Title: Noninvasive NAVA Versus NIPPV in Low Birthweight Premature Infants

NCT #: NCT03137225

Document approval date: 09/08/2016

Document Type: Protocol and Statistical Analysis Plan

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ID: HM20005575 View: SF - Study Identification

Study Identification

1. * **Select the Principal Investigator:**
   Henry Rozycki
2. * **Study Title:**
   Noninvasive NAVA Versus NIPPV in Low Birthweight Premature Infants
3. * **Is this a student or trainee project in which activities will be carried out by that individual under your supervision:**
   - (•) **Yes**
   - ( ) No
4. **Select any associated VCU IRB protocols:**

ID	PI

There are no items to display

5. **Select all individuals who are permitted to edit the IRB protocol and should be copied on communications (study staff will be entered later). These individuals will be referred to as protocol editors:**

Last Name	First Name	E-Mail	Phone	Mobile
	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		

ID: HM20005575 View: SF - Student/Trainee Investigator Contact

[redacted]

ID: HM20005575 View: SF - Research Determination

Research Determination

1. * **Select one of the following that applies to the project:**

- (•) **Research Project or Clinical Investigation**
- ( ) Exception from Informed Consent for Planned Emergency Research
- ( ) Humanitarian Use of Device for Treatment or Diagnosis
- ( ) Humanitarian Use of Device for Clinical Investigation
- ( ) Emergency Use of Investigational Drug, Biologic or Device
- ( ) Treatment Use (Expanded Access to Investigational Product for Treatment Use)
- ( ) Center or Institute Adminstrative Grant Review

ID: HM20005575 View: SF - Federal Regulations

Federal Regulations

1. * **Is this a Clinical Trial:**
   - (•) **Yes**
   - ( ) No
2. **Is this an Applicable Clinical Trial that must be registered and reported to clinicaltrials.gov:**
   - (•) **Yes**
   - ( ) No
3. * **Is this a FDA regulated study:**
   - ( ) Yes
   - (•) **No**
4. * **Is this study supported by the Department of Defense (DoD):**
   - ( ) Yes
   - (•) **No**
5. * **Check if any of the following funding sources apply to this research:**

None of the above

ID: HM20005575 View: SF - Personnel

Personnel

1. * **Indicate all VCU/VCUHS personnel, including the PI, who will be engaged in this study:**

Name	Roles	Roles - Other	Responsibilities	Responsibilities - Other	Qualifications	Qualifications - Other	COI Investigator
[redacted]							
[redacted]							
[redacted]							
[redacted]							

[redacted] **Identify all non-VCU personnel who will be engaged in this study AND who DO NOT have IRB approval for this study from their own institution.**

Name	Roles	Roles - Other	Responsibilities	Responsibilities - Other	Qualifications	Qualifications - Other	COI Investigator

There are no items to display

3. **CV/Biosketch: (required for PI, Medically/Psychologically Responsible Investigators and Student/Trainee Investigators)**

ID: HM20005575 View: SF - Conflict of Interest

Conflict of Interest

1. * **To the best of your knowledge, do you (as PI) or any other engaged individual hold a financial conflict of interest related to this study?**
   - ○ Yes
   - ◉ **No**

2. **If Yes, provide:**
   - **Name(s) of the engaged conflicted individual(s)**
   - **Brief description of the financial conflict of interests**

3. * **Describe any potential non-financial conflicts of interest for members of the research team that could impact the conduct of the study (if None, please state "None"):**
   None

4. **Describe any institutional conflict of interest with this research that you or any member of the research team may be aware of:**
   None

ID: HM20005575 View: SF - Communication Plan for Research Team

Communication Plan for Research Team

1. * **Describe the process that will be used to ensure that all persons at all involved sites assisting with the research are adequately informed about the protocol and their research related duties and functions:**
   Investigators will brief and inform clinical personnel of study design by poster in break room, email and personal interactions before first enrollment; however, clinical personnel will be not be performing any research related duties. Members of the research team will meet after each subject to review protocol, data acquisition and to go over any problems identified.

ID: HM20005575 View: SF - IRB Panel Setup

IRB Panel Setup

1. * **To which IRB is this study being submitted for review:**

- (●) **VCU IRB**
- ( ) Western IRB
- ( ) NCI Central IRB
- ( ) Other IRB (Request to Defer to Another Institution)

ID: HM20005575 View: SF - Review Setup

Review Setup

1. * **Does this study involve greater than minimal risk:**
   (●) **Yes** ( ) No
2. * **Review Type Requested: (subject to IRB approval)**

- (●) **Full Board**
- ( ) Expedited
- ( ) Exempt

ID: HM20005575 View: SF - Research Description

Research Description

1. * **Describe the study hypothesis and/or research questions. Use lay language whenever possible.**
   We hypothesize that in very low birth weight infants who require respiratory support via noninvasive ventilation, that synchronizing the ventilator breath with the baby's breath using neurally adjusted ventilatory assist (NAVA) will reduce the number and/or severity of apnea/bradycardia/desaturation episodes compared to nasal intermittent positive pressure ventilation (NIPPV).

2. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
   The specific goal is to measure the number and severity of cessation of breath/low heart rate/low blood oxygen level events (ie, apnea/bradycardia/desaturation events) in a 4 hour period while receiving one of the two types of non-invasive ventilation modes (either NIPPV or NAVA) currently used in very low birthweight infants.

3. * **Describe the study's background and significance, including citations, or upload a citation list in document upload. Use lay language whenever possible.**
   Very low birthweight (VLBW) premature infants in the NICU frequently require respiratory support for prolonged periods of time. Invasive mechanical ventilation (which requires intubating the baby with a tube to provide breaths) can lead to ventilator-induced lung injury. Because of this, noninvasive respiratory support has become increasingly popular, as this form of ventilation has been shown to reduce the incidence of permanent lung injury. (1)
   There are several methods to provide non-invasive support. The gentlest is continual flow of air and oxygen via nasal cannula. However, premature infants often develop apnea, either becasue the signals from their immature brain are not yet sufficient or because the muscles in the back of their throat do not get enough nerve signals to maintain suffiicient opening. As a result, babies on nasal cannula often develop clinical apnea/bradycardia/desaturations. Before putting these babies back on invasive ventilation, clinicians often try to provide the baby with machine breaths while still on non-invasive ventilation. This method is called nasal intermittent positive pressure ventilation and studies have demonstrated that this method reduces the need for re-intubation in VLBW infants (1) and reduces the rate of apneic events.
   A newer method of non-invasive breathing support that has been FDA approved and used in VLBW infants, synchronizes the machine generated breath with the patient's own breath. Neurally adjusted ventilatory assist (NAVA) does this by replacing the standard nasogastric tube with a nasograstric tube that has sensors which detect the baby's natural diaphragm activity, which signal the ventilator to breath in synchronization with the baby. Studies have shown that the efficacy of nasal ventilation is significantly enhanced when the machine breath is synchronized with the patient breath (2). Synchronization also reduces diaphragmatic dysfunction (3). It can improve gas delivery, reduce work of breathing, and make patients demonstrably more comfortable (4).

   Neurally Adjusted Ventilatory Assist (NAVA) is a mode of partial support. NAVA can be used both in intubated patients (invasive NAVA) as well as in extubated patients who require noninvasive positive pressure ventilation (noninvasive NAVA) (5). Invasive NAVA has been shown to deliver equivalent ventilation while requiring lower peak inspiratory pressure, as well as reduced respiratory muscle load, compared to conventional pressure support ventilation.

   Currently, the choice of using NIPPV or NAVA is at the clinician's discretion. Both are regularly and frequently used in the VCU Health System's NICU. There are no studies that have examined whether NAVA triggered synchronized ventilation is more effective than non-synchronized NIPPV. In addition, there is limited data on the synchronicity and mechanics of non-invasive NAVA in VLBW infants. Information comparing clinical and lung mechanical outcomes between NIPPV and NIV NAVA would significantly benefit VLBW care providers and, consequently, their patients in getting the best evidenced-based therapy.

1. Tang S, Zhao J, Shen J, Hu Z, Shi Y. Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure in neonates: a systematic review and meta-analysis. Indian Pediatr. 2013 Apr;50(4):371-6.

2. Gizzi C, Montecchia F, Panetta V, Castellano C, Mariani C, Campelli M, Papoff P, Moretti C, Agostino R. Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2015 Jan;100(1):F17-23.

3. Petrof B, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. Current opinion in critical care 2010; 16(1): 19-25

4. Stein H, Firestone K. Application of neurally adjusted ventilatory assist in neonates. Seminars in Fetal and Neonatal Medicine 2014; 19(1): 60-69.

5. Moerer O, Beck J, Brander L, Costa R, Quintel M, Slutsky AS, et al. Subject-ventilator synchrony during neural versus pneumatically triggered non-invasive

helmet ventilation. Intensive Care Med 2008; 34:1615-23.

4. * **Briefly describe the study design, including all interventions or interactions with research participants and access to identifiable data. Use lay language whenever possible.**
STUDY DESIGN

a. Subjects

Subjects: VLBW (< 1501 grams birthweight) infants in the VCU Health System NICU who are receiving either NPPV or non-inasive NAVA therapy as ordered by their clinical providers. Investigators are clinicians who work in the NICU and will therefore be able to identity eligible subjects.

NAVA and NIPPV are different modes for the way non-invasive ventilation breaths are triggered. Both utilize the same delivery system, ventilator, cannula, etc. In NIPPV, the ventilator breaths are triggered by time, i.e. the ventilator sends a breath to match the prescribed rate like one every 3 seconds for a rate of 20 breaths per minute, no matter whether the patient is inhaling or exhaling. In NAVA, the normal feeding tube is replaced by a special tube that has a sensor located around where the diaphragm surrounds the esophagus. The sensor picks up the electrical signal of the diaphragm muscle contracting, and this mark of the beginning of inhalation is used to trigger a machine breath, so the machine and the patient are coordinated. Aside from the catheter connection, all other procedures are the same. b). Randomization - the order of modes will be assigned based on a random number table using a 5 block design to match the DSMB reporting needs. c) The change from one mode to the next involves activating a switch on the ventilator. There are no procedures that need to be done to the subject. They will remain in their current environment, connected to all the routine and study-related monitoring equipment. d) During the study, which involves both modes, the subjects will be monitored as routine by the staff, as well as one of the study faculty (Rozycki or Moores). In the event that one of us needs to step away briefly, an attending neonatologist and a neonatal fellow are on site in the NICU

As part of routine care, infants on either mode have a nasograstric tube in place. Those subjects who are receiving NIPPV will have their nasogastric tubes replaced by a NAVA nasograstric tube. The subject will then be randomized to one of the two modes (NIPPV or non-invasive NAVA). After a one hour stabilization period, during which small adjustments to the non-inasive settings can be made to clinically optimize the settings, the study will begin. A Nellcor pulse oximeter probe will be placed on an extremity to provide a continuous non-invasive downloadable measure of saturation (blood oxygen level) and heart rate. Data from the ventilator will be downloaded in real-time to a laptop. These data will be recorded for 4 hours continuously. After that, the ventilator will be switched to the other mode (NIPPV to NAVA or NAVA to NIPPV), at the same PEEP and respiratory rate. Again, one hour will be allowed to adjust the ventilator settings. Data will then be collected for 4 hours on the second ventilation mode. At that time, the clinician will be informed if either mode was significantly better and the clinician will decide which mode the patient will return to.We will not know which mode is better until the data are analyzed in aggregate. We're concerned about safety perspective where the subject is on Mode A as chosen by the clinician, and we find that during the time they are on Mode A, they have far more events than when we have them on Mode B. This would be valuable information, since the choice of NPIIV vs. NAVA is currently not clearly indicated. To address this, we will provide the clinician with the results that are available at the time of the study. This will be number of events that are routinely measