Title: Impact of CPAP Level of V/Q Mismatch in Premature Infants

NCT02983825

Last Protocol Approval Date: 2/20/19

Modification

Basic Info

Confirmation Number:	**chjddjdg**
Protocol Number:	**825874**
Created By:	**BAMAT, NICOLAS**
Principal Investigator:	**BAMAT, NICOLAS**
Protocol Title:	**Impact of continuous positive airway pressure (CPAP) level on ventilation/perfusion mismatch in premature infa phase II clinical trial.**
Short Title:	**CPAP and V/Q in premature infants**
Protocol Description:	**Purpose: To measure the responsiveness of ventilation/perfusion (V/Q) mismatch to a strategy of individualized CPAP level selection. Population: Up to 30 infants of corrected gestational age 27-35 weeks, chronologic age greater than 24h, requiring oxygen supplemental oxygen while on CPAP. Approach: single-arm prospective phase-II clinical trial with application of a protocol of step-wise changes in CPAP level guided by improvements in V/Q mismatch, measured using a non-invasive technique.**
Submission Type:	**Biomedical Research**
Application Type:	**FULL**

PennERA Protocol Status

Approved

Resubmission*
No

Are you submitting a Modification to this protocol?*

Yes

Current Status of Study

Study Status

Currently in Progress

If study is currently in progress, please enter the following

Number of subjects enrolled at Penn since the study was initiated

12

Actual enrollment at participating centers

15

If study is closed to further enrollment, please enter the following

Number of subjects in therapy or intervention

0

Number of subjects in long-term follow-up only

0

IRB Determination
If the change represents more than minimal risk to subjects, it must be reviewed and approved by the IRB at a convened meeting. For a modification to be considered more than minimal risk, the proposed change would increase the risk of discomfort or decrease benefit. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented unless the change is necessary to eliminate an immediate hazard to the research participants. In the case of a change implemented to eliminate an immediate hazard to participants, the IRB will review the change to determine that it is consistent with ensuring the participant′s continued welfare. Examples: Convened Board Increase in target enrollment for investigator initiated research or potential Phase I research Expanding inclusion or removing exclusion criteria where the new population may be at increased risk Revised risk information with active participants Minor risk revisions that may affect a subject′s willingness to continue to participate Expedited Review Increase in target enrollment at Penn where overall enrollment target is not exceeded or potentially sponsored research Expanding inclusion or removing exclusion where the new population has the same expected risk as the previous, based on similarities of condition Revised risk information with subjects in long-term follow-up Minor risk revisions with no subjects enrolled to date
Expedited Review

Modification Summary
Please describe any required modification to the protocol. If you are using this form to submit an exception or report a deviation, enter 'N/A' in the box below.
Increase in total enrollment in order to apply the study intervention in 20 subjects. To date, 4 subjects have enrolled (defined by provision of informed consent) who subsequently became ineligible and could not undergo the intervention. We will increase total enrollment to 30 subjects, in order to allow for these subjects who enroll but become ineligible after consent, but will consider accrual complete when 20 subjects undergo the study intervention.

Risk / Benefit
Does this amendment alter the Risk/Benefit profile of the study?
No

Change in Consent
Has there been a change in the consent documents?
No

If YES, please choose from the options below regarding re-consenting

Deviations

Are you reporting a deviation to this protocol?*

No

Exceptions

Are you reporting an exception to this protocol?*

No

Protocol Details

Resubmission*
Yes

Study Personnel

Principal Investigator

Name:	**BAMAT, NICOLAS**
Dept / School / Div:	**4392 - PE-Pediatrics**
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Pager:	
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HS Training Completed:	**Yes**
Training Expiration Date:	**09/07/2017**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

Name:	**MCANLIS, CAROLYN**
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HS Training Completed:	**Yes**
Training Expiration Date:	**03/02/2018**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**ABBASI, SORAYA**
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Fax:	**-**
Pager:	
Email:	**abbasis@uphs.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**04/05/2018**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**WOODFORD, EMILY**
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Fax:	**-**
Pager:	
Email:	**Emily.Woodford@pennmedicine.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/24/2021**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Other Investigator

None

Responsible Org (Department/School/Division):

4392 - PE-Pediatrics

Key Study Personnel

Name:	**MANCINI, TONI**
Department/School/Division:	**Health System**
HS Training Completed:	**Yes**
Training Expiration Date:	**02/15/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**HANDLEY, SARA**
Department/School/Division:	**PE-Pediatrics**
HS Training Completed:	**Yes**
Training Expiration Date:	**08/07/2018**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**CHAUDHARY, AASMA**
Department/School/Division:	**Health System**
HS Training Completed:	**Yes**
Training Expiration Date:	**10/25/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?
Yes

If Yes, please be aware that for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

Investigator Initiated Trial*
Is this an investigator initiated trial?
No

Drugs or Devices*
Does this research study involve Drugs or Devices?
No

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
No

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
No

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?

Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
No

Primary Focus*
Clinical Trial (prospectively assigning subjects to health-related interventions to evaluate outcomes)

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
	Drug
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
x	**Diagnostic test/procedure (research-related diagnostic test or procedure)**
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Department budget code

None

Multi-Site Research

Other Sites

Site:	**The Children's Hospital of Philadelphia**
Contact:	
Pi:	**Nicolas Bamat**
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Site:	**Pennsylvania Hospital**
Contact:	
Pi:	**Nicolas Bamat**
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Phone:	
Email:	

Management of Information for Multi-Center Research

The following documents are currently attached to this item:

There are no documents attached for this item.

Protocol

Abstract
Background: Infants born prematurely are at high risk of developing bronchopulmonary dysplasia (BPD). BPD is associated with death as well as long-term respiratory and neurodevelopmental impairments in childhood survivors. Very few evidence-based therapies for preventing BPD exist. Of these, the preferential use of nasal continuous positive airway pressure (CPAP) over mechanical ventilation (MV) is the most novel. CPAP applies a continuous distending airway pressure to lungs prone to collapse, while avoiding the ventilator-induced lung injury of MV known to contribute to the development of BPD. Sometimes, two levels of alternating pressure are applied, with higher and lower pressure levels alternating. This is called bi-level non-invasive support. When there is only one pressure level, this is the CPAP level. In bi-level support, the lower pressure level is considered the CPAP level. By promoting open lungs, CPAP helps prevent atelectasis. This improves oxygenation, in large part by reducing ventilation/perfusion (V/Q) mismatch. However, the overall benefit of preferential CPAP over MV is modest. An explanation for this limited benefit may be that most infants at highest risk for BPD fail CPAP and are nonetheless exposed to MV and its associated harms. Poor oxygenation is responsible for most CPAP failures. Strategies to improve oxygenation while on CPAP are needed to achieve a more substantial benefit. A knowledge gap exists for a basic aspect of CPAP therapy: how much pressure should be used? While a greater airway distending pressure benefits under-inflated lungs, excessive pressure may result in lung over-distension and risk harm. Strategies for determining a best CPAP level individualized to the needs of each premature infant are needed to help prevent BPD and are currently lacking (Figure 1). Objectives: to evaluate the utility of a promising strategy for

individualized CPAP level selection: identifying the lowest pressure level that minimizes V/Q mismatch. While traditional methods for measuring V/Q mismatch are invasive or technically burdensome, our team has expertise in the use of a simple, non-invasive technique: a computerized oxygenation model enabling bedside quantification of V/Q mismatch on the basis of the curvilinear characteristics generated by multiple fraction of inspired oxygen (FiO2) and peripheral oxygen saturation (SpO2) pairs. This technique uses data that is readily available at the infants bedside without a need for patient travel, additional instrumentation or blood draws, making it valuable in this vulnerable population. The primary specific aim of this research proposal is to measure the responsiveness of V/Q mismatch to a strategy of individualized CPAP level selection. In other words: can we detect measurable improvements in V/Q mismatch when applying a protocol for individualized best CPAP level selection? We hypothesize that V/Q mismatch will, on average, improve by 10% of baseline V/Q mismatch at the best identified CPAP level. We will perform a phase II, single-arm prospective clinical trial, enrolling up to 30 premature infants of corrected gestational age 27-35 weeks, chronologic age greater than 24 hours and requiring supplemental oxygen while on CPAP. Infants with congenital anomalies or with a history of or concerns for air leak syndromes will be excluded. We will first measure V/Q mismatch at baseline CPAP, set by the clinical team. Subjects will then undergo a protocol of stepwise CPAP level changes, with improvements in V/Q mismatch relative to baseline defining a positive response and guiding any additional CPAP level changes. Best CPAP will be defined as the lowest pressure level associated with a progressive response. Our primary outcome will be the difference in measured V/Q mismatch between baseline and best CPAP, with a paired t-test for parametric results or a Wilcoxon signed-rank test for non-parametric results testing our hypothesis that V/Q mismatch will improv

Objectives

Overall objectives

The objective of the proposed research is to evaluate a promising strategy for CPAP level selection: a physiologic approach minimizing V/Q mismatch and measured non-invasively at the infants bedside. We propose the following specific Aims and hypotheses in support of this objective: Aim 1 (primary): measure the responsiveness of V/Q mismatch to a strategy of individualized CPAP level selection. We hypothesize that V/Q mismatch will, on average, improve by 10% of baseline V/Q mismatch at the best identified CPAP level. Aim 2: describe the distribution of best CPAP levels as identified by our strategy. Best CPAP levels will be described as both absolute values and relative to baseline (+2 cm H2O, -1 cm H2O, etc.). For this exploratory aim, we hypothesize that a best CPAP will be identified above the baseline in greater than 50% but less than 80% of subjects. Demonstrating that most but not all infants benefit from higher pressures will highlight the importance of individualized CPAP level selection in premature infants.

Primary outcome variable(s)

Primary outcome measure: V/Q mismatch. This parameter will be calculated by computer software on the basis of the curvilinear characteristics generated by a best-fit curve connecting the FiO2/SpO2 pairs obtained during the study protocol. With lower V/Q and greater mismatch, the curve is progressively displaced to the right relative to a curve corresponding to an ideal reference lung (interrupted, left-most curve in Figure 2, see attached documents). The V/Q ratio is displayed on the software output after the FiO2/SpO2 pairs are input. Additionally, this parameter is also displayed as the degree of right-shift relative to the ideal reference lung (greater values indicate more mismatch), providing a positive continuous number with units of % FiO2 as an alternative measure to the ratio value with greater ease of use. This will be measured twice at baseline without a change in CPAP level and then following each CPAP level change. The primary outcome measure is the responsiveness of V/Q mismatch to a strategy of individualized CPAP level selection, measured as the improvement in V/Q mismatch between the second baseline level and best identified CPAP level for each subject (see Figure 3 in attached documents.) For infants not responding to either +1 or -1 cm H2O CPAP level changes, baseline CPAP will be defined as best, with zero assigned as the improvement in V/Q mismatch.

Secondary outcome variable(s)

Secondary outcome: best CPAP level. Our second Aim is to describe the distribution of best CPAP levels as identified by our strategy. We hypothesize that best CPAP will vary between infants, resulting in a distribution of values. Best CPAP level will be identified as the lowest CPAP level associated with an improvement greater than 5% in V/Q mismatch relative to the preceding CPAP level, as described in the study protocol. This will be "measured" once at the conclusion of the study protocol. Excessive

airway pressures can result in lung over-distension and can plausibly result in adverse cardiopulmonary interactions through transmission of positive pressure to the heart and intra-thoracic vessels (however, this has not been observed in any modern CPAP level studies performed in premature infants, see Table 1). We will measure the impact of CPAP level changes on the following readily available clinical cardiovascular parameters during the study protocol: Mean arterial blood pressure will be measured with a neonatal blood pressure cuff used for routine clinical care and placed on an upper extremity or through pressure transduction of an indwelling arterial catheter, when present (uncommon in our subject population), with units of mm Hg. This outcome will be recorded at the end of each baseline and CPAP level period by the research team. Heart rate will be measured and displayed by the study pulse oximeter, with units of beat per minute. This outcome will be recorded at the end of each baseline and CPAP level period by the research team. Additional data to be collected will include: i) demographic data; (gestational age, birth weight, gender, race, etc.) ii) baseline variables (receipt of antenatal steroids, Apgar scores, age in hours and FiO2 at intervention, most recent hemoglobin level, CPAP pressure source and interface, etc.) and iii) important or pertinent in-hospital neonatal outcomes (survival to discharge, BPD, brain injury by ultrasound, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, duration of: MV days, CPAP and supplemental oxygen, etc). This data will be used to explore associations between these variables and both a) baseline V/Q mismatch and b) the responsiveness of this parameter to CPAP level changes, with a goal of supporting hypothesis generation for subsequent research

Background

Bronchopulmonary dysplasia (BPD) is a chronic lung disease resulting from premature birth that affects nearly 70% of infants born 28 weeks gestational age (GA) (1). BPD and its precursor, respiratory distress syndrome (RDS), are a leading cause of death in very premature infants (2). In turn, survivors require increased health expenditures and have adverse long-term respiratory and developmental outcomes in childhood (3-5). Despite the significant burden of BPD on pediatric health, very few preventive interventions exist (6). Of these, a strategy of minimizing mechanical ventilation (MV) with preferential initial nasal continuous positive airway pressure (CPAP) is the most novel (7-8). CPAP provides a continuous distending airway pressure, maintaining lung volumes and preventing atelectasis (a reduction in or collapse of the air sacs responsible for gas exchange) (9-10). This improves oxygenation by: a) reducing ventilation/perfusion (V/Q) mismatch (inefficient matching of lung areas receiving fresh air for gas exchange (ventilation) with lung areas receiving blood (perfusion) for gas exchange) and b) intrapulmonary shunt (blood passing from the right side of the heart through the lungs and to the body without any gas exchange). Sometimes, two levels of alternating pressure are applied in this way, with the higher and lower pressure levels alternating. This is called bi-level non-invasive support. When there is only one pressure level, this is the CPAP level. In bi-level support, the lower pressure level is considered the CPAP level. CPAP helps prevent BPD by providing these physiologic benefits while avoiding MV and subsequent ventilator induced lung injury (VILI), a key component in the pathogenesis of BPD. However, the benefit of preferential CPAP is modest. It is estimated that 1 death or case of BPD is averted per 25 treated infants (7-8). Consistent with this limited benefit, 46-83% of very premature infants at highest risk of BPD fail initial CPAP and nonetheless require MV (11-12). Oxygenation failure the result of excessive V/Q mismatch and shunt is the most frequent cause (12-14). An improved application of CPAP resulting in less oxygenation failure would further reduce death or BPD. A critical knowledge gap exists for a basic aspect of CPAP therapy: how much pressure should be used? There is a lack of evidence informing this question. Multi-center trials assessing CPAP versus MV have used pressures as disparate as 4-8 cm H2O and have not specified how these were determined (11, 12, 15). While higher pressures applied to under-inflated lungs likely improve oxygenation, excessive pressure may result in over-distension, increasing the risk of harms such as air leak syndromes (12) or adverse cardiopulmonary interactions (16). We propose evaluating a novel physiologic approach for individualized CPAP level selection: identification of the lowest pressure level minimizing V/Q mismatch, a key contributor to poor oxygenation and CPAP failure. While traditional methods for measuring V/Q mismatch are invasive or technically burdensome (17-18) , our research team has expertise in the use of a simple, non-invasive technique: a computerized oxygenation model enabling bedside quantification of V/Q mismatch (detailed within Methods) (19). In published research using this technique, our research team recently demonstrated a significant association between gestational age and the degree of V/Q mismatch, as well as high inter-rater reliability and validity with this approach for predicting BPD (20-21). Identification and application of an optimal pressure level by targeting a reduction in V/Q mismatch may improve oxygenation, decrease CPAP failure, avoid injurious MV and further reduce death or BPD (see Figure 1 in attached documentation). Table 1 summarizes existing prospective studies assessing the impact of CPAP level changes in premature

infants over the last 20 years.

Study Design

Phase*
Phase II

Design
Phase II, single-arm prospective clinical trial. The goal of a phase II clinical trial is to determine whether an intervention has a biologic effect and to monitor safety. In our proposal the intervention is a strategy of individualized CPAP level selection and the biologic effect is a response in V/Q mismatch. Please see Risk/Benefit section for a complete discussion of safety considerations.

Study duration
Estimated length of time to enroll all subjects and complete the study: 10-12 months (please see Figure 4 in attached documentation for a diagram describing expected enrollment). Length of a subject's participation time in study: each subject will participate in activity study procedures for 60-120 minutes. Each study will participate in the study from the time of enrollment through hospital discharge. The projected dates of the proposed study, from IRB approval to data analysis and manuscript preparation are November 2016 to January 2018. Projected dates of active subject enrollment are January 2017 to November 2017. Please see Figure 5 for a project timeline.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
This study is feasible as we have the patient population, equipment and expertise to undertake the study if adequately supported. We have secured partial funding and are awaiting a second funding decision. The budgetary needs are primarily for a respiratory therapist trained to be hired as a clinical research coordinator. We will work with the clinical research support office (CRSO) at the Children's Hospital of Philadelphia to identify and hire a specific individual in a timely fashion upon award notification. The clinical research coordinator will take assume the responsibilities of daily screening and enrollment of the study population, communication with and between the clinical team, research team and the IRB, implementation of the study interventions and data collection and management. An allotment of adequate time to complete the research is detailed in Figure 5 (attached documents). There are adequate facilities for the research. The equipment necessary for conducting the study is used in the routine clinical practice of the HUP ICN, PAH ICN, and the CHOP N/IICU. This equipment includes pulse oximeters, continuous positive airway pressure generating devices and nasal interfaces, blood pressure cuffs and pressure transducers and cardio-respiratory monitors. All study interventions are simple maneuvers performed in daily clinical practice. Only the timing and sequence of their implementation require additional basic training. Dr. Bamat will lead the project implementation and training. Dr. Bamat, Dr. Handley and a respiratory therapist trained as a clinical research coordinator will perform the study interventions. Regular research meetings with all participating staff will ensure full understanding of the protocol and all research related duties.

Characteristics of the Study Population

Target population
Premature infants requiring supplemental oxygen while on CPAP or bi-level non-invasive respiratory support in the HUP ICN, PAH ICN, or the CHOP N/IICU.

Subjects enrolled by Penn Researchers
30

Subjects enrolled by Collaborating Researchers
0

Accrual
This study will enroll up to 30 patients in order to evaluate 20 subjects. Infants will be screened for eligibility by the research team using routinely available clinical data from the electronic health record. Informed consent will be obtained from parents or guardians approached within the HUP ICN, PAH ICN, or the CHOP N/IICU during the eligibility window as described below. The diagram depicted in Figure 4 summarizes expected enrollment in consideration of our eligibility criteria and additional barriers to successful recruitment and study application. This estimate suggests a 10-month window of active enrollment will be required to meet our recruitment goals, making our one-year recruitment goal feasible. Aim 1 guides sample size considerations. Using a paired test of correlated means, a sample size of 20 evaluated infants will provide 80% power to detect an overall average percent change of 10% from baseline, assuming a 15% standard deviation of the difference and a two-sided alpha level of 0.05.

Key inclusion criteria
I1. 27-35 weeks corrected gestational age (CGA) by best obstetric estimate, determined by the clinical obstetric team during antepartum admission and chronologic age, measured from date of birth I2. Chronologic age greater than 24 hours, measured from time of birth. I3. On CPAP support between 4-8 cm H2O for greater than 24 hours, as document on the bedside infant flow sheet. I4. Supplemental oxygen requirement, with a fraction of inspired oxygen (FiO2) 0.25 for at least 2 consecutive hours, as documented on the bedside infant flow sheet. (Infants without an oxygenation requirement are unlikely to have significant V/Q mismatch. Further, FiO2 titrations (see Procedures) are required to apply the non-invasive technique, resulting in limited applicability to infants with little or no supplemental oxygen requirement).

Key exclusion criteria
E1. Congenital anomalies, as determined by the clinical supervising physician. E2. Current or prior air leak syndrome, as determined by the clinical supervising physician.

Vulnerable Populations

- x **Children Form**
- **Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form**
- x **Fetuses and/or Neonates Form**
- **Prisoners Form**
- **Other**
- **None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
We recognize that the participants of this study are neonates and therefore a vulnerable population. However, informed consent will be obtained from legal guardians able to understand and evaluate the risks and benefits of participation in this trial. This is to be done in both verbal and written form. Only parents with English as their native language will be approached. Surrogate consent from the legal guardian will be obtained only after efforts are made to ensure full comprehension of the study protocol. Furthermore parents will be reassured that there will be no repercussions in case of refusal. Parents will also be ensured that the persons obtaining consent will not be directly responsible for clinical care of the patient at that time.

Subject recruitment
All candidates for inclusion will come from the Intensive Care Nurseries (ICN) at the Hospital of the University of Pennsylvania, Pennsylvania Hospital, or the newborn/infant intensive care unit at CHOP. Their potential for enrollment is based on information routinely gathered as part of their clinical care. For all identified candidate subjects, the research team will contact the attending physician to discuss

appropriateness and safety of patient participation; the attending physician will be given the opportunity to deny participation at their professional discretion.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
The Non-Invasive V/Q Mismatch and Shunt Technique: A non-invasive computerized technique that quantifies V/Q mismatch and shunt has been developed and provides a unique opportunity for research in premature infants. The technique can be applied using oxygenation data readily available at the bedside without travel outside of the HUP ICN, PAH ICN, or the CHOP N/IICU, additional instrumentation or phlebotomy. This is particularly valuable in premature infants requiring continuous monitoring in a specialized hospital environment and at high risk of frequent phlebotomy contributing towards anemia and a subsequent need for blood transfusions. The technique characterizes the relationship between FiO2 and peripheral oxygen saturation (SpO2) (see Figure 2 in attached documentation). Step-wise changes in delivered FiO2 result in changes in SpO2 measured by non-invasive pulse oximetry, a standard of care monitoring device. Multiple paired values of FiO2 and SpO2 are then plotted graphically. A computer program (22) connects the pairs by overlying a best-fit curve. The primary impairments of gas exchange accounting for oxygenation failure in premature infants - V/Q mismatch and shunt - have predictable effects on the shape of the curve relative to an ideal reference lung (interrupted, left-most curve in Figure 2). A progressive right shift of the curve is noted as V/Q mismatch worsens, while a progressive depression of the curve is noted as shunt worsens. In other words, the degree of V/Q mismatch is characterized by the relative right-shift in the position of the up-slope of the curve, while the degree of shunt is characterized by the position of the plateau of the curve. Avoidance of oxygen toxicity in premature infants generally limits routine clinical SpO2 targeting to a maximum of 95% (23). For infants without notable shunt, reliable characterization of the plateau of the curve, and quantitative estimation of shunt, requires targeting multiple SpO2 values in excess of 95% - an unjustified risk in this population. In contrast, the position of the up-slope of the curve is well characterized by assessing SpO2 values between 85-95%. This curvilinear characteristic thus provides a quantitative measure of V/Q mismatch that can be measured at the bedside, and alternatively quantified as the degree of right shift from the ideal reference lung curve, with units of % FiO2. Study Protocol: Prior to initiation of the study protocol, the following criteria will be met to prioritize patient safety: 1.

No active consideration of endotracheal intubation; as determined by the clinical Attending of record. 2. No hemodynamic instability, defined as a baseline heart rate less than 100 beats per minute (bpm) or greater than 180 bpm; or a mean arterial blood pressure of less than 30 millimeters of mercury (mm Hg). 3. No supplemental FiO2 requirement greater than 0.45. 4. No capillary/arterial partial pressure of carbon dioxide greater than 65 mm Hg on last blood gas analysis, unless performed more than 6 hours prior. 5. No more than 6 apnea/bradycardia/desaturation events requiring tactile stimulation or more than 1 requiring positive pressure bag ventilation in the preceding 6 hours. Initiation of the study protocol will be deferred until these criteria are met. Figure 3 depicts the study protocol as applied in one hypothetical subject. Of note, the protocol will vary between subjects with respect to the direction and extent of CPAP level changes, as determined by the absence or presence of a response at each step-wise CPAP level change. This is described in detail below. Subjects will undergo the study interventions in their routine clinical environment. The clinically selected CPAP interface and pressure source will be maintained. A study pulse-oximeter, with low motion artifact and a short averaging time, will be placed on a post-ductal limb and used for SpO2 measurements. V/Q will first be measured on two separate occasions 30 minutes apart at baseline CPAP, set by the clinical team. The repeat baseline measures will allow an estimate of the stability of V/Q as a function of time (further discussed in Confounding under Analysis Plan). To measure V/Q mismatch, gradual changes in delivered FiO2, followed by SpO2 measurement, will be applied to obtain three FiO2/SpO2 pairs, one each for SpO2 values in the ranges of 85-87%, 89-91% and 93-95%. To obtain each SpO2 range, FiO2 will be titrated gradually until SpO2 falls within the desired values. After 60 seconds of stabilization at the identified FiO2 value, SpO2 will be recorded every 30 seconds for 2 minutes if an adequate signal waveform is present, providing up to four SpO2 values. These values will be averaged to calculate the SpO2 value used for the FiO2/SpO2 pair, acknowledging the inherent instability of pulse-oximeter values over time in premature infants. A computer software program will immediately calculate V/Q from the identified FiO2/SpO2 pairs at the bedside. Next, CPAP will be increased by +1 cm H2O. A period of 15 minutes will elapse to allow equilibration of lung volumes in response to the CPAP level change (24). V/Q calculations as described above will be repeated. A positive response will be defined as an improvement in V/Q at the new pressure level of 5% relative to the preceding CPAP level. Responders will undergo subsequent stepwise +1 cm H2O increases up to +3 cm H2O from baseline or 8 cm H2O; whichever is less. Infants not responding to the initial +1 cm H2O increase will return to baseline CPAP for 15 minutes and then be assessed at -1 cm H2O from baseline. Infants responding at this lower CPAP level will undergo an additional decrease to -2 cm H2O from baseline or 3 cm H2O; whichever is greater. The allowed range of -2 to +3 cm H2O reflects our institutional practice of typically setting a baseline CPAP level of 5 or 6 cm H2O and a CPAP pressure range of 4 to 8 cm H2O used in international trials. Best CPAP will be defined as the lowest (and last) CPAP level at which a positive response, as defined above, is measured. The baseline CPAP level will be defined as best for those infants not responding to either +1 or -1 cm H2O CPAP level changes, with a corresponding V/Q improvement of zero. Upon completion of the study protocol, infants will be returned to their baseline CPAP level. The study protocol will typically require between 60 and 120 minutes. Throughout the study, a set of pre-defined stopping criteria will be monitored to ensure subject tolerance of the study procedures. These criteria are designed to be conservative safety measures and will result in study termination and provision of supportive care, as needed. Patient Safety Considerations: Extensive patient safety considerations minimizing the risks associated with implementation of this phase II design research protocol have been incorporated: 1. Many of the key eligibility (inclusions and exclusion) criteria reflect the deliberate selection of a premature infant population that is inherently less vulnerable and at lower risk of common morbidities of prematurity and less likely to suffer any adverse outcomes from implementation of the study procedures. a). I1. Corrected gestational age 27-35 weeks (GA): this selects a study population in which respiratory distress syndrome is common and CPAP is frequently used, while avoiding less mature infants with a CGA less than 27 weeks who are more prone to physiologic instability. We exclude this population in consideration of safety for this phase II study despite a high risk of CPAP failure and a potential for benefit from our long-term research goals of establishing methods to prevent CPAP failure. b) I2. Chronologic age of greater than 24 hours. This avoids study of infants during the first 24 hours of life when they may be more prone to physiologic instability. c) I3. On continuous CPAP support for greater than 24 hours. This prioritizes safety by restricting study to subjects demonstrating stability on CPAP therapy, in contrast to infants newly transitioned to CPAP without a period of demonstrated tolerance. d) I4. Supplemental oxygen requirement, with a fraction of inspired oxygen (FiO2) 0.25 for at least 2 consecutive hours. This ensures that CPAP level changes are only performed in infants requiring supplemental oxygenation, suggesting V/Q mismatch and/or shunt from atelectasis. These subjects would plausibly benefit from carefully monitored changes in continuous distending airway pressure to counteract the pathophysiology resulting in the oxygen need. This criteria avoids CPAP

level changes in infants on CPAP but not requiring supplemental oxygen as they are less likely to benefit from changes in pressure level. e) E2. Exclusion of infants with current or prior air leak syndrome. This avoids study in infants with suggestion of a pathophysiology that could worsen with increased CPAP levels. 2. To further avoid study in infants with physiologic instability, the following criteria will be met prior to initiation of the study procedures; with deferral of the study until they are met: a. No active consideration of endotracheal intubation; as determined by the clinical Attending of record. b. No hemodynamic instability, defined as a baseline heart rate less than 100 beats per minute (bpm) or greater than 180 bpm; or a mean arterial blood pressure of less than 30 millimeters of mercury (mm Hg). c. No supplemental FiO2 requirement greater than 0.45. d. No capillary/arterial partial pressure of carbon dioxide greater than 65 mm Hg on last blood gas analysis, unless performed more than 6 hours prior. e. No more than 6 apnea/bradycardia/desaturation events requiring tactile stimulation or more than 1 requiring positive pressure bag ventilation in the preceding 6 hours. 3. Stepwise changes in CPAP level, with assessment after each CPAP level change and restriction of further pressure changes to instances in which there is a response suggestive of improving physiology - defined as greater than a 5% improvement of baseline V/Q mismatch. Infants who are at inadequate lung volumes at baseline CPAP are likely to show benefit with higher pressure levels, while infants with adequate lung volumes at baseline CPAP are unlikely to show any physiologic benefit at higher pressure levels. Similarly, infants with over distended lung volumes at baseline may benefit from lower pressure levels, while infants with adequate lung volumes at baseline CPAP are unlikely to show benefit with lower pressure levels. This key element of study procedures will protect against the risk of over-distension or loss of lung volumes secondary to the study procedures. 4. Stopping Criteria. The following "stopping criteria" will be monitored in each subject throughout the study procedures and will result in study termination, provision of supportive care and a return to baseline settings when appropriate: a) a drop in mean arterial pressure to a mmHg value less than 30 mm Hg and in excess of 10% from the baseline value, or in excess of 20% of baseline value. b) an increase in heart rate to greater than 190 bpm and in excess of 10% from the baseline value or in excess of 20% of the baseline value. c) with an adequate pulse waveform, a sustained drop in SpO2 to less than 80% for greater than one minute or a drop in SpO2, to less than 75% for greater than 30 seconds or less than 45% for any duration of time. d) a two-fold increase in the hourly frequency of cardiorespiratory events (apnea/ bradycardia/desaturation) relative to the average frequency in the four hours prior to study initiation. For infant without any events in the four hours prior to study initiation, greater than one event per hour will be used as a threshold. Further, any single event requiring bag- mask positive pressure ventilation will lead to study termination.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
Results will be summarized using basic descriptive statistics. For Aim 1, a paired t-test for parametric results or a Wilcoxon signed-rank test for non-parametric results will be used to test our hypothesis that V/Q mismatch will improve at best CPAP level compared to baseline. For Aim 2, we will calculate the proportion of subjects in which best CPAP level is identified above the baseline pressure level to assess our hypothesis that this occurs in greater than 50% but less than 80% of subjects. Further, best CPAP for the cohort will be summarized as mean and standard deviation (if parametric) or median and interquartile range (if non-parametric). No formal statistical testing of significance will be performed for this second descriptive Aim. The change in V/Q over the two baseline periods, as well as the change in heart rate and blood pressure between baseline and best CPAP levels will be tested using the statistical approach as Aim 1. We predict the null hypothesis of no significant difference for these comparisons. Should a significant change in V/Q be identified between baseline periods, we will perform an additional analysis comparing the change in V/Q between baseline periods to the change in V/Q between baseline and best CPAP level to account for the independent impact of time on V/Q

mismatch. Confounding: key elements of our study design limit confounding for Aim 1, to measure the responsiveness of V/Q mismatch to a strategy of individualized CPAP level selection. The use of a pre-post within-patient analysis limits confounding from variation in between-patient characteristics. A remaining important source of confounding is the possibility that V/Q simply improves over time irrespective of CPAP pressure changes. We account for this by measuring V/Q on two separate occasions 30 minutes apart at baseline CPAP in the study protocol, facilitating an assessment of the stability of V/Q over time.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
Several strategies will be employed to maintain confidentiality of identifiable data and to adequately protect patient privacy. Use of identifiable private information will be limited to consent documentation and a study enrollment log. The study enrollment log will link the patient information to a unique patient study ID. This ID will be used in all other paper-based and computer-based files. Paper-based records will be scanned and made into PDFs following completion of each subject's protocol. Destruction of paper-based records will occur at the completion of the study. Only study personnel will have access to computer based files, which will be maintained within an institutionally secured and managed network drive or an institutionally secured & managed device within the offices of the Division of Neonatology. The study enrollment log linking patient identifiable information to other data will be destroyed within 5 years of study completion. Data will not be shared with non-study personnel.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).
The nature of the research study will not result in any substantial additional risk to patient privacy.

Patient families will be contacted by telephone via phone calls or text only using numbers designated by them at the time of admission to the HUP ICN, PAH ICN, or the CHOP N/IICU. Families will not be physically approached about the research study nor have the research study discussed with them outside the confines of the HUP ICN, PAH ICN, or the CHOP N/IICU. Whenever possible, communication will occur in person rather than over telephone. Collection of personal health information will be limited to that necessary to facilitate the collection of study data and will be codified into a patient study ID and safeguarded as described above.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
No

*Data Protection**

x	**Name**
	Street address, city, county, precinct, zip code, and equivalent geocodes
x	**All elements of dates (except year) for dates directly related to an individual and all ages over 89**
x	**Telephone and fax number**
	Electronic mail addresses
	Social security numbers
x	**Medical record numbers**
	Health plan ID numbers
	Account numbers
	Certificate/license numbers
	Vehicle identifiers and serial numbers, including license plate numbers
	Device identifiers/serial numbers
	Web addresses (URLs)
	Internet IP addresses
	Biometric identifiers, incl. finger and voice prints
	Full face photographic images and any comparable images
	Any other unique identifying number, characteristic, or code
	None

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable

Consent

1. Consent Process

Overview
We will obtain informed consent from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Informed consent will be obtained by direct communication and interaction between a member of the research team and the parents or legal guardians of the infant while present at the HUP ICN, Pennsylvania Hospital ICN, or the CHOP N/IICU. Written information regarding the nature of the study will be initially provided to the parents or guardians, as well as further information face-to-face. This information handout will be written in non-medical language, and will explain the voluntary and non-binding nature of participation in the study, the relevance of the study, the objective of the study, the study procedures, potential risks and that participation will not change the standard course of care. It will also explain the steps that will be taken to ensure privacy and confidentiality. We will ensure that the parents or guardians are able to read and comprehend the handout. All materials will be written in a 8th grade reading level. As the exclusion criterion indicates, we will not enroll those who are not English speakers. Following sufficient time for the handout to be read and comprehended, a member of the treatment or research team will approach the parents or guardians to obtain informed consent. We will ensure that the parents or guardians understands the contents of the handout and allow them to ask any questions or concerns, which will be fully addressed. Prior to signing the consent form, a member of the treatment team will summarize the central components of the study and consent process, and verify understanding of the consenting parties. Following obtaining of the informed consent, the parents or guardians will be reminded of the voluntary and non-binding nature of the consent and reminded that they may withdraw support at any time. The parents or guardians will be approached and the consent process will be performed within the physical boundaries of the HUP ICN, PAH ICN, or the CHOP N/IICU. An assessment by the research team interacting with the parents or guardians will determine if they are competent to provide consent, for instance if literacy or language barriers prevent the parents or guardians from being able to read the provided documentation.

Children and Adolescents
Not applicable

Adult Subjects Not Competent to Give Consent
An assessment by the research team interacting with the parents or guardians will determine if they are competent to provide consent, for instance, if literacy or language barriers prevent the parents or guardians from being able to read the provided documentation. Otherwise, not applicable.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
Potential study risks are limited to the physiologic risks associated with changing CPAP and inspired supplemental oxygen. No direct psychological, social, economic, monetary, legal, or those risks that result from a loss of confidentiality is in any way anticipated. With respect to the physiologic risks associated with changing CPAP and FiO2, several study design elements minimize the risk for harm in this phase II study. They are extensively detailed within "Patient Safety Considerations" in the "Procedures" section of this application. In summary, the eligibility criteria select a population in whom the study objectives are relevant, but who are less vulnerable to injury than extremely premature infants. The principal risks associated with the study procedures are those associated with over and under-distension of the lungs with CPAP level changes and the possibility of transient hypoxia and hyperoxia during FiO2 changes. The former are minimized by the gradual step-wise changes in CPAP, ensuring that additional pressures are only tested when there is suggestion of improving physiology, and an evaluation restricted to a typical CPAP level range of 3 to 8 cm H2O. Previous CPAP level trials in premature infants have studied levels as low as 0 cm H2O and as high as 9 cm H2O without reported concerns for harm (See Table 1). The latter will be limited by careful adherence to an accepted SpO2 target range. Additional safety criteria to be verified immediately prior to application of the study interventions and comprehensive safeguards to protect against adverse events during the study interventions are described within "Procedures" Further, with respect to the physiologic risks imposed by the CPAP and FiO2 changes, the likelihood and seriousness of these risks are minimal for the following reasons: 1. The CPAP levels evaluated reflect those used in routine clinical practice and levels assessed in international trials of CPAP therapy. 2. The CPAP level changes are transient and of short duration; the baseline clinical CPAP level is returned to at study termination. 3. The tested SpO2 levels will be within 85-95%, the range consistent with acceptable target SpO2 levels in international clinical practice. 4. A member of the research team will remain at the bedside throughout the study procedures, ensuring a greater degree of oxygen titration to target saturation levels than is often possible in routine clinical care. 5. All prior studies (Table 1) using CPAP level changes similar to and in times in excess of the range proposed in this study have either not reported concerns for adverse events or reported a lack of significant increase in adverse events as a result of study.

Potential Study Benefits
1. Individual subject: A. We do not expect direct patient benefit from the study intervention as the intervention is not applied with a therapeutic intent but to measure changes in physiological responses and all subjects included in the study may not experience/need lung re-recruitment. For infants in need of lung re-recruitment, the study procedure could potentially serve as a carefully monitored lung recruitment maneuver, guided by improvements in V/Q mismatch. In infants for whom the

supplemental oxygen need required for study inclusion reflects atelectasis, study participation may recruit atelectactic lung that remains ventilated despite a subsequent return to baseline CPAP levels. The potential benefit of lung recruitment maneuvers of this type - with temporary increases in continuous distending pressure followed by a return to a lower pressure resulting in sustained benefit - is supported by recent neonatal literature in infants on positive end expiratory pressure (25-26). B. We do not propose to maintain infants on best CPAP as defined in this protocol. However, the information gained during through the study procedures will be shared with the clinical team. Information regarding the oxygenation response to changes in CPAP level in a specific infant are of clear clinical interest, but are rarely obtained due to the time and personnel resources required for careful measurement. The study procedures provides this information, which may be considered by the clinical team together with many additional factors when making clinical judgements. 2. There are benefits that may accrue to society for future premature infants newborns through completion of this study. These are considerable as they would help in defining respiratory management strategies for newborn care, an area of considerable morbidity in this population.

Alternatives to Participation (optional)
We will include the following language in the informed consent: "If you choose not to participate in this study, your baby will continue to receive the usual clinical care provided in the HUP ICN, PAH ICN, or the CHOP N/IICU. The alternative to enrolling your child in this study is not to participate. No negative consequences will result from choosing not to participate in the study."

Data and Safety Monitoring
Safety and privacy will be ensured as stated previously in Study Procedures, Confidentiality, Subject Privacy/ Protected Health Information and Potential Study Risks. A committee compromised of the research team and two additional neonatologists not directly involved in the study will meet to review safety data after 7 and 14 subjects are enrolled. We will document the proportion of subjects requiring early study termination on the basis of these stopping rules, with an expectation of less than 20% of enrolled subjects. Safety monitoring following application of the study protocol will include monitoring for air leak syndromes (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum; as determined by the clinical supervising physician during routine clinical care) and respiratory deterioration, defined as an increase in baseline FiO2 greater than 0.10 in the 48 hour following the study intervention, excluding infants in whom the rate of rise in FiO2 prior to study interventions demonstrates a comparable FiO2 trend. We anticipate these outcomes in no more than 10% of enrolled subjects.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
As previously described, many considerations to minimizing risk have been taken in the study procedures. The risk incurred from participating in the study is small; the protocol only deviates from standard of care practices in the HUP ICN, PAH ICN, or the CHOP N/IICU by changing CPAP and FiO2 levels. The changes are within the range used in neonatal clinical practice and implemented for short periods of time. The infants will be monitored closely for any physiologic instability suggestive of possible evolving harm through a set of conservative "stopping rules" providing an opportunity to terminate the study and prevent harm. The study's potential benefit to society, as described above, justifies the small risk posed to the recruited subjects.

General Attachments

The following documents are currently attached to this item:

Additional forms (woodfordgcp20191231.pdf)

Additional forms (woodfordhumansubjects20210924.pdf)

Cover Letter (cpapvqmodificationcoverletter2.20.19.doc)