Prematurity-Related Ventilatory Control (Pre-Vent): Role in Respiratory Outcomes: Multicenter Common Protocol

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Principal Investigators: **J. Randall Moorman**
Douglas E. Lake

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Version Number	Version Date	Summary of Revisions Made:	Sections Modified or Added
1, labeled "Preliminary"	1/23/17	First UVA IRB-HSR-approved version	n/a
2	2/23/18	4 Primary Outcomes measures updated to match clinicaltrials.gov: 5.1 Deleted Phrase: "…or be aware of their child's participation, thus…" 7.4 Replaced Analysis Plan with new Analysis Plan 9 Added Paragraph: "At the 3 sites using waiver of consent: NU, UAB and Miami, an Information Sheet will be provided to parent/guardian of all enrolled subjects. Template Information Sheet will be provided by UVA and may be modified to follow local IRB oversight and guidelines. Two sites (Case Western and WashU) who have elected to use informed consent forms will do so following their local IRB oversight and guidelines."	4 Study Design 5.1 Selection of the Study Population 7.4 Analysis Plan 9 Informed Consent Process
3	4/18/18	Increased subject population to include 500 mothers 9 Clarified that waiver of consent is not requested at all 5 clinical sites. A3, 1.5 Added NHLBI's definition of "Serious." A3, 6 Updated Table to refer to the NHLBI OSMB-approved umbrella DSMP.	Protocol Summary Page, 4 Study Design, 5.1 Selection of the Study Population, 5.2 Inclusion /Exclusion, 6.1 Study Procedures, 7.2 Sample Size considerations, 7.3 Participant Enrollment and Follow up 9 Informed Consent Process Appendix 3, Section 1.5 Appendix 3, Section 6
4	9/29/20	Deleted Statistical Considerations Section and added Appendix 11, Statistical Analysis Plan	7 Statistical Considerations, Appendix 11

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)
- ICH GCP E6
- Completion of Human Subjects Protection Training

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.
http://www.fda.gov/cder/guidance/959fnl.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:*

Signed:  Date: 9/29/2020

Name: Randall Moorman
Title: Professor of Medicine

Principal Investigator:*

Signed:  Date: 9/29/2020

Name: Doug Lake
Title: Professor of Medicine

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List of Abbreviations

AE	Adverse Event
BPD	Bronchopulmonary Dysplasia
BTRF	Biorepository and Tissue Research Facility
CA	Chronological Age (Birth Date= 0 days CA, next day = 1 day CA)
CFR	Code of Federal Regulations
CI	Confidence Interval
CRC	Clinical Research Center
CRF	Case Report Form
CRM	Cardiorespiratory Monitoring
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
ELBW	Extremely Low Birth Weight
FWA	Federal-Wide Assurance
GA	Gestational Age
GCP	Good Clinical Practice
GE	General Electric
GO	Grand Opportunities
HRC	Heart Rate Characteristics
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IRB	Institutional Review Board
IRB-HSR	Institutional Review Board for Health Science Research
LDCC	Leadership Data Coordination Center
MICU	Medical Intensive Care Unit
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NHLBI	National Heart, Lung and Blood Institute
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSMB	Observational Safety Monitoring Board
PB	Periodic Breathing
PI	Principal Investigator
PMA	Post-Menstrual Age
RCT	Randomized Controlled Trial
SC	Steering Committee
STBICU	Surgical, Trauma and Burn Intensive Care Unit
TB	Terabyte(s)
UVA	University of Virginia
VLBW	Very Low Birth Weight
W&M	William and Mary

PROTOCOL SUMMARY PAGE

Title: Prematurity-Related Ventilatory Control (Pre-Vent): Role in Respiratory Outcomes: Multicenter Common Protocol

Population: Sample Size: 2500

Gender: Male and Female

Age and General Health Status:

- Neonates: < 29 weeks Gestational Age (GA), and < 1 week chronological age (CA). Health status will be viable but in variable states of health, as they are extremely premature, and in the Intensive Care Unit.
- Mothers of neonates: Child-bearing age, Generally healthy, but variable

Geographic Locations:

- Birmingham, AL
- Chicago, IL
- Cleveland, OH
- Miami, FL
- St. Louis, MO

Number of Sites: 5 Sites and 1 LDCC

Study Duration: 5 years

Subject Duration: Up to 30 weeks

Objectives: The objective of this common multicenter protocol is to test the hypothesis that **algorithmic tools** using clinical NICU **cardiorespiratory monitoring** data can **detect ventilatory control instability** and **predict severe Bronchopulmonary Dysplasia (BPD)** and other chronic and acute respiratory consequences of ventilatory control instability and autonomic dysregulation**.**

Primary outcome measures are:

1. Clinical Outcome [Time Frame: 40 weeks post-menstrual age.]
   - "Favorable": Either (1) an inpatient at 40 weeks post-menstrual age and not on oxygen, nor on other flow/pressure respiratory support, nor on inhaled/oral/IV respiratory medications, OR (2) discharged prior to 40 weeks post-menstrual age not on respiratory meds, oxygen, or other respiratory support.
   - "Unfavorable": Either (1) Deceased at 40 weeks, (2) inpatient on meds/O2/support at 40 weeks post-menstrual age, or (3) previously discharged prior to 40 weeks on meds/O2/support

