.

We have chosen to stratify the randomization scheme by clinical site, and gestational age (two strata 23 & 24 weeks versus 25 & 26 weeks). Stratifying on any more variables (such as gender) is not feasible with the potentially small enrollment numbers expected at some sites. We will perform a planned adjustment following the end of the trial to adjust for gender. Use of separate randomization schedules by site (ie stratified by centre, with each site having the same allocation ratio of treatment groups) ensures comparability of the treatment groups with regard to the patient mix coming from the various sites in the trial. This assurance is important because the populations can differ widely with regard to subject characteristics. Further, there may be subtle differences in the standard of care from site to site, despite the fact that this study has a well-defined plan and strict inclusion and exclusion criteria. Finally, stratification by gestational age is needed, as it is well known that mortality outcomes improve as the gestational age increases.

While there are clearly subject-specific variables that will be observed and recorded before randomization that could be used for stratification, such as gender, there are a number of problems with including more stratification variables. Of most concern, stratification by multiple variables would likely result in small numbers per group and a fairly large chance of departure from the desired allocation ratio. Since we are proposing a study with 300 subjects per group, the groups should be large enough that stratification should not be necessary to assure that the two arms will have approximately equal representation of the major confounding variables. However, a careful post-hoc analysis will be carried out to assure that the allocation was, in fact, equal. Analysis procedures involving post-stratification, and multiple regression will be used to adjust for any baseline group differences.

4.5. Intervention Maneuvers in Delivery Room

Because this is an international multi-site trial, we are aware that International sites may have minor modifications of the below, all of which will be assessed for trial approval by the Steering Committee. However we do make reference below to “site clinical local practices”. If such minor variations in these will not affect the validity and integrity of the trial, they will be allowed.

At all sites where antenatal consent has been obtained, or in some sites where the local IRB has granted waiver, eligible infants (23⁰-26⁶ completed weeks GA) will be taken to a resuscitation trolley, placed in a

plastic wrap and have a SpO₂ probe attached to the right hand (NRP p.54).⁴ The infant's airway will be cleared and the infant will be commenced on mask or nasal prong CPAP at 5-7 cm H₂O and FiO₂ 0.3 via a T-piece.

A wide range of authorities have now accepted this in the peer-reviewed press as a standard procedure in 2013-2014. We have ensured that we are fully compliant with ILCOR 2010 and NRP 2011 standards, using CPAP or PEEP. We have discussed aspects of this in the study background section, and referenced the January published latest statements from the Fetus and Newborn Committee of the AAP.^{5, 6} (Appendix 7) Our NRP compliant approach is attested to in several other ways, including the approval of the DSMB that includes Dr. Kattwinkel (one of the co-founders of the AAP NRP program); the inclusion in our group of a NRP committee member (Dr. Ades from CHOP-HUP); and consistency with the Quality Program initiatives of the DR processes in HUP. (Appendix 8). For the trial, the time of birth has been set as final emergence of the infant from delivery. The time of cord clamping will be recorded. Finally, the time for the Study Intervention (see Figure 1 below) is measured from the point of the infant being placed on the resuscitation trolley (defined as time zero).

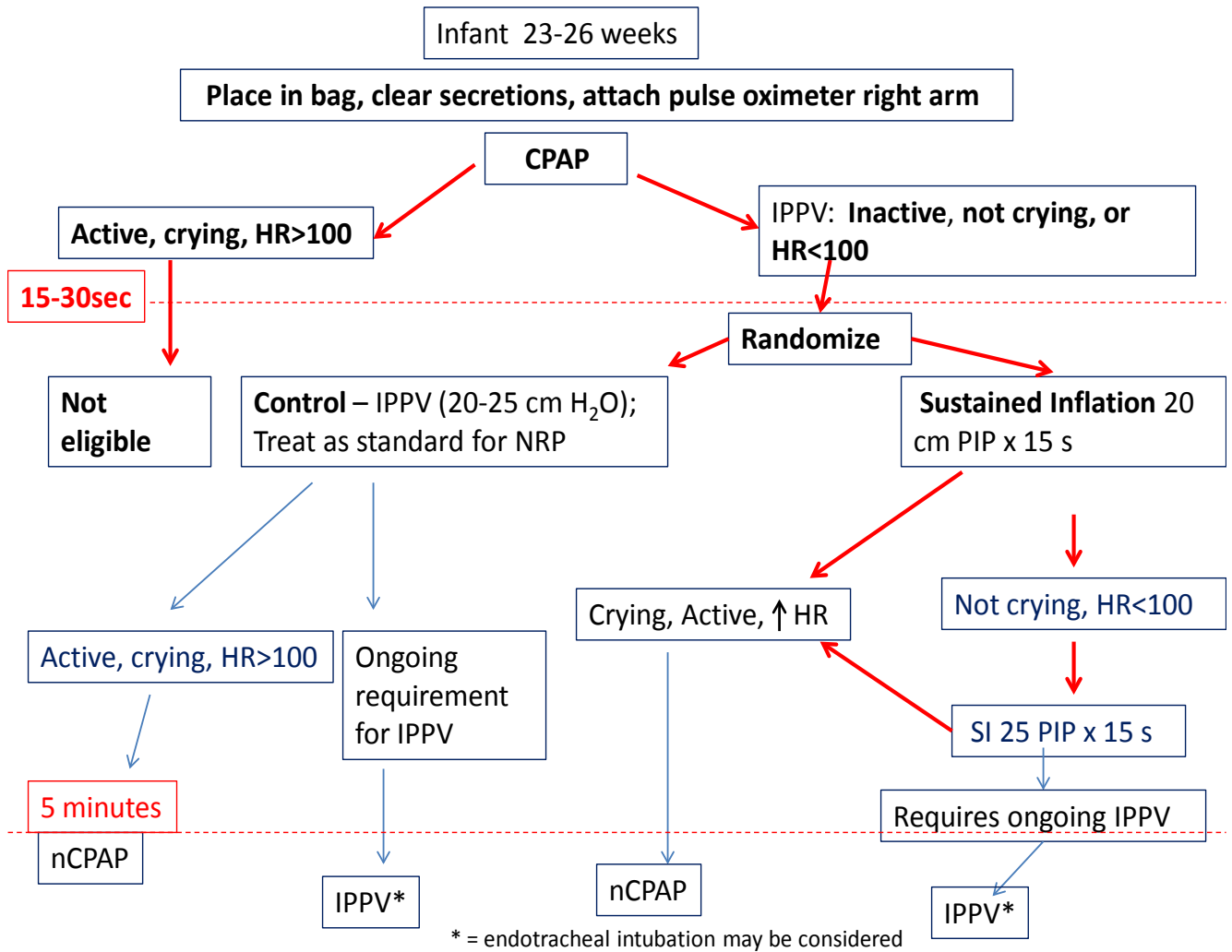
Thereafter, an infant with inadequate respiration defined as gasping or apneic; or is bradycardic defined as HR<100 bpm and not rising (as labelled in the algorithm diagram: Figure 1) will be eligible for the SAIL trial. Time in which to determine eligibility is 30 seconds, however an infant can declare himself/herself in less time. The initial 30 seconds are congruent with NRP guidelines.

Infants who are not eligible for the SAIL trial will be continued on CPAP, and all further resuscitative measures will be made according to local clinical protocols.

For infants who are eligible for the SAIL trial, the randomization envelope will be opened, and the treatment allocation will be announced to the clinical team. Thereafter, the protocol algorithm will be followed for babies who are randomized to the SI intervention. Infants who are randomized to the control arm will be treated according to local clinical protocols. (See 4.5.1 for more detail on the control arm infants).

Regarding choice of pressures: "The primary measure of adequate initial ventilation is prompt improvement in heart rate. Chest wall movement should be assessed if heart rate does not improve. The initial peak inflating pressures needed are variable and unpredictable and should be individualized to achieve an increase in heart rate or movement of the chest with each breath. Inflation pressure should be monitored; an initial inflation pressure of 20 cm H₂O may be effective, but 30 to 40 cm H₂O may be required in some term babies without spontaneous ventilation if circumstances preclude the use of pressure monitoring, the minimal inflation required to achieve an increase in heart rate should be used." The choice of pressure is discussed further below under section 4.5.2.

Figure 1: The overall schema for eligible versus non-eligible infants



4.5.1. Control Arm Infants

Infants randomized to this arm will follow standard NRP guidelines. While starting on CPAP, this may include the provision of T-piece resuscitator (positive pressure) ventilation with peak pressures set initially at 20 cm H₂O for 15 seconds, and if needed subsequently, increased to peak pressure of 25 H₂O cm, or as local clinical practices allow. Corrections by MR. SOPA are to be applied as recommended by NRP guidelines. These are discussed in fuller detail below under 4.5.2.

4.5.2. Intervention Arm Infants

All respiratory support is to be administered via the T-piece resuscitator and either face mask, nasopharyngeal tube (NPT) or a shortened endotracheal tube placed as an NPT. The Mountain trial has reported that there is no difference in interface. ([Appendix 9](#)) SI will be delivered via T-piece resuscitator, as this device has been shown to be the only one capable of effective delivery of CPAP and SI (Hussey SG 2004, Klingerberg C 2011).

The choice of initial pressure for the SI is based on pathophysiology, literature, local practice or other and available data. While animal studies suggest that inflation pressures as high as 35 cm H₂O are needed in animals with no spontaneous effort and no antenatal steroids⁷⁻¹¹, human trials suggest that when the lungs are partially aerated as a result of the infant's respiratory effort, pressures as low as 20 cm H₂O may be sufficient. A single SI with a pressure of 25 cm H₂O was used in a recent cohort study¹² without apparent adverse effects. Escalating SI pressure ranging from 20 to 30 cm H₂O for up to 3 SIs was used by the other two studies. The first reported that 67% of infants required 25 cm and 8% received SI of 30 cm H₂O.¹³ SIs of 20 cm H₂O were adequate in 60% of infant in the other trial, while 40% of infants required 25 cm H₂O and of those, the majority had an inadequate response and required intubation¹⁴. At that center, SI of up to 30 cm H₂O is now used as part of standard DR care.

Thus, eligible infants will be given the first SI using pressure of 20 cm H₂O. An assessment for respiratory effort and heart rate will be made. Infants with adequate respiratory effort and heart rate above 100 bpm will continue on CPAP as study intervention has ended for these infants and they revert to standard NRP procedures.

For those infants following the first SI who remain without adequate respiratory effort, a second SI using a pressure of 25 cm H₂O for 15 seconds will be delivered. In the interval between the first SI and the second SI, the team will follow standard NRP procedures as described in the next paragraph (MR SOPA). Decisions about adequacy of the SI will be based on infant's response as judged by improving HR, respiratory effort and SPO₂.

During this period between SIs, as per NRP recommendations, adjustments can be made to ensure no residual lack of seal or obstruction is impeding the infant, resuscitation will proceed according to the first four steps of the "MR. SOPA rule". (i.e. Mask Readjustment; Suction airway; Open mouth.) In both the NRP algorithm as well as the SI algorithm, MR. SOPA is incorporated in the step outlined as "take corrective ventilation steps". Last, if the infant is eligible for a second SI, the clinician will

ensure airway patency and deliver the second SI with a pressure 5 cm higher than the initial pressure. This step is in accordance with the P step of MR. SOPA.

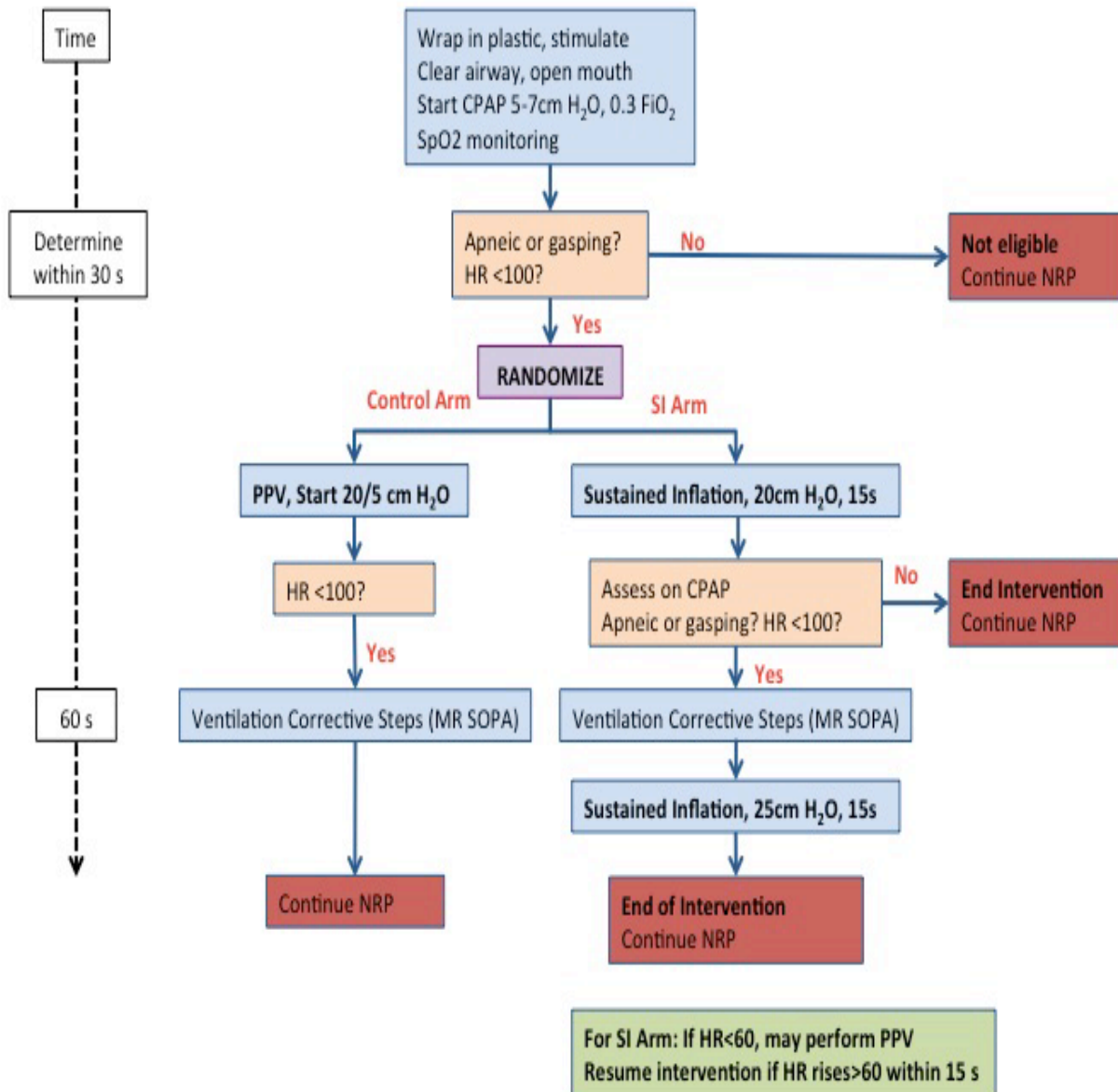
The final 'A' in MR. SOPA stands for Airway. There will be rare situations where the clinician must respond with intubation immediately – such infants will be also randomized into an SI or standard arm. While these infants data will be pooled, it will also be treated separately in a sub-group analysis. At any point in the algorithm, if the HR is < 60 and not increasing, PPV may be given with rate in accordance with NRP and peak inspiratory pressure equal to the SI that would otherwise be performed. Observation after a 15 second period will assess whether there is an improving heart rate. If the heart rate improves to >60, the algorithm will be resumed from the point of departure.

Throughout the entire period, cardiac compressions will start if HR remains < 60 despite effective respiratory support for > 30 seconds.

Finally, Figure 1 shows two red lines. The first is the initial assessment point which by 30 seconds must be completed as according to NRP. However the second dotted redline indicates that by 5 minutes there may have been a progression towards intubation. This decision point may be reached by 2 minutes or even before.

The modified but NRP compatible procedures are shown for the SI arm in more detail in Figure 2.

Figure 2: Algorithm For infants In Intervention arm directly compared to the NRP algorithm.



Control Arm: NRP

Sustained Inflation Arm

The potential risks of this maneuver are described in Section 8 and in the adverse event reporting section. The main risk anticipated is the potential for a pneumothorax. However, we do note that not only has an excess risk not been seen in the available randomized data to date, but the pressures stipulated in the algorithm are within the ranges of those recommended by NRP for conventional resuscitation. The DCC will monitor carefully for potential excess risk, and some of the secondary objectives are also part of the materials in adverse event reporting and will be transmitted at appropriate intervals to the DSMC.

4.5.3. Data Collection for Non-eligible Infants

To complete the patient flow description, this protocol addresses infants in the inclusion GA who are not eligible to be randomized. By definition this includes infants whose parent has refused to consent. We seek approval to capture limited data for this group of infants. There are two reasons for collecting this valuable information:

- The dearth of information about DR practices in this birthweight range of infants
- The known high potential for selection bias following the use of antenatal consent procedures.^{17, 18}

Data Collection for these infants will not include any HIPPA protected privileged information. We will be collecting the following information from parents who refused consent:

Data Collection Topic	Specific Data Elements
Delivery Room Data	Month/Year of birth; time of cord clamping (recorded as mm:ss after birth); birth weight; Apgar score at 1 and 5 min; gender; NRP guidelines used in the resuscitation of the infant such as respiratory status; procedures if any (intubation, chest compression, administration of epinephrine; surfactant delivery; UAC/UVC placement; chest tube placement; final respiratory status before leaving DR; and outcome of resuscitation.
Maternal Data Form	gravid para status, exposure to antenatal steroids and type; maternal ethnicity/race; antenatal corticosteroids (if yes, number of courses); any medications given to prolong pregnancy including tocolytics; diagnosis of diabetes during pregnancy (insulin dependent); placental abruption; chorioamnionitis; membranes rupture \geq 24 hours before delivery; mode of delivery

4.5.4. Training and Standardization of Research Intervention

A training video has been produced for use in training the staff at all participating clinical sites. (It will also be translated into Italian; neither the Dutch nor German sites will need translation). The video will be used to train the research team about the protocol but also can be viewed when the team has been alerted that a potentially eligible SAIL baby may be born shortly. This video can be accessed from the SAIL Trial Website which will be created and maintained by the DCC. Should any university site deem this an unsafe site, the video will be sent as a file to the respective hospital site coordinator to load on appropriate computers. Should any university site deem this an unsafe site, the video will be sent as a file to the respective hospital site coordinator to load on appropriate computers

To assess fidelity of the research intervention across sites, a variety of methods will be used.