2. Physiological Outcome [Time Frame: 36 weeks and 1 day to 37 weeks and 0 days, post-menstrual age]

Reported Value will be the percentile value of scores, as plotted on a standard curve of scores for peers. The score is calculated by aggregating the following measurements:

- Periodic Breathing Percentage (%)
- Apnea events

- Bradycardia events
- Desaturation events
- Combined events (example Apnea with Bradycardia and Desaturation

Secondary outcome measures include other respiratory outcomes including prolonged immature control of breathing, time on respiratory support and medications, chronic lung disease, and pulmonary hypertension. Other secondary outcome measures include non-respiratory morbidities related to prematurity, including sepsis, necrotizing enterocolitis, retinopathy of prematurity, and neurologic outcomes.

1 KEY ROLES

Individuals:

Principal Investigator: J. Randall Moorman

Principal Investigator: Douglas E. Lake

Institutions:

Leadership Data Coordination Center (LDCC)	University of Virginia 1215 Lee St., Box 800158 Charlottesville, VA 22908 Randall Moorman 434-982-1677 rm3h@virginia.edu
Clinical Research Center	Case Western Reserve University Rainbow Babies and Children's Hospital, Division of Neonatology suite 3100, 11000 Euclid Ave Cleveland, OH 44106 Anna Maria Hibbs 216-844-3387 annamaria.hibbs@cwru.edu
Clinical Research Center	Northwestern University 225 East Chicago Avenue, Box 165, Chicago, Illinois 60611-2605 Aaron Hamvas 312-227-3300

	ahamvas@luriechildrens.org
Clinical Research Center	University of Alabama at Birmingham 176F Suite 9380, Women and Infants Center 619 South 19th Street Birmingham, AL 35249-7335 Namasivayam Ambalavanan 205-934-4680 nambalavanan@peds.uab.edu
Clinical Research Center	University of Miami P.O. Box 016960, R-131 Miami, Florida 33101 Eduardo Bancalari 305-585-6408 EBancalari@med.miami.edu
Clinical Research Center	Washington University School of Medicine 1 Children's Place St. Louis, MO 63130 James Kemp 314-747-5173 kemp_j@kids.wustl.edu

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Hypothesis
The hypothesis of the common protocol is that algorithmic tools using clinical NICU cardiorespiratory monitoring data can detect ventilatory control instability and predict severe BPD and other respiratory and nonrespiratory outcomes.

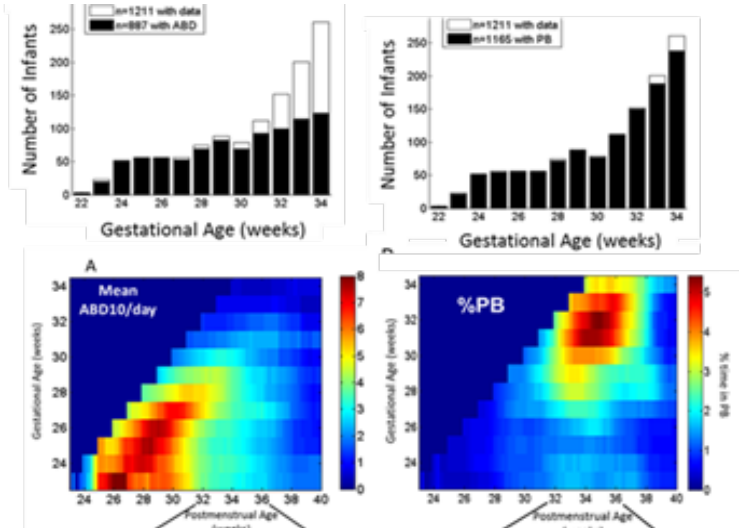
Previous Studies
Since 1999, the UVA group has translated large NICU monitoring data into information for the bedside clinician. The PIs of the LDCC, JR Moorman and DE Lake, have studied NICU Big Data since 2000, developed heart rate characteristics monitoring and led the team that showed, in the largest RCT of very low birth weight (VLBW) infants, that it improved NICU survival. With KD Fairchild the group has complete bedside monitoring data from more than 610 VLBW infants with recorded ventilator status and identified episodes of sepsis and necrotizing enterocolitis. With very substantial input from JB Delos at the College of William and Mary, they developed methods for detection of central apnea and periodic breathing. Currently, they have accumulated a legacy data set of 75 patient-years of monitoring data, beginning with a Grand Opportunities (GO) NIH grant in 2009 (JR Moorman and J Kattwinkel, co-PIs). These data are annotated by clinicians or episodes of sepsis, urgent intubation, transfusion, and necrotizing enterocolitis.

Specific to the current hypothesis, the UVA group has worked in the areas of immature breathing events (central apnea and periodic breathing), heart rate characteristics monitoring, cardiorespiratory interaction, and early detection of respiratory decompensation leading to urgent unplanned intubation. Each is detailed next:

Immature breathing events – central apnea and periodic breathing
Quantitative tools for detection of immature breathing have been developed using a large data set initiated using a GO grant (Moorman and Kattwinkel, co-PIs). A strength of the development plan was validation of 100 or more individual events by multiple clinicians, demonstrating a more than 90% diagnostic accuracy. These tools allowed clinical studies of alarms, transfusions, prolonged apneas (surprisingly common and benign), and prolonged periodic breathing (associated, in one case, with Sudden Infant Death Syndrome). A number of papers were published on these topics[1-7]1-7. Two manuscripts by KD Fairchild and coworkers describe the natural history and clinical associations of each in the same group of 610 VLBW infants for whom is noted times on ventilator, sepsis, necrotizing enterocolitis and intraventricular hemorrhage. The major findings are:

1. the syndromes have distinct time courses, shown in the heat maps below
2. increased apnea was associated with acute but not chronic illness
3. periodic breathing, if very prolonged, was sometimes associated with morbidity

Figure 1. Incidence (top) and natural history (bottom) of central apnea (left) and periodic breathing (PB) (right).



Heart rate characteristics (HRC) monitoring

The UVA group discovered that diagnosis of neonatal sepsis was preceded by abnormal HRC of reduced variability and transient decelerations. They developed mathematics to capture this phenotype, related these measures to clinical signs and lab tests, validated a statistical model at another center, and performed a randomized clinical trial. The outcome was that display of HRC index led to increased survival, especially in extremely low birth weight (ELBW) infants (1 life in 23 saved), and especially in the 25% of infants with sepsis (1 life in 12 saved). They published a number of papers on this topic[1,3,8-37]1,3,8-37.

Cardiorespiratory interaction

The UVA group developed a novel measure of breath-by-breath sinus arrhythmia, and showed its maturation over the NICU course[6]6. The fundamental process was to identify the phase of respiration in which heartbeats are most likely to occur. Cardiorespiratory interaction was identified when heartbeats preferentially fall in specific phases. Maturation led to more interaction.

Respiratory decompensation leading to urgent unplanned intubation

The UVA group performed multivariable statistical modeling to develop a risk estimate for this clinical event[3]3, exemplifying clinical decision support tools based on modeling of monitoring data.

Previous studies: large scale computing

The UVA group prepared identical data sets from the UVA Neonatal (NICU), Medical ICU (MICU) and Surgical Trauma Burn ICU (STBICU), identified subacute potentially catastrophic illnesses (hemorrhage leading to transfusion, lung failure leading to emergent intubation, and sepsis). They studied 9200 patients (610 were VLBW infants), 150 patient years of data (about half in the NICU, where the stays are longer), and 75TB of cardiorespiratory monitoring (CRM) data. They wrote code, deployed dedicated computing clusters (288 cores), calculated 25 time series measures, and computed multiple imputations. They developed multivariable regression expression adjusted for repeated measures, and examined variables of importance. This led to Figure 3, and a remarkable conclusion – in infants, all 3 illnesses present with the same physiological signature, dominated by bradycardia-desaturations (as measured by the cross-correlation of heart rate and O_2 saturation).

Previous studies: stochastic modeling

A generalizable method for estimating the future burden of an immature breathing event is necessary. The stochastic modeling below has been developed as an example of the computational models to be considered, in addition to traditional inference models and others.

The *rationale* is that apnea arises from an excitable neurological system, the respiratory control center in the brainstem, which has stochastic properties. Here, apnea is considered one of a spectrum of breathing states that are visited randomly and without memory of prior states. The probabilities of the transitions determine the present and future state of such systems. In this framework, central apnea of prematurity arises from transitions to an apnea state that are less probable with maturation. A great practical advantage of this framework is that the mathematics of these systems, called Markov chains, is well understood. The first step is to prepare a diagram of the states and the possible transitions (Figure 4, middle). Here, an apnea state might be entered from any of several breathing states. While indistinguishable to the observer – in each, the infant is breathing normally – these breathing states differ by their likelihood of

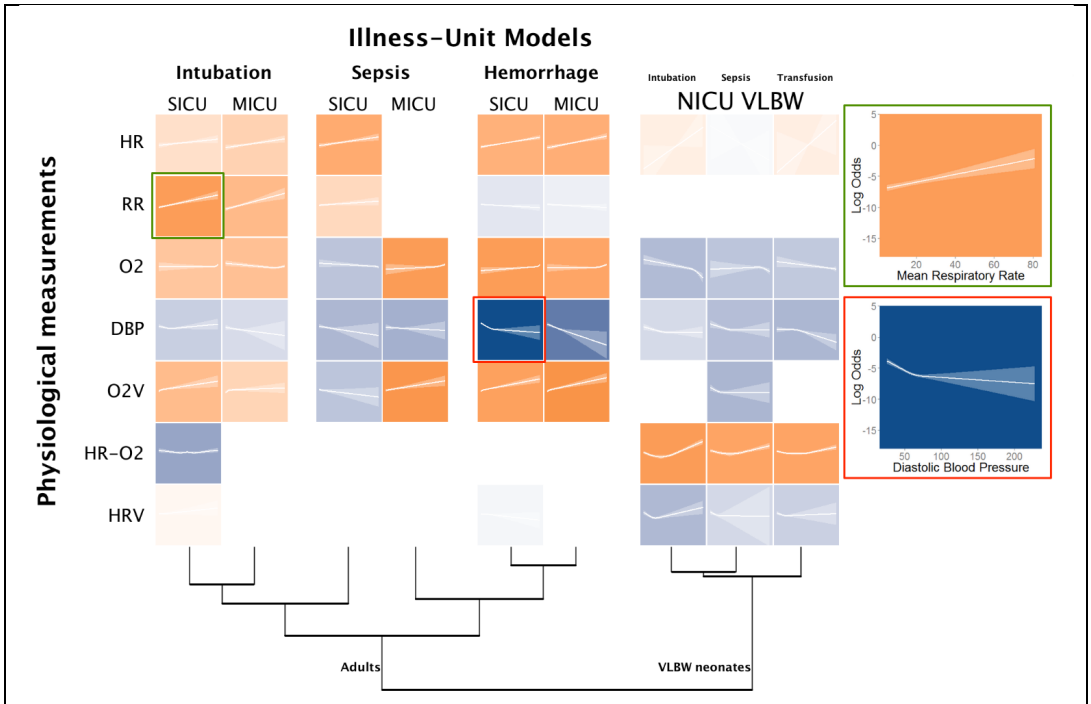


Figure 3. Big Data and High Performance Computing in ICUs

transition to the apnea state. Each is represented by their position relative to apnea – closer breathing states are more likely to pause.

Detect	***Model***	***Predict***
(a) Cardiorespiratory monitor record, showing our signal processing technique to identify central apneas. (b) Apneas cluster at days 18 and 25, suggesting a statistical model called a Markov chain.	Markov state diagrams. (a) is the full state model, were A is apnea and B's are breathing states. (b) and (c) show how transition probabilities change from 27 weeks PMA (b) differs from 40 (c)	*Estimated future apnea burden from Monte Carlo simulation using the model (line) closely matches observed values (circles).* Error bars on the observations are 95% CI.

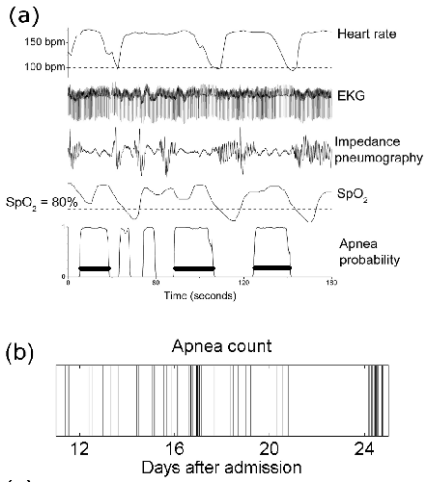
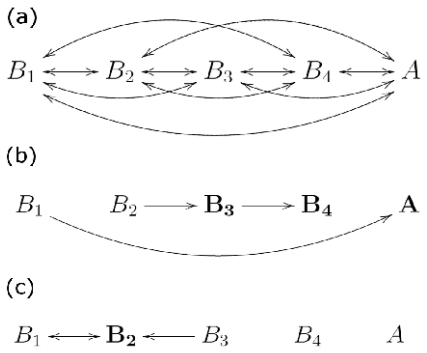
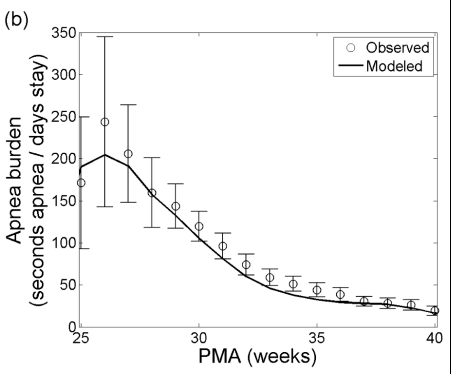

		

Figure 4. Stochastic modeling		

Clinical, Epidemiological and Public Health Background and Context

Chronic respiratory disease impacts thousands of premature infants annually in the U.S. leading to prolonged stays in Neonatal Intensive Care Units (NICUs), increased mortality, and respiratory morbidity. With improved neonatal care, many survivors of extremely low gestational age birth develop bronchopulmonary dysplasia (BPD) defined by instability of oxygenation and persistent needs for respiratory support as they prepare for discharge home from the NICU at 36 weeks postmenstrual age (PMA). This inability to maintain oxygenation during the NICU course and at 36-40 weeks PMA is managed with a range of supportive measures including low to high flow nasal cannula, varying concentrations of oxygen, nasal continuous airway pressure, and mechanical ventilation.

Preterm birth can interrupt not only the rapid increase in surface area for alveolar-capillary gas exchange that takes place during the late stages of pregnancy, but also may interrupt neurodevelopment and maturation of ventilatory (neurorespiratory) control. The ventilatory control system is required to regulate ventilation and provide oxygen to tissues and remove carbon dioxide. Neurons in the brainstem and higher centers in coordination with input from mechanoreceptors and chemoreceptors constitute the ventilatory control system. More than half of premature neonates have apnea of prematurity with significant episodes of interrupted breathing, resulting in significant hypoxemia and life-threatening bradycardias. Immature breathing mechanisms in the postnatal environment may contribute to BPD and/or result in respiratory decompensation, need for resuscitation, and mechanical ventilation. The trajectory of maturation of neurorespiratory control in premature babies is not clear, and how

this contributes to acute and chronic respiratory outcomes of premature infants including BPD is unknown.

Despite the use of continuous cardiorespiratory monitoring in the NICU, episodes of periodic breathing and intermittent hypoxic periods are not captured even by the sophisticated monitors. Some episodes may accompany bradycardia. In premature infants, because of the intermittent nature of apnea, bradycardia, and desaturation episodes, events are infrequently recorded or reported. Clinical care givers often use physiologic responses to evoked challenges, such as titrating inspired oxygen concentrations to make a diagnosis of BPD, but better tests for this condition are lacking. Mathematical modeling algorithms that can utilize continuous recordings as input data from ICU monitors could inform the detection and analysis of breathing patterns in the premature. The ultimate goal is to gain greater insight into the pathogenesis of chronic respiratory disease of the premature, identify novel BPD phenotypes and physiological biomarkers, and discover targets for new prevention and treatment strategies, to improve outcomes for very vulnerable children at the beginning of life.

2.2 Scientific Rationale

- The justification for the selection of neonates is that neonatal physiology is being studied; this cannot be studied in older subjects. Large numbers are required to allow sufficient precision of the algorithms. Data already in existence is not sufficient.

- Animal subjects would not be applicable since the clinical signatures of ventilatory states differ from humans. Computer simulations have not been established that provide the clinical variation needed to develop models.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Immediate Risks

- There are no immediate physical, psychosocial, legal, economic or other risks to subjects foreseen.

Long Range Risks

- Data breach is a potential long range risk. With the data security in place at the 6 large University Medical Centers, as well as the innovative security measures designed to allow the bulk of CRM data to remain local, this is expected to be rare. Since the LDCC oversees highly sensitive protected health information including HIPAA identifiers, a breach could be potentially very serious.

- There are no long range physical risks to subjects foreseen.

The above risks are necessary in order to meet the objectives of the multicenter protocol

Alternative Data Gathering Procedures:

The data collection procedures have no human subject involvement other than standard medical care, thus no alternatives are considered.

Data transfer and storage alternatives are available and have been considered extensively. The methods selected have been deemed the most secure options by the PIs, and are reviewed by the Steering Committee, CRC-IRBs and UVa-IRB, and OSMB. Alternative methods may be reconsidered upon further review and technological developments.

Justification of Risks

The potential value is for society at large, especially particular groups similar to those studied (premature infants and their parents), in a potential better understanding of the physiology of prematurity and potential for improved care in the future. If the research network can create new mechanistic insights and tools relevant to maturation of neonatal breathing, debilitating chronic lung disease might be reduced. The minimal risks of breach of patient confidentiality is more than balanced by the possibility that this research could develop new knowledge that reduces morbidity and mortality.

2.3.2 Known Potential Benefits

There are no potential physical, psychological, social, legal, economic or any other benefits to the research subjects from participating in the study.

3 OBJECTIVES

Statement of Purpose

This protocol is aligned with HL-RFA-16-016, “Prematurity-Related Ventilatory Control,” a NIH cooperative agreement to a multicenter observational study of breathing and respiratory outcomes in premature infants, that is managed by a Leadership and Data Coordination Center (LDCC) housed at UVa.

The objective of this program is to investigate mechanisms of ventilatory control that contribute to instability of oxygenation and risk of respiratory morbidity and mortality in premature infants during and after the Neonatal Intensive Care Unit (NICU) using a prospective observational cohort. The central hypothesis of the coordinated program is that quantification of immature breathing will identify physiological biomarkers that can serve as targets for prevention and treatment that improve outcomes. This is an important step toward the identification of new opportunities for preventive interventions for high risk premature infants.

The proposed research is relevant to the public health because understanding mechanisms of ventilatory control in premature infants will lead to better therapies for chronic lung disease. In this way, it is relevant to the NIH mission to apply research discoveries to protect and improve health.

The objective of this Multicenter Research Protocol is to test the hypothesis that algorithmic tools using clinical NICU cardiorespiratory monitoring data can detect ventilatory control instability and predict severe BPD and other chronic and acute respiratory consequences of ventilatory control instability and autonomic dysregulation**.**

The aims are twofold:
Aim 1. Detect ventilatory control instability and develop externally validated statistical models of immature breathing burdens in 500 extremely preterm infants using readily available clinical NICU cardiorespiratory monitoring data

Aim 2. Relate these modeled burdens of immature breathing to acute and chronic outcomes

Method of Assessment

The LDCC will assess these objectives with the following study outcome measures

- Detection of ventilatory control instability and development of statistical models of immature breathing in extremely preterm infants using readily available clinical NICU cardiorespiratory monitoring data.
- External validation of these detection algorithms and statistical models
- Using the modeled burdens of immature breathing to predict acute and chronic respiratory and non-respiratory outcomes
- External validation of these prediction algorithms.
- Computational tools to estimate future burden of immature breathing patterns that will be useful in future studies

- Increased understanding of mechanisms of ventilatory control that contribute to instability of oxygenation and risk of respiratory morbidity and mortality in the NICU

4 STUDY DESIGN

- This is a study of a prospective observational cohort. There is no intervention. Controls will not be used. A placebo will not be used.
- No specimens will be collected.
- Data collection from infants and mothers will continue throughout the entire duration of the NICU stay.
- Subjects and their families will not be aware of their participation.
- Data will be collected from existing data collected for clinical purposes, both by capturing physiological monitor data that would normally be discarded, and by reviewing the infant's and mother's medical record.
- Study Outcome Measures: Primary variables include waveform data that will need to be transformed into compatible file formats before analysis. Clinical data will be entered manually into standardized eCRFs before analysis.
- The primary outcome to be measured during the study are:
    1. Clinical Outcome [Time Frame: 40 weeks post-menstrual age.]
        - "Favorable": Either (1) an inpatient at 40 weeks post-menstrual age and not on oxygen, nor on other flow/pressure respiratory support, nor on inhaled/oral/IV respiratory medications, OR (2) discharged prior to 40 weeks post-menstrual age not on respiratory meds, oxygen, or other respiratory support.
        - "Unfavorable": Either (1) Deceased at 40 weeks, (2) inpatient on meds/O2/support at 40 weeks post-menstrual age, or (3) previously discharged prior to 40 weeks on meds/O2/support

    2. Physiological Outcome [Time Frame: 36 weeks and 1 day to 37 weeks and 0 days, post-menstrual age]
    Reported Value will be the percentile value of scores, as plotted on a standard curve of scores for peers. The score is calculated by aggregating the following measurements:
        - Periodic Breathing Percentage (%)
        - Apnea events
        - Bradycardia events
        - Desaturation events
        - Combined events (example Apnea with Bradycardia and Desaturation
- The secondary outcomes to be measured during the study include but are not limited to other respiratory and nonrespiratory consequences:
    - Wheezing
    - Obstructive apnea
    - NICU length of stay
    - Risk of re-admission
    - Reason for readmission

- Mortality
- sepsis
- necrotizing
- enterocolitis
- retinopathy of prematurity
- neurologic outcomes.
- Other clinical outcomes, as defined in the Manual of Procedures and the Case Report Forms

5 Study Population

5.1 Selection of the Study Population

- The target sample size is 500 infants and 500 mothers. The actual number to be enrolled is 2500, since we estimate that roughly 25% of babies on whom cardiorespiratory monitor data is automatically collected onto the local study servers ("enrolled babies") will meet the inclusion/exclusion criteria.
- Retention is not an issue since no follow-up is required.
- Subjects will be both genders. An even distribution of genders is expected among infants. Mothers will be female.
- All races and ethnicities will be recruited and distribution is expected to be similar to the populations represented in the NICU at each site.
- Age of all infants will be less than 29 weeks Gestational Age (GA) and less than 1 week Chronological Age (CA), at the time of enrollment. Age of mothers is child-bearing age.
- The age restriction in infants is rational because this is a study of the physiology of very premature infants; the mechanisms of ventilatory control of more mature neonates are not under investigation here.
- The study population will be drawn from inpatients in Neonatal Intensive Care Units (NICUs) at participating hospital sites with cardiorespiratory monitoring, and their mothers.
- The PI is not an employee, member or volunteer at the clinical sites. The PI will not have direct access to the clients (patients) at the clinical sites. The PI is an employee of UVA Health Science Center, who will establish IRB approved Material Transfer Agreements / Data Usage Agreements with the clinical sites in order to receive their patients' data.
- The neonate subjects will be in variable states of health since they are premature and in the intensive care unit. Mothers' health is generally healthy but variable.
- It is necessary to use minor subjects because this is a study of neonatal physiology.
- Parents/guardians will not be allowed to see any results of their or their child's participation, such as individual risk estimation for acute illness. Parents will not give informed consent. Parents will not be notified of the limitation on their access to collected and recorded data.
- There will be no pre-screening of infants. Data will be collected on all infants placed in a bed for which monitoring and data collection capabilities are set up. Therefore all such infants will technically be enrolled in the study, regardless of meeting the inclusion/exclusion criteria.

- Each enrolled infant will be screened using the medical record for inclusion/exclusion criteria to determine whether the site will collect further data from the medical record. This screening data will be maintained at the site on a Screening Log, and not sent to the LDCC, except in aggregate form. Enrolled infants who do not meet inclusion/exclusion criteria will not be entered through the web-interface into the Multicenter Common Database (MCD).

5.2 Inclusion/Exclusion Criteria

Inclusion criteria:
Infants:

- Neonatal Intensive Care Unit patient on cardiorespiratory monitor which has been configured to collect data to store for this study
- < 29 wks GA
- < 1 wk CA

Mothers:

- Mother of an infant that has passed the screening for inclusion/exclusion.

Exclusion Criteria:

- Unlikely to survive or decision not to pursue full care
- Major congenital or chromosomal anomaly

No restrictions or requirements on use of other drugs, treatments, or contraception apply.

5.3 Subject Compensation

Subjects will not be compensated or reimbursed.

6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

- The LDCC will gather the following clinical data on infants.
    - Results of calculations on continuous monitoring data (example EKG waveforms) extracted at clinical sites from cardiorespiratory monitors. To be transmitted electronically via secure web-based sharing.
    - Clinical data on enrolled subjects who meet inclusion/exclusion criteria, to be entered manually into Electronic Case Report Forms (example: time of intubation) at the clinical sites, and transmitted via a secure, web-interface (REDCap) to the Multicenter Common Database (MCD) at housed at UVa. This may come from maternal charts.
    - No HIPAA identifiers will be received, other than location and dates (of treatment, births, transfers, readmissions). This constitutes a Limited Data Set.
- Clinical data will be stored on secure servers at Stacey Hall at the UVA Health System. Data will be stored at UVA for 5 years beyond closure date of this protocol with the UVA IRB-HSC.
- The LDCC in conjunction with the UVA Clinical Trials Office will employ standard accepted practices to assure that the data collected are accurate, consistent, complete and reliable and in accordance with ICH GCP guidelines and 21 CFR Part 11.
    - The overall duration of the project is 5 years. Data collection will continue the entire length of the NICU stay.
    - No samples will be collected

6.2 Laboratory Evaluations

No laboratory evaluations will be performed for research purposes.

Figure 1

7 SUBJECT CONFIDENTIALITY

Subject confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor (NIH) and their agents. This confidentiality is extended to cover all clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of NIH.

The clinical study sites will permit access to all documents and records that may require inspection by the UVA LDCC, NIH or their authorized representatives, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study.

The LDCC will use information obtained from the subjects to carry out the research described in the Multicenter Research Protocol, as well as provide it to clinical sites during the lifetime of the LDCC 5-year Program to carry out other research. At the close of the study, the clinical data and/or de-identified cardiorespiratory monitoring may be transferred to an NIH Data Repository and become openly available to other agencies. De-identified cardiorespiratory monitoring data will be published on Physionet.org, an NIH funded Data Repository. Data will be stored at UVA for 5 years beyond closure date of this Protocol with the UVA IRB-HSC, after which UVA and clinical site copies of the data will be destroyed, or a new IRB approval will be obtained to store the data. Aggregate data, but no Private Health Information, will appear in publications. Long-range use will include using the data to refine algorithms and develop new algorithms after the close of this study.

7.1 Future Use of Stored Specimens

No specimens will be collected or stored under this protocol

8 INFORMED CONSENT PROCESS

A waiver of consent will be requested from the UVA IRB-HSR and applicable clinical site IRB's based on:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alterations will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

At the 3 sites using waiver of consent, NU, UAB and Miami, an Information Sheet will be provided to parent/guardian of all enrolled subjects. Template Information Sheet will be provided by UVA and may be modified to follow local IRB oversight and guidelines.

Two sites (Case Western and WashU) who have elected to use informed consent forms will do so following their local IRB oversight and guidelines.

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SUPPLEMENTS/APPENDICES

APPENDIX 1: SITE ROSTER

Leadership Data Coordination Center (LDCC)	*Institution:* University of Virginia *Address:* 1215 Lee St., Box 800150 Charlottesville, VA 22908 *Contact:* Randall Moorman *Phone:* 434-982-1677 *E-mail:* rm3h@virginia.edu
Clinical Research Center	*Institution:* Case Western Reserve University *Address:* Rainbow Babies and Children's Hospital, Division of Neonatology suite 3100, 11000 Euclid Ave Cleveland, OH 44106 *Contact:* Anna Maria Hibbs *Phone:* 216-844-3387 *E-mail:* annamaria.hibbs@cwru.edu
Clinical Research Center	*Institution:* Northwestern University *Address:* 225 East Chicago Avenue, Box 165, Chicago, Illinois 60611-2605 *Contact:* Aaron Hamvas *Phone:* 312-227-3300 *E-mail:* DWeese-Mayer@luriechildrens.org

Clinical Research Center	*Institution:* University of Alabama at Birmingham *Address:* 176F Suite 9380, Women and Infants Center 619 South 19th Street Birmingham, AL 35249-7335 *Contact:* Namasivayam Ambalavanan *Phone:* 205-934-4680 *E-mail:* nambalavanan@peds.uab.edu
Clinical Research Center	*Institution:* University of Miami *Address:* P.O. Box 016960, R-131 Miami, Florida 33101 *Contact:* Eduardo Bancalari *Phone:* 305-585-6408 *E-mail:* nclaure@miami.edu
Clinical Research Center	*Institution:* Washington University School of Medicine *Address:* 1 Children's Place St. Louis, MO 63130 *Contact:* James Kemp *Phone:* 314-747-5173 *E-mail:* kemp_j@kids.wustl.edu

APPENDIX 3: DATA AND SAFETY MONITORING PLAN

This study has been deemed minimal risk. Because this study poses minimal risk to the subject, **adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected.**

1. Definitions

1.1 How will you define adverse events (AE)?

An adverse event will be considered any undesirable sign, symptom or medical condition considered **related to the intervention**. Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

1.2 How will you define an unanticipated problem (UP)?

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject's confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g serious loss of social status, loss of job, interpersonal conflict.)

1.3 What is the definition of a protocol violation (PV)?

A protocol violation is defined as a divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare. Examples of protocol violations may include the following:

- Inadequate or delinquent informed consent
- Inclusion/exclusion criteria not met
- Unreported serious adverse events
- Improper breaking of the blind
- Use of prohibited medication
- Incorrect or missing tests
- Mishandled samples
- Multiple visits missed or outside permissible windows
- Materially inadequate record keeping
- Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
- Subject repeated non-compliance with study requirements

1.4 What is the definition of a protocol deviation (PD)?

A protocol deviation occurs when, without significant consequences, the activities on a study diverge from the Institutional Review Board-approved protocol, e.g., missing a visit window because the subject is traveling. Not as serious as a protocol violation.

1.5 What is the definition of serious?

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

a. death
b. a life-threatening adverse reaction
c. inpatient hospitalization or prolongation of existing hospitalization
d. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
e. a congenital anomaly/birth defect.
f. important medical events that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above

2. What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation	**Pick One**
There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.	Occurs rarely

3. When will recording and reporting of unanticipated problems/adverse events begin?

After subject signs consent or is otherwise enrolled.

4. When will the recording/reporting of unanticipated problems/adverse events end?

When subject completes participation in the protocol

5. What is your plan for safety monitoring?

Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually. Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will also be performed by the NIH-appointed Observational Safety and Monitoring Board through semiannual reports.

6. What is your plan for reporting an Unanticipated Problem, Protocol Violation or Data Breach?

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported
Events that do not meet the definition of AE, unless listed in this table	None	N/A	N/A
Non-Serious Adverse Events	Site PI to UVA LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI to Pre-Vent Steering Committee	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC to notify the Chair of the OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI sends full report to LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC sends full report to OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
Serious adverse events	Site PI to UVA LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI to Pre-Vent Steering Committee	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC to notify the Chair of the OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI sends full report to LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC sends full report to OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	PI to UVa IRB only if occurring at UVa site	14 days of UVa PI awareness	Cover Letter and Event Report Form

Unanticipated Problem that is not a SAE	Site PI to UVA LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI to Pre-Vent Steering Committee	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC to notify the Chair of the OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI sends full report to LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC sends full report to OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	PI to UVa IRB only if occurring at UVa Site	14 days of UVa PI awareness	Cover Letter and Event Report Form
Protocol Deviation or Violation	Site PI to UVA LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI to Pre-Vent Steering Committee	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC to notify the Chair of the OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	Site PI sends full report to LDCC	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	LDCC sends full report to OSMB	See NHLBI OSMB Umbrella DSMP	See NHLBI OSMB Umbrella DSMP
	PI to UVa IRB only if occurring at UVa site, only if Major Violation	Annually	Annual Continuation Status Report
Data Breach	UVA PI to UVa	As soon as possible	UVa Corporate Compliance and

	Corporate Compliance and Privacy Office, only if occurring at UVa site AND UVA PI to UVA ITC: if breach involves electronic data, only if occurring at UVa site AND UVA PI to police if breach includes items that are stolen, only if occurring at UVa site	and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY	Privacy Office- Phone 924-9741 ITC: Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Stolen on UVA Grounds: UVa Police- Phone- (434) 924-7166 Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI

Data and Safety Oversight Responsibility

1. Who is responsible for overseeing safety data for this study?

__X___DSMB/ DSMC

2. What is the composition of the reviewing body and how is it affiliated with the sponsor?

Members of the study team may NOT also be members of the DMSB.

__X___Other- The OSMB will be appointed by NHLBI. UVA team members may not appoint OSMB members, or even inquire about the interest of possible OSMB members, because anyone so contacted would not be eligible to serve as a member of the peer review committee that evaluates the proposal. An NHLBI scientist other than the NHLBI's Pre-Vent Program Scientist will serve as the Executive Secretary to the OSMB.

3. **How often will aggregate review occur?**

For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

__X___Semi-Annually

4. **How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?**

A copy of these reports must be sent to the IRB if applicable as soon as they are received by the PI. Do not wait until the next continuation to submit them to the IRB.

__X___Semi-Annually

5. **How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?**

__X___Separate report from DSMB/DSMC or UVa PI