- A main feature of our methods here hinge on the use of video recordings. Video capability during resuscitation for quality control purposes is available at UCSD, Calgary, Ulm, and Milan. A random sample of infants at each of these sites will be evaluated by the quality team (led by the Philadelphia team of Drs. Ades, Foglia, Posencheg, and Nadkarni).
- A training checklist will be generated for those who perform SI and will include simulation. The PI at each site will be responsible to ensure that each person performing SI has been properly trained.

4.6. Random Allocation in the Delivery Room

Following informed consent, the mechanics of the randomization maneuver in the DR addresses the following aspects:

- Twins and multiples will be randomized as a unit, using a single envelope.
- Envelopes will be kept immediately outside the DR, at a safe designated site suitable for each site.

There will be between 3-5 envelopes for each of the gestational age strata in each location. This will ensure that in the hurry around a pending delivery there is no excess fumbling. Selection will be sequential and the lowest number marked on the envelope will be taken.

The next numbered envelope will be taken into the DR by the NICU-DR team. Opening of the envelope, and thus randomization, will only be performed when the infant has been delivered and deemed to require respiratory assistance. Within 15-30 seconds the assessment of whether or not the baby is eligible to be randomized is possible to make in a safe manner.

We have undertaken extensive simulation of this procedure and it does not introduce time-delays. We provide here a video clip showing this procedure in action at one of these simulations on the SAIL Trial website. Our procedure is modeled on those undertaken during the pivotal COIN trial where a member of our Steering Committee (P.Davis Melbourne) was a co-investigator. In addition Dr Kirpalani was one of the site investigators for the COIN trial at McMaster University, Canada, where the process of randomization also did not impede safe practices in the DR.

Thus opening of the envelope will not impede appropriate delivery of care. All opened envelopes and assignments will be kept in the logs of the site. The research study coordinator will be available as a back-up for the clinical Neonatal DR delivery team.

5. Study Data

The following is a table of details that will be collected, and it is itemized by day of collection. It should be noted that only the details of the sustained inflation maneuver itself, and the screening log for eligible patients, is unique to this study. All other data points are routinely measured. There are no blood tests or data being collected that are not already routine clinical data.

Data Collection Topic	Specific Data Elements	Specific time interval
Eligibility and Randomization Data Form	Clinical data: meets inclusion criteria and none of exclusion criteria; eligibility confirmed Research: date and time of randomization, and allocation of treatment arm (control vs intervention)	First 30 seconds of birth
Delivery Room (DR) Data Form	RESEARCH DATA collected: time infant is placed on resuscitation trolley; time of specific maneuver; 1 st sustained inflation and exact pressure measurement x 15 seconds; time of 2 nd sustained inflation and exact pressure measurement x 15 seconds; and use of ventilator vs T-piece	Research intervention takes place within the first 30 seconds up to 1 - 2 minutes of life
	Clinical data: time of birth, time of cord clamping, NRP guidelines used in the resuscitation of the infant such as respiratory status; blood gas values including glucose and hemoglobin/hematocrit values; procedures if any (intubation, chest compression, administration of epinephrine; surfactant delivery; UAC/UVC placement; chest tube placement and additional medications; final respiratory status before leaving DR; and outcome of resuscitation. Additional clinical information: date and time of birth, birth weight, Apgar score at 1 and 5 min, and gender	Certain clinical time points as dictated by the resuscitation process in the DR; data should be completed within first 48 hours

Data Collection Topic	Specific Data Elements	Specific time interval
Respiratory function measurements of inflations and physiologic monitoring (Obtained only at a subset of sites)	Inflation characteristics: pressure, flow, tidal volume, exhaled CO ₂ Physiologic monitoring: heart rate, oxygen saturation, delivered oxygen concentration	First 10 minutes of life
Delivery Room Video recording (obtained only at a subset of sites; transferred and destroyed after analysis)	Video recordings of the infant during the initial resuscitation and stabilization	Up to the first 30 minutes of life
Adverse Events	See Section 9.2 for detailed information.	Specific events during the first 10 days of life; thereafter continuing AE reporting structures are in place until the infant reaches 36 weeks GA
SNAPPE Score	Clinical data: severity score that is compiled by using clinical parameters within the first 12 hours of life, such as lowest pH, PaO ₂ and corresponding FiO ₂ and MAP, urine output and presence of seizures	Completed by first week of life
Daily Respiratory Status for First Week of Life	Clinical: current respiratory status at noon each day to include if applicable, respiratory support (CPAP, noninvasive PPV, invasive PPV); specific ventilatory settings; surfactant administration Infant's respiratory rate, highest FiO ₂ from previous time point and corresponding SpO ₂	Completed for every day for the first week of life

Data Collection Topic	Specific Data Elements	Specific time interval
Daily Assessment for First Week of Life	<p>Clinical: birth weight and head circumference; antibiotics, antifungals, indomethacin or ibuprofen, caffeine or other methylxanthines; furosemide or other loop diuretic; thiazide diuretic; corticosteroids, inhaled corticosteroids, inhaled nitric oxide, inhaled bronchodilator; vitamin A IM, erythropoietin; red blood cell transfusion, any paralytic agent; any anticonvulsants, any milk feed or formula, any breast feeding and any parental nutrition</p> <p>Clinical radiographic data, if available: head ultrasound or MRI, number of CXR, abdominal films</p>	Completed for every day for the first week of life
Maternal Data Form	Clinical: mother's age, gravid para status, exposure to antenatal steroids and type; maternal ethnicity; maternal education, any medications given to prolong pregnancy including tocolytics; placental abruption; chorioamnionitis; membranes rupture ≥ 24 hours before delivery; mode of delivery	Completed within one week of enrollment
Weekly Respiratory Status until 36 wks PMA	<p>Clinical: current respiratory status at noon once/week to include if applicable, respiratory support (CPAP, noninvasive PPV, invasive PPV); specific ventilatory settings</p> <p>Infant's respiratory rate, highest FiO₂ from previous time point and corresponding SpO₂</p>	Collected weekly from 2 nd week of life until 36 weeks PMA
Weekly Assessment until 36 wks PMA	Same as above with the exception of weekly head circumference instead of at birth and date of successful extubation defined as extubation for greater than 48 hours	Can be completed once a week (does not need to be a specific day of the week)
Respiratory Status at 36 wks PMA	<p>Clinical data: exact 36 wks PMA date; respiratory status (RA, NC, CPAP, invasive/non-invasive PPV),</p> <p>If applicable pass/fail Oxygen Reduction Test (ORT)</p>	Can be completed within one week of reaching 36 wks PMA

Data Collection Topic	Specific Data Elements	Specific time interval
Discharge Status	Clinical data: date of discharge or death, co-enrolled in other clinical trials, and respiratory status	Once a baby has been discharged, reached 44 weeks PMA or died, whichever occurs first
Record of Death	Clinical: date of death, primary cause of death; autopsy performed, if yes, provide narrative	If applicable
Neonatal Outcome Data	Clinical data: PDA (treated Y/N), IVH (grade), ROP stage > 1, BPD, and positive blood culture sepsis, and other complications	Once a baby has been discharged, reached 44 weeks PMA or died, whichever occurs first
Late Outcome Data	Clinical data: final date of discharge, transfer or death if after 44 weeks PMA; reason for continued hospitalization beyond 44 weeks PMA	If applicable, for infants who remain in hospital past 44 weeks PMA
Transfer Form	Clinical data: date of transfer, transfer to medical facility, foster care, etc.	If applicable, for infants who are transferred to an outside facility prior to reaching 36 weeks PMA
Follow-up Assessment at 22-26 months cGA	Clinical data: the incidence of ambulatory and non-ambulatory CP defined by Gross Motor Function Score (GMFCS); hydrocephalus shunt, microcephaly, or seizure disorder; presence of respiratory disease necessitating readmission before 22-26 months follow-up; all individual components of the composite outcome of Neurodevelopment Impairment NDI or death, including cognitive outcomes at follow-up at 1 SD cut-off on the Bayley Scale of Infant Development BSID III standardized scales, BSID III cognitive, language and motor scores at 2 SD cut-offs (<70) at follow-up.	Once a baby has had a 22-26 month cGA follow-up visit in clinic

5.1. Maintaining Adherence to Algorithms and Minimizing Protocol Deviations

Extensive education and training will be undertaken to ensure technical proficiency and compliance with the protocol. A 'boot-camp' will be run at the start of the study by experienced study members (Peter Davis, Arjan tePas, Helmut Hummler, Anne Ades, Vinay Nadkarni, Robert Berg, Aasma Chaudhary). This will 'certify' the site PIs, who will then be in a position to train their own site-members. This training will be developed by the CCC Co-PIs and carried out locally by each site PI. A limited run-in period during

which SIs will be implemented in delivery room care will precede study initiation at each center in order to establish a level of comfort and overcome the learning curve effect. To further ensure adherence, we will complete a training video to be used as a refresher and training material for delivery room staff, fellows, and attendings. This will certify a site PI, who will be the gold standard trainer at her/his site. Site visits will be performed after 10 infants have been enrolled at each site, to examine site comfort and performance of the SI, as well as records kept, and trial functioning. At each site, a single SI per 2 months will be videotaped and reviewed at HUP for reproducibility and consistency. In addition, experts in simulation – Anne Ades, Elizabeth Foglia and Aasma Chaudhary will develop SI education.

5.1.1. Potential Confounders and Strategy to Limit Impact

Severity of initial illness: Randomization should achieve balance at baseline. Adjustment for SNAPPE scores on admission to the NICU will be performed during the analysis of the primary outcome.

Site Variation: Randomization will be stratified by site.

General respiratory management in the DR and beyond: Local unit protocols will be followed with respect to aspects of respiratory support not specifically addressed in the study interventions. In general, after initial resuscitation, CPAP will be the initial mode of respiratory support in reasonably vigorous infants. Intubation will be reserved for infants who remain apneic, are without adequate respiratory effort, or have persistent bradycardia. Surfactant for RDS prophylaxis will not be given in the DR prior to SI (if so randomized), even if the infant is intubated. Caffeine will be administered to infants if needed for respiratory support.

Extubation and intubation guidelines: Continued need for mechanical ventilation is associated with BPD. We adopt a uniform guideline to intubation and extubation, though clinical circumstances may preclude strict adherence to guidelines at all times. There is no consensus about weaning babies from mechanical ventilation. Therefore, the proposed extubation guidelines are based on consensus and criteria used in several current and recent large clinical trials. On a daily basis the infant will be assessed for ability to wean from ventilation. We will strongly encourage extubation to be attempted within 24 hours after meeting all following criteria: $PCO_2 \leq 55$ mm Hg and a $pH \geq 7.25$, FiO_2 of ≤ 0.4 with an SpO_2 of $\geq 88\%$ or higher, mean airway pressure of ≤ 8 cm of water, and hemodynamic stability and without evidence of clinically significant patent ductus arteriosus. All infants will have received caffeine prior to an extubation attempt. Extubation may be attempted at higher settings at the discretion of the clinical team. Following extubation all infants should be placed on nasal CPAP or NIPPV, not on nasal cannula or oxihood. In unplanned extubations, the infant will be given an opportunity to remain extubated, if heart rate and oxygen saturations are maintained without excessively high FiO_2 or work of breathing. Extubation will be considered successful if the infant remains extubated for at least 48 hours. Reintubation will be at the discretion of the clinical team managing the infant.

Demographic variables: The next section describes the analytical plan to examine the key covariates of gender, antenatal corticosteroids, multiples, and week of gestation.¹⁹

All of these instructions and definitions will be written into an Operating Manual to be used as the initial source for teaching sites and their staff, and on-going re-education.

6. Statistical Analysis

The Data Coordinating Center (DCC) will be housed at the University of Pennsylvania and submitting a separate IRB approval request to the IRB. The DCC is comprised of four parts: Biostatistics, Project Management, Data Management and Research Technology.

Biostatistical support will provide centralized randomization, publication support, interim analyses and statistical analysis plans under the direction of Drs. Ratcliffe and Localio. Project management will coordinate activities between the scientific and operations teams and manage sites. Data Management will include case report form (CRF) design, management and entry, data quality assurance and reporting. Information Systems will include database design and system support.

6.1. Statistical Plan

6.1.1. Sample Size Determination

Sample size is based on a possible reduction in risk of neonatal mortality/BDP in infants at 36 weeks PMA receiving the SI intervention compared to those who receive the standard PEEP/CPAP. The significance level was set at $\alpha=0.038$ (due to the interim analyses), and power at 80%. Based on information from the recent multi-center NICHD SUPPORT trial² and the COIN trial,²⁰ we estimate that the baseline rate of neonatal mortality/BDP in the standard or care (control) arm by 36 weeks is 65%.

In order to detect an absolute risk reduction of 12.5%, 263 subjects per treatment arm are required. We anticipate virtually no loss to follow-up for the primary endpoint as infants will likely still be hospitalized because of their condition, will be under constant and continuing medical care. We have inflated the estimate by 1.12 to allow for twins and multiples to be randomized together. With this inflation in mind, the target sample size for this study is 300 subjects per arm.

For the secondary outcomes available in all subjects, with 263 subjects per arm (ignoring the twin correction factor), there will be 80% power to detect a difference of 0.24 standard deviation units in continuous outcomes, and a hazard ratio of 0.77 in survival outcomes under a proportional hazards assumption. Some secondary outcomes will not be available due to death of the infant, or loss to follow-up after discharge from the NICU. Overestimating these rates at 50%, we assume 130 subjects per arm will be available for the longer term secondary outcomes. With this sample size we will still have sufficient power to detect a clinically meaningful difference of at least 17% in event rates (or odds ratio of at least 2.0).

6.1.2. Methods of Analysis

The proposed study is a two-arm parallel design of two alternative courses of treatment. A conventional “as-randomized” analysis (or “intention-to-treat” analysis) will estimate whether the

experimental therapy is superior to conventional therapy in avoiding treatment failure, and is at least as good as conventional therapy in avoiding adverse events.

SAS will be used for secondary data management and descriptive statistics. SAS datasets will be downloaded at least weekly from the study database for analysis. Graphics will be prepared using Stata v11 (or later) (Stata Corp, San Antonio TX, 2009) and the R programming package (The R Foundation for Statistical Computing, Vienna, Austria, 2011). Analyses will be implemented in SAS.

6.1.2.1. Descriptive Statistics

Although randomization at baseline should balance observed and unobserved differences between the treatment arms by measured and unmeasured confounders, extra precautions are needed to guard against the potential bias of baseline covariates with chance imbalance from finite sample sizes. Initial analysis will describe the distribution of data. We will characterize both treatment arms by demographic variables and all covariates of interest. Means, standard deviations, medians, and ranges will be computed for measured continuous variables; marginal distributions will be used for categorical factors. Graphical methods including histograms, scatterplots, and boxplots, will be used in order to understand aspects of data quality and examine assumptions (such as normality) underlying statistical models.

6.1.2.2. Analysis of Primary Outcome

The primary endpoint to be used for efficacy evaluation is the rate of Death or BPD at 36 weeks gestation age. The primary hypothesis to be tested is that the treatment therapy results in a decreased event rate. Although a proportion's test is used for sample size calculations, rates will be compared using logistic regression, which will allow for control of covariates, as well as investigation of effect modification. Potential covariates include gender, gestational age, initial heart rate, maternal corticosteroids use, and small for gestational age (SGA). Clinical site will be used as a stratifying factor to control for any confounding by site through residual, site-level treatment imbalance. The logistic regression will be estimated using a generalized estimating equation (GEE) in order to adjust for the inherent correlation expected with multiples. Standard regression diagnostics will be used to assess model adequacy, and to examine for potential outlying or influential data points.

Prior studies offer no basis for assuming a priori interactions between treatment arms and subgroups defined by sex, race/ethnicity, gestational age, site or a combination of these groups, beyond that already controlled for in the randomization. For that reason, preplanned tests for interactions with treatment assignment are not warranted, and not powered for. We propose, however, to table all results by subgroups for descriptive purposes and to explore in secondary analyses possible subgroup differences by treatment group, solely for purposes of generating hypotheses for future studies. In particular, there is interest in exploring subgroups defined by:

- Consenting procedure which may vary by site (antenatal vs. deferred consent). While consenting procedure differences may result in some selection bias, this will be implicitly adjusted for with

the already planned clinical site stratification factor. Additionally, the sample size still results in 80% power at $\alpha=0.038$ for the primary outcome even if the selection bias results in a reduced control arm rate.

- Route of treatment (facemask vs. nasopharyngeal tube). While not expected to modify the intervention effectiveness, exploring this difference will be important for future study design and clinical practice.
- Enrollment date. Clinical practices unrelated to this intervention, as well as increased intervention experience, could result in changes in the clinical effectiveness of the intervention over time (positively or negatively). We will explore graphically any temporal trends in the intervention effect, and will allow/test for a time-varying treatment effect via a functional logistic regression model, if needed (for which the original power calculations are conservative).²¹

6.1.3. Analysis of Secondary Outcomes

Secondary outcomes will be analyzed using similar procedures to the primary outcome. Comparisons between treatment arms will use logistic regression (dichotomous outcomes), linear regression (continuous outcomes), or survival analysis (survival time outcomes), as appropriate.

6.2. Interim Analysis

Since neonatal safety is a consideration in this study, we have chosen to use a group sequential design. Thus, in addition to the final analysis, we are planning on performing two interim statistical analyses during the course of this study. The purpose of the interim analyses will be to determine whether or not there is sufficient evidence of a difference between the treatment arms in the primary endpoint such that the trial should be discontinued prior to reaching the target accrual goal. The interim analyses will be performed after approximately 1/3 (200 subjects) and 2/3 (400 subjects) of the total required patients have completed their primary outcome. An additional safety review will be undertaken after 1/6 (100 subjects) have completed their primary outcome.

The primary outcome for the interim analyses will be the comparison of death/BPD between the treatment arms. This comparison will be accomplished by means of a simple generalized estimating equation (GEE) model for death/BPD versus treatment (since adjustment for multiples will be needed). An approximate O'Brien-Fleming boundary will be used at each interim look to calculate the nominal significance level to which interim p-values are compared.²² Using the O'Brien Fleming spending function, the three analyses (2 interim + final) should use the following incremental α values (0.0002, 0.012, and 0.038) in order to achieve an overall $\alpha=0.05$.

Stopping criteria are for:

(1) Clear superiority. Whether the experimental treatment is clearly inferior to standard therapy. For these calculations, we trade off the power to detect a difference and the size of that difference. Assuming $\alpha=0.0002$ for boundaries for the initial interim analysis when 200 children have been followed to completion, power is limited except to detect large reductions in outcomes of death and BPD. For example, power is approximately 0.81 to detect a reduction from 65% in the conventional therapy to

32.5% in the experimental therapy, a 50% relative reduction. For the second interim analysis, using $\alpha=0.012$, power with 400 children followed is about 0.85 to detect an absolute reduction from 65% to 40% in the risk of death plus BPD. Thus, early or premature stopping for superiority is unlikely, without dramatic improvement from experimental treatment.

(2) Inferiority. Power is limited to identify inferiority of the experimental treatment, with 0.8 power to demonstrate a 15% point increase in the risk of outcome from 65% in the standard therapy to 80% in the intervention.

(3) Futility. Early stopping based on futility of the primary outcome will not be considered independently of the secondary clinical and safety outcomes. In the event that the intervention arm has equivalent BPD/death rates to the standard care arm, it would still be clinically useful to know if the intervention improves any of the secondary outcomes (that are closer to the time of the intervention) or decreases the serious adverse event rate.

(4) Safety.

(a) Early stopping based on inferior safety and non-inferior efficacy must be based largely on descriptive data and close examination of adverse events. With 200 subjects per group at a second early stopping review, and assuming that the experimental therapy is actually no worse than conventional care, observed risk in the experimental group would have to be at most 0.5 (risk of death and BPD) to have 80% power to show non-inferior efficacy (with $\alpha = 0.012$).

(b) To justify stopping for non-inferior efficacy and superior safety again will require a substantial observed improvement in the experimental arm at the second early stopping time.

(c) Another safety outcome is the rate of pneumothorax, pulmonary interstitial emphysema (PIE), and/or other serious adverse events (that have been adjudicated as potentially relating to the intervention; see section 8.2.2). In order to minimize the risk, this safety outcome will be compared between treatment arms after 1/6 (100 subjects) have completed the primary outcome, as well as at the two planned interim analyses for the primary outcome (1/3 and 2/3), since we would not expect any statistically significant differences in the rate after 100 subjects (with O'Brien-Fleming $\alpha 0.000002$). Instead, we will look for a clinically meaningful double the risk in the intervention versus standard care arms.

In summary, given the projected number of patients to be enrolled, early stopping will be unlikely unless the observed effect of experimental care is clearly better or worse than standard care at the planned early stopping assessment times.

The results of the interim analyses will be judged by the DSMC. This committee will act completely independently of the clinical investigators, including the Principal Investigators. However, the ultimate decision to stop the study will rest with the steering committee.

Note: An adaptive design was not used for this study. The efficacy improvement was minor over the conventional design.

7. Trial Management

Project and data management support will be provided by the research team at the Clinical Research Computing Unit (CRCU), and the staff statistician at Biostatistics Analysis Center (BAC). Both of these groups are under the direction of Drs. Ratcliffe (co-PI), and Localio. Initial stages of data management will be done by experienced clinical data managers (CDMs), database developers, , supported by computer system analysts, programmers, and information technology (IT) specialists. These persons will be responsible for data quality and timeliness, documentation of processes and procedures, and training of data management staff.

Every effort will be made to monitor data collection and entry and to correct errors, inconsistencies, ambiguities, and omissions in real time. Data will be entered directly into a secure, backed-up, 24-hour, web-based database using electronic case report forms (CRFs) developed by CRCU staff with the assistance of project investigators and statisticians. Data entry screens will incorporate range and logical edit checks, both within and across forms. Data entry will be followed daily with manual and programmed checks and edits for errors and omissions. A data monitoring plan written before the start of data collection will serve as a reference guide for the development of case report forms (paper and electronic versions), data handling conventions, reporting, data dictionaries, supporting meta data, as well as project closeout activities, communication and coordination plans among the PIs, clinical teams, sites coordinators, and staff and faculty-level statisticians.

7.1. Data Security

Access to direct identifiers will be limited to staff who meet all relevant training requirements and are assigned to (or support) this project, and who must have access to these identifiers for purposes of quality control and monitoring. All other persons, including statisticians and investigators will be blinded to identifiers until such time as for reasons of safety or clinical care, those identifiers must be shared. All investigators, statisticians, and staff will have completed the HIPAA and Human Subjects Protection training. All data with identifiers will be stored on firewall-protected secure servers.

7.2. Data Sharing

It is required of investigators at the University of Pennsylvania that research results generated under sponsorship by NIH are made available to the scientific community and public in a timely manner. The primary method by which data are shared with the scientific community is through peer-reviewed publications and presentation at meetings. In addition data and results created from NIH supported research will be submitted to NIH in the annual progress reports required under the terms and conditions of this award. This study will also be registered with clinicaltrials.gov.

At the end of the study, limited access to the data may be granted to investigators external to the project. Such requests must be authorized by the PIs and the steering committee of the trial. To facilitate requests, the DCC will provide fully annotated final analytic datasets used to support published results. Such files will not contain any information on human subjects that could be used for their

identification. Depending on the type of request sharing of unpublished data may require a data sharing agreement, which will stipulate the conditions of their use.

7.3. Data Safety Monitoring Committee (DSMC)

A data monitoring safety committee (DSMC) will be established to: (1) protect all study patients, (2) safeguard the interests of all study patients, (3) monitor the overall conduct of the trial, (4) advise the investigators in order to protect the integrity of the trial, and (5) supervise the conduct and analysis of all interim analyses. To this end the DSMC will receive regular reports from the trial on any injuries or adverse events, any developments that jeopardize the continued success of the trial, and data by which to accomplish the evaluation of pre-determined early stopping rules.²³ All Serious Adverse Events will be sent within 72 hours to the DSMC; reports of adverse events and recruitment will be sent monthly; demographics will be included with the interim and final safety and efficacy analyses.

Two interim statistical analyses are planned during the course of this study. The primary endpoint to be used for efficacy and safety evaluation is the rate of Death or BPD at 36 weeks gestation age. The primary hypothesis to be tested is that the treatment therapy results in a decreased event rate. A secondary safety outcome to be evaluated is the rate of serious adverse events (SAEs) between the two groups. Interim analyses will be performed by the project statisticians, independently from the trial leadership. The results of the interim analyses will be provided to the DSMC. Additionally, the code used to produce the analyses will be provided to the DSMC biostatistician for independent, secondary verification of the results.

7.3.1. Composition and Function of the DSMC

This is an investigator-initiated study sponsored by the Pregnancy and Perinatology Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

The NICHD scientists (T. Raju and M. Willinger) will receive AEs and SAEs and assure that they are sent to the Chair of the DSMC. Dr. Raju will participate during the open segment of the DSMC meeting. Dr. Willinger will sit on the DSMC, but will not be a voting member. In addition, Dr. Raju (Chief, Pregnancy and Perinatology Branch, NICHD) retains close contacts with investigators, but will not be a voting member.

A DSMC has been appointed to work closely with the NICHD using NIH operating rules. There are no conflicts of interest with these individuals, who are not research collaborators of, and are at separate institutions from the investigators.

The already named members of the DSMC are:

Chair: Dr Alan Jobe

Professor of Pediatrics, University of Cincinnati, whose primary focus is care of the newborn lung.

Members:

Dr John Kattwinkel	Emeritus Professor of Pediatrics, Division of Neonatology, University of Virginia, whose primary focus is evidence-based practice in neonatal resuscitation.
Dr Elizabeth Thom	Center Director of the Biostatistics Center at George Washington University, and Principal Investigator of the Data Coordinating Center for the NICHD Maternal-Fetal Medicine (MFM) Network, whose biostatistical expertise is in the conduct of multi-center clinical trials.
Dr. Jonathan Fanaroff	Associate Professor of Pediatrics, Case Western Reserve University School of Medicine, whose primary focus is ethics of neonatology research.
Dr. Marian Willinger	(Non-voting member) Program Scientist/Medical Officer, is also appointed to the Board to ensure co-oversight by the NICHD.

All members of the DSMC are completely independent of the study and the PIs and will be required to sign documentation to this effect. The DSMC will conform to the recommended standards of the NIH (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm>).

It will be the responsibility of the trial investigators to notify the IRB or IRBs involved of any issues that are relevant to patient safety or to early stopping of the study. The executive committee will discuss with the DSMC how frequently to review sites at the start-up phase to ensure safety, consent and enrollment. The DSMC will have at least one annual in-person meeting and teleconferences, as necessary, organized by the Data Coordinating Center (DCC).

In brief the Committee will:

- Review the research protocol, review model informed consent documents, and plans for data and safety monitoring, including all proposed revisions;
- Review methodology used to help maintain the confidentiality of the study data and the results of monitoring by reviewing procedures put in place by investigators to ensure confidentiality;
- Monitor study design, procedures and events that will maximize the safety of the study participants and minimize the risks;
- Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study site(s), and other factors that may affect study outcome;

- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the studies;
- Review serious adverse event documentation and safety reports and make recommendations regarding protection of the safety of the study participants.

The DSMC is fully empowered to require any other specific changes to the trial (pertaining to patient safety and trial feasibility issues) prior to any local IRB submissions and prior to any start to enrollment. As is usual in such studies, the Steering Committee has the final responsibility for the trial and is the final seat of decisions.

The DSMC deliberations will summarize topics discussed, recommendations made and will be signed by the board chair. All participating sites and their site PIs will receive a sanitized summary of board recommendations, to be forwarded to the IRB of each site.

Any potential and actual Conflicts of Interest (COI) for board members will be reviewed and managed appropriately.

8. Research Ethics

8.1. Consent Options

We will obtain an antenatal consent of parents of likely eligible infants 230-266 GA, who may be likely to conform to the inclusion and exclusion criteria. In this case a log will be maintained of all screened mothers-infants indicating who are eligible and which enrolled.

We recognize that there are serious personal burdens to mothers, practical difficulties, and finally, serious scientific concerns arising from the antenatal consent process. These are summarized as follows:

Firstly; there is already an additional burden to distraught mothers who have been informed that they are at risk of preterm delivery. This is a difficult time to absorb the message that a possible randomization will be performed on their high-risk infant. Moreover, some of these these mothers may not even, in fact end up delivering an eligible baby. This is because threatened preterm delivery is an imprecise diagnose whereby approximately 50% of mothers may not in fact deliver until after 26 +6/7 weeks. Data for this is shown in Rich W et al^{17, 18}, and we discuss its implication for selection bias in the text below.

Secondly, there is a limited time whereby parents can process and consider an informed consent process as can be seen from a detailed analysis of administration of antenatal corticosteroids in the Hospital of University of Pennsylvania study, which found the following:

“Median time from presentation to delivery in those who received 1 dose (n= 85) was 7.96 hours (IQR, 4.1-17.3). In those who did not receive ANCS (n=64), the median time from presentation to delivery was 1.27 hours (IQR, 0.53-2.42; P

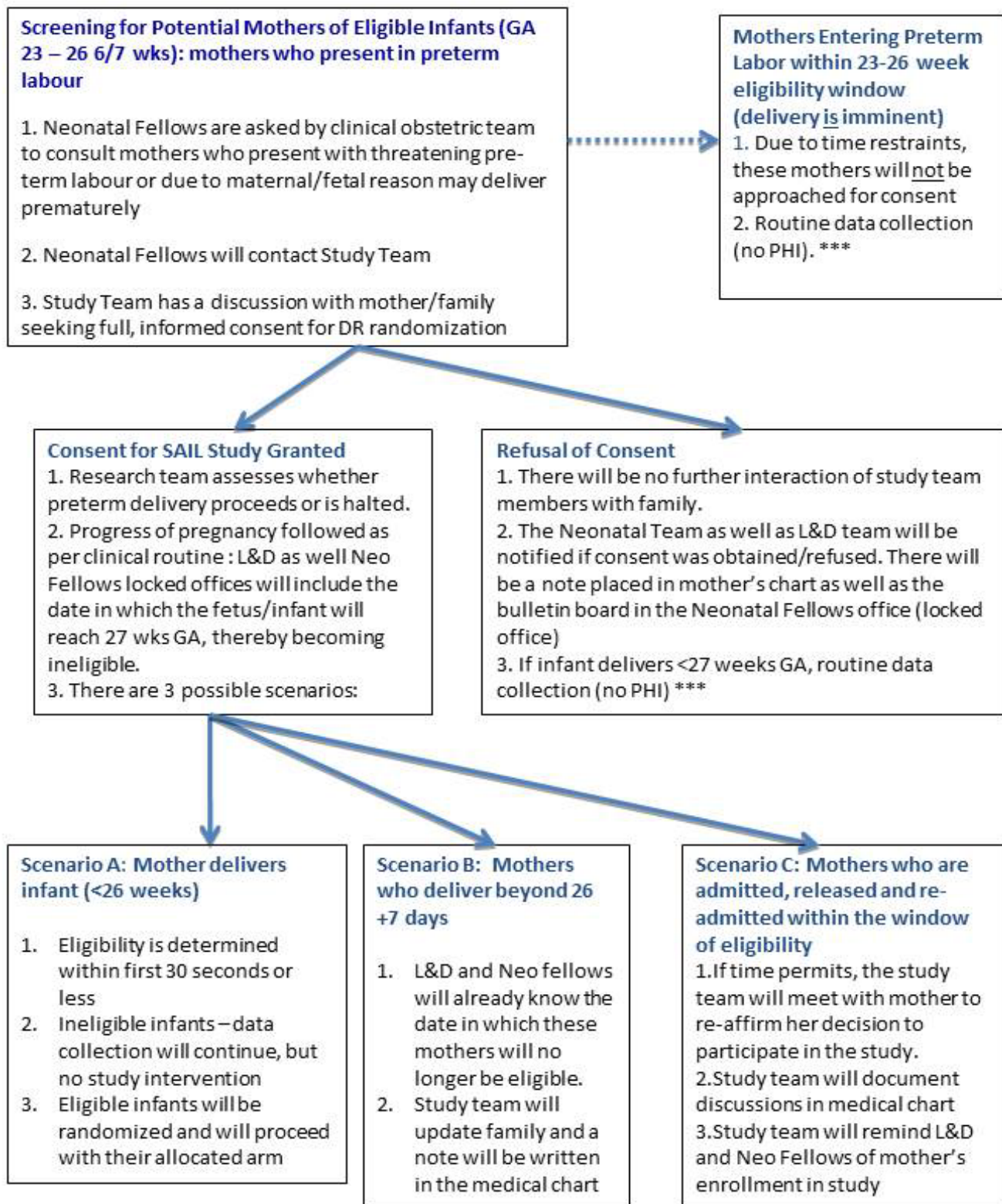
<.0001). Sixty-two percent of those who received only 1 dose of ILCS delivered in <12 hours after the initial presentation. Of the 64 patients who did not receive ANCS, 18.7% (n =12 women), 21.8% (n =14 women), 21.8% (n =14 women), and 37.5% (n=24 women) delivered at <30 minutes, 30-59 minutes, 60-120 minutes, and >120 minutes after presentation, respectively.” In addition when comparing mothers who had two doses of ANCS to those who had none or only one dose, a dose response relationship is seen such that the latter have a much higher proportion of infants < GA 30 weeks.²⁴

Finally, there is a serious potential for selection bias of the antenatal consent process, as noted by Rich W, et al.^{17, 18} This paper outlines the major problems of generalizability, and it is acknowledged by the authors of the SUPPORT trial that this has affected its findings.² Nonetheless, after careful discussion with the IRB, we will adopt the full informed antenatal consent procedures. This is largely because of the uncertainty surrounding the current point estimates of potential risk. This is discussed in detail below.

8.1.1. Consent Approach and Consent Form for Families

The diagram below explains the practical sequence of events.

Figure 3: Screening and Consent Process Outline



*** IRB approval will be obtained for data collection. [see Table in section 4.5.3]

8.2. Risks of Study Participation

The main risk of this maneuver is occurrence of pneumothorax (air-leak). [Pneumothorax is the most serious of the spectrum of air-leaks. However we will also track Pulmonary interstitial Emphysema (PIE) as potential complications (see section 9.2.3)]. While this risk is described in relation to the experimental procedure (Sustained Inflation), it is also encountered as a potential risk of any delivery room resuscitation. It is therefore explicitly acknowledged as a risk in the Newborn Resuscitation Program (NRP) teaching manual of the American Academy of Pediatrics and the American Heart Association 6TH Edition 2011; Editor J.Kattwinkel.⁴ [Page numbers in the next paragraph refer to this text]. It is relevant that all care-givers whether in the USA, Canada, Europe or Australia (where the SAIL recruiting sites are) are required to have successfully completed an NRP course or equivalent, in order to deliver care to these infants.

The main predisposing etiological factor for pneumothorax is widely acknowledged to be the amount of airway pressure delivered to the lungs. As written in the NRP Guideline:

“inadvertent high-inflating pressures being delivered to the patient may result in a pneumothorax” p.82;

“high pressure may be generated in the baby and cause a pneumothorax or other air-leak” p.117;

“Sufficient pressure to achieve a rise in heart rate and adequate ventilation should be provided, but excessive inflation pressure or too much CPAP can... create a pneumothorax” p.277.

NRP also therefore has to proffer a standard treatment for pneumothorax which is outlined in considerable depth.

Accordingly, the NRP recommends that there be pressure limits on the degree of inflation to be used during resuscitation of these infants:

“If positive pressure ventilation is required, use the lowest inflation pressure necessary to achieve an adequate response. An initial inflation pressure of 20 to 25 cm H₂O is adequate for most preterm newborns... if you still not have any chest movement, you may need to increase the ventilating pressure cautiously..” p. 276.

These suggested pressures are themselves a revision downwards from the original pressures stated by the NRP Guidelines of 2006.

It is important therefore to note that the current NRP recommended range of peak pressure, is actually no different from that being applied at the airway by the sustained inflation maneuver in the current study. The first SI given is of a pressure of 20 cm H₂O and the second is a pressure of 25 cm H₂O.

Finally, in the randomized studies to date there has not been any increase in serious outcomes, like death rates, from the sustained inflation maneuver. However, in regard to the main potential risk to be discussed, we tabulate below the conflicting data on the rates of airleak in these studies.

Risks of air-leak in randomized studies where two groups can be compared

Study	Rates of pneumothorax in control group using standard NRP	Rates of pneumothorax in Sustained inflation group	P values reported
Lindner 2005	4/30 (13%)	3/31 (10%)	Ns
Te-Pas 2007	7/103 (7%)	1/104 (1%)	0.069
Lista Unpublished 2013 (private communication)	2/124	8/126	0.102

Nonetheless, the point estimates for risk are based on insufficient data to enable a precise estimate. Therefore this risk is explicitly discussed in the consent form.

There may be unforeseen risks that may accompany the presence/treatment for a pneumothorax such oxygen desaturation, hypotension, bradycardia. These unforeseen risks are possible in standard of care NRP guidelines as well as the sustained inflation arm of the study.

8.3. Data Confidentiality

All named study PIs at the US sites, and their research coordinators are CITI certified in conduct of clinical trials, as a requirement of their participation in any study. We will encourage those at the international sites to do the same. The basic rights of study participants will be respected and maintained by the investigators and by all who are involved in the collection or processing of individually identified data. All data collection and processing procedures are designed to protect individual rights and to comply with all applicable laws and ethical principles including confidentiality. Among the rights that must be protected are:

- the right to informed consent, which requires that prospective participants in a research project and, if needed, their family members, be provided adequate information about the potential risks, benefits, and requirements of participation so that each can make an informed decision about participation
- the right to decline, which requires that prospective participants be fully informed that their participation is completely voluntary, that they may withdraw at any time, that access to adequate health care will be provided whether or not they participate in the research, and that they may refuse to answer any question
- the right to privacy, which requires guarantees of confidentiality of information and other specific protection as specified in the Privacy Act of 1974.

The basic rights of study participants will be respected and maintained by the investigators and by all who are involved in the collection or processing of individually identified data. Our data collection and processing procedures are designed to protect individual rights and to comply with all applicable laws

and ethical principles. All staff who conduct or support research involving human subjects are required to undergo training on the protection of human subjects in research.

We do not mandate any additional blood sampling, thus not departing from the standard practice of the NICU. Minimizing risks from procedures used to collect data is the responsibility of the clinical centers and the DCC, although procedures to minimize risk will be described in the study protocols and include medical management common for this study population. Confidentiality procedures for subject data will be established by the trial investigators before data are transferred to the DCC. All subject-identifying data will be kept solely at the clinical centers.

The data collection forms will include unique study ID numbers only and basic demographic data as participant identifiers. Thus, the files maintained at DCC will contain limited identifying information and protect subject confidentiality. Safeguards are in place to greatly decrease the chances that characteristics of a case can be linked to the individual participating in the study.

The DCC will receive subject data from the clinical centers identified by a study ID only and will never have contact with the subjects. All procedures related to DCC activities, including data transmission and data security procedures, are reviewed and approved by the DCC IRB prior to receipt of any study data at U Pennsylvania.

At select sites, we will obtain video recordings of the infant resuscitation in order to assess adherence to the study treatment algorithm and to perform assurance for the RFM data processing.

At many SAIL study sites, video recordings are standardly made during newborn resuscitation for quality improvement and audit, educational and research purposes. Each site will be responsible for obtaining IRB approval at their own site, and parental consent to allow short-term viewing and analysis of these videos for the SAIL trial.

As detailed in the MOP, video recordings are used as quality assurance during the data processing for the RFM. Video files provide a method to clearly identify actions such as mask repositioning or spontaneous breathing, and they improve interpretation of respiratory waveforms under these conditions.

Once generated, the videos will be labeled under the SAIL identifier and securely transferred to the UPenn DCC. All videos will be securely stored under the SAIL identifier at the DCC. Once the videos are reviewed for all research-related activities, they will be destroyed within 18 months at the SAIL DCC.

9. Regulatory Oversight

All clinical centers and the DCC have IRB committees that convene on a fixed schedule every month to review protocols and associated informed consent forms and data collection procedures for all research to ensure that they are in compliance with all applicable human subject regulations. IRB approval must be granted prior to beginning any study, and study progress and procedures must be reviewed by the IRB at least annually.

Potential subjects or their legal guardians must be fully informed about the details of any research study in which they are considering participation and what their involvement will entail. Specific consent forms are developed for each protocol and reviewed and approved by the IRBs at the DCC and at each clinical center. The DCC reviews forms used at the sites to ensure that essential elements of consent are presented and comply with federal law.

All US clinical centers and the DCC have Federal wide Assurance (FWA) by the Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS). This FWA is an agreement between each center, DCC and the U.S. government that all research with human subjects will be conducted according to appropriate federal regulations and allows us to undertake its own Institutional Review Board (IRB) review and monitoring of research with human subjects. Each institution participating in the trial holds an FWA, which ensures that the institution's human research activities, overseen by their regulatory authorities, comply with the requirements set forth in 45 CFR 46, as well as the terms of Assurance. The DCC is responsible for obtaining appropriate clearances at our institution with respect to HIPAA and Human Subjects Research regulations and verifying similar clearances at the clinical centers.

Trial study procedures are subject to the approval of the IRBs at the participating clinical centers and the DCC. For this trial, the protocol, informed consent (IC), and other study documents used at each center must be reviewed and approved by the respective IRBs and the DCC before the study is initiated. The IRBs monitor the research process to ensure that the procedures for protecting human subject rights are followed. Every protocol is reviewed by each IRB at least annually. Each IRB reviews SAE reports and approves all proposed changes to a research protocol before any changes are implemented. If necessary, the IRBs will mandate changes needed to protect the rights and welfare of human subjects or suggest solutions for problems that arise during a project.

After IRB approval, infants eligible for the trial will be identified by the clinical center PI or study staff from among the infants who are cared for in the Neonatal Intensive Care Units. The PI or their staff will explain to the parents (1) consent forms that have been specifically written to address the nature, duration, and purpose of the study; (2) means by which it is to be conducted; (3) possible benefit or lack of benefits; (4) potential risks, hazards, and discomforts; and (5) possible alternative procedures. Specific decisions regarding the operational details of how consent will be sought (including the timing and the level of details presented regarding various aspects of the study) are made at the level of each clinical center under the guidelines of their local IRBs and practice policies and traditions.

NICHHD will defer to local IRB ruling for the conduct of the trial at all the clinical centers. Should a local IRB determine safety issues and require actions, including any related to suggested changes to the consent form, the local center research staff (investigator/coordinator) will notify the DCC, the NICHHD Program Scientist. NICHHD will direct the DCC in further action. Note that any changes to the protocol itself (directed either by any IRB or the DSMC) will require discussion and approval by the trial subcommittee and NICHHD. The DCC will maintain all communications between the clinical center(s) and NICHHD through resolution of all IRB issues.

9.1. Conflict of Interest

We will ensure that no member appointed to the DSMC has a conflict of interest, and they will be required to sign to that effect. No one on the study team including the steering committee of the trial, has any financial interests related to resuscitation devices, nor do they act as consultants to any delivery room based commercial agencies.

9.2. Collecting and Reporting Adverse Events

A comprehensive manual of procedures will include a detailed section about reporting adverse events so that this is done uniformly across the sites. The trial will adhere to standard adverse event definitions as follows:

9.2.1. Adverse Events (AE)

“Adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the intervention, whether or not the event is considered related to the treatment or clinically significant. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an Adverse Event”.

Adverse events will be monitored during the study to ensure timely detection of events that may affect safety or continued participation. In this trial, this extremely high-risk and fragile population will each experience expected and unexpected adverse events. Adverse events and their relationship to study, severity, time of experience, expectation, actions taken to resolve the event and final outcome will be recorded as documented in the medical record, or if reported by the NICU team even before documentation. These event rates will be part of reporting the final results of the study and for the DSMC safety monitoring.

Secondary outcomes of interest in this trial that can be compared across the two treatment groups include: death; Bell Stage 2-3 necrotizing enterocolitis; periventricular leukomalacia or echodense lesions or ventriculomegaly; apnea mandating either caffeine or respiratory support; bronchopulmonary dysplasia; retinopathy of prematurity requiring intervention; and each component of the primary outcome (available only after the 22 to 26 month follow-up visit). Rates of these events, historically observed among similar extremely low gestation/birth weight infants, will be provided to the DSMC for comparison. Common, serious neonatal morbidities will also be collected. These include data on in-hospital growth, the incidence and severity of intraventricular hemorrhage, seizures, patent ductus arteriosus (PDA) and its treatment, nosocomial sepsis (and organisms), hearing impairment, and pneumothorax.

9.2.2. Serious Adverse Events (SAE)

The serious adverse event (SAE) definitions are listed below. Based on the premature infant population studied, the SAE categories of events that result in congenital anomaly/birth defect or

require intervention to prevent permanent impairment or damage (devices) do not apply when defining events.

An adverse event or suspected adverse reaction is considered *serious* if in the review of the investigator or the sponsor, it results in any of the following:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Prolongation of Hospitalization	An event that prolongs the patient's hospital stay.
Results in persistent or significant disability/incapacity	An adverse event that may result in a substantial disruption of the ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the infants body function/structure, physical activities and/or quality of life.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, prolongation of hospitalization). An example of such events would be an allergic bronchospasm requiring intensive treatment.

Expedited Serious Adverse Events (SAE)

The sponsor NICHD will determine if individual serious adverse events a) meet the criteria for expedited reporting and b) ensure that they are promptly reported to the DSMC.

Unexpected Adverse Event

An unexpected AE is defined as any adverse event, the specificity or severity of which is not listed in the study protocol, product inserts, or informed consent document.

Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. This will be determined by the site PI and study team, according to the basis of the below classification:

- 1) Definitely
- 2) Probably
- 3) Possibly

- 4) Unlikely
- 5) Unrelated

9.2.3. Clinical Events Defined

The chart below shows the specific clinical events that are defined as serious for the SAIL Study and the reporting requirements established for the clinical sites:

Adverse Event definitions:	Time Frame
Oxygen requirement of FiO ₂ ≥ 40% for 2 hours or more	Within the first 48 hours post delivery
Grade 1 or 2 IVH	Head ultrasound findings with the first 10 days of life (report based only)
Infant requiring > 30% Oxygen or mechanical support	Respiratory support assessment at day of life 28

Serious Adverse Event definitions:	Time Frame
Death	Within the first 48 hours post delivery
Administration of epinephrine or use of chest compressions	Within the first 48 hours post delivery
Pneumothorax, pulmonary interstitial emphysema (PIE) and pneumopericardium. These will be supplemented by data on: <ul style="list-style-type: none"> a) any chest tube in-situ post DR b) need for new chest tube after arrival in NICU 	Radiographic evidence within the first 10 days of life
Grade 3 or 4 IVH	Head ultrasound findings with the first 10 days of life (report based only)

9.2.4. Unanticipated Problems

An Unanticipated Problem is defined as any incident, experience, or outcome that meets *all* of the following criteria:

- 1) Is not expected in terms of nature, severity, or frequency in relation to (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and (b) the characteristics of the subject population being studied; **and**
- 2) Is related or possibly related to participation in the research; **and**
- 3) Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously know or recognized.

9.2.5. Adverse Event Management and Reporting

If an adverse event meets any of the criteria listed above of Serious, Unexpected and at least Possibly Attributable to the study therapy or intervention, it will be reported by study team at the recruiting site to the NICHD, the Data Coordinating Center (DCC), and the local IRB (per site specific

IRB procedures) as a serious adverse event via the Medwatch Safety Reporting Form 3500A or a form that mimics it.

Adverse Event/Serious Adverse Event forms will be completed by site research staff (investigators and/or coordinators) for each reportable (as defined by protocol) adverse event that infants may experience from the time of randomization through the predefined intervention and/or events monitoring period. Events will be documented by clinical site staff using case report forms (CRF), reviewed and signed by the site investigator for accuracy and completeness then entered into the specified Data Management System (DMS) as instructed in the manual of procedures.

1. A preliminary SAE alert must be submitted within 24 hours of first knowledge of the event.
2. A more complete SAE report should be submitted (on Medwatch form 3500A or a similar form developed by the DCC) within 72 hours.
3. A final report must be submitted by the site to the DCC within one week, including when applicable, autopsy findings.
4. The final report will then be submitted to the DSMC Chair for independent adjudication of relatedness to the intervention.

The Program Scientist at NICHD and/or the DCC will determine whether expedited DSMC reviews are necessary. The DSMC can recommend further action and the DCC will be responsible for notification to the local site team and NICHD. NICHD may request the DCC notify required parties through established communication mechanisms via technical memos.

Reporting to the Food and Drug Administration will not be required for this trial as it involves no new drug or device intervention mandating an IND/IDE.

10. Synopsis

It is expected that trial completion in 12 sites will take 5 years, including 2.5 years of recruitment.

This project has huge public health implications due to large burden from death and BPD in this population. The study intervention (SI) is poised to reduce this burden, and the trial would be at the 'right time', for a not-yet established therapy with promising pilot data. Moreover the potential benefits are lifelong, if the strategy is successful. In addition to the outstanding track record and expertise of the US based co-PIs, the overseas co-PIs are essential for successful trial completion. The key benefits of the foreign sites include content expertise in DR research and sustained inflation. Most of the animal and human data on this novel technique comes almost exclusively from Europe and Australia. Similar large scale RCTs (TIPP, CAP, PINT) have been completed internationally. In addition PD is a member of ILCOR, confirming the critical importance of the question and guaranteeing translation to clinical practice. We submit that the involvement of all these highly committed international sites, but under US leadership, and in collaboration with the US sites – can only further promote the currently high profile of neonatal

trial research led by the US. A deserved field to further this is Delivery room resuscitation. This has been for too long, a neglected area for randomized trial evidence based medicine.

11. References

1. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics*. 2004; 114: 1305-11.
2. Network SSGotEKSNNR, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. *The New England journal of medicine*. 2010; 362: 1959-69.
3. Pfister RH and Soll RF. Initial respiratory support of preterm infants: the role of CPAP, the INSURE method, and noninvasive ventilation. *Clinics in perinatology*. 2012; 39: 459-81.
4. Kattwinkel J. *Neonatal Resuscitation (NRP) Textbook - 6th Edition (English version) - 2010 American Academy of Pediatrics and American Heart Association Guidelines for Neonatal Resuscitation*. 2011.
5. Committee on F, Newborn and American Academy of P. Respiratory support in preterm infants at birth. *Pediatrics*. 2014; 133: 171-4.
6. Polin RA, Carlo WA, Committee on F, Newborn and American Academy of P. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*. 2014; 133: 156-63.
7. Hooper SB, te Pas AB and Lewis RAMCJ. Establishing Functional Residual Capacity at Birth. *Neoreviews*. 2010; 11: e474-e83.
8. Sobotka KS, Hooper SB, Allison BJ, et al. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. *Pediatric research*. 2011; 70: 56-60.
9. te Pas AB, Siew M, Wallace MJ, et al. Effect of sustained inflation length on establishing functional residual capacity at birth in ventilated premature rabbits. *Pediatric research*. 2009; 66: 295-300.
10. te Pas AB, Siew M, Wallace MJ, et al. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. *Pediatric research*. 2009; 65: 537-41.
11. te Pas AB, Wong C, Kamlin CO, Dawson JA, Morley CJ and Davis PG. Breathing patterns in preterm and term infants immediately after birth. *Pediatric research*. 2009; 65: 352-6.
12. Lista G, Fontana P, Castoldi F, Cavigioli F and Dani C. Does sustained lung inflation at birth improve outcome of preterm infants at risk for respiratory distress syndrome? *Neonatology*. 2011; 99: 45-50.
13. Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M and Hummler HD. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. *Pediatric research*. 2011; 70: 176-80.
14. te Pas AB and Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. *Pediatrics*. 2007; 120: 322-9.

15. Hussey SG, Ryan CA and Murphy BP. Comparison of three manual ventilation devices using an intubated mannequin. *Archives of disease in childhood Fetal and neonatal edition*. 2004; 89: F490-3.
16. Klingenberg C, Dawson JA, Gerber A, Kamlin CO, Davis PG and Morley CJ. Sustained inflations: comparing three neonatal resuscitation devices. *Neonatology*. 2011; 100: 78-84.
17. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics*. 2012; 129: 480-4.
18. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics*. 2010; 126: e215-21.
19. Tyson JE, Parikh NA, Langer J, et al. Intensive care for extreme prematurity--moving beyond gestational age. *The New England journal of medicine*. 2008; 358: 1672-81.
20. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *The New England journal of medicine*. 2008; 358: 700-8.
21. Ratcliffe SJ, Heller GZ and Leader LR. Functional data analysis with application to periodically stimulated foetal heart rate data. II: functional logistic regression. *Statistics in medicine*. 2002; 21: 1115-27.
22. O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979; 35: 549-56.
23. Damocles Study Group NHSHTAP. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005; 365: 711-22.
24. Chandrasekaran S and Srinivas SK. Antenatal corticosteroid administration: understanding its use as an obstetric quality metric. *American Journal of Obstetrics and Gynecology*. 2013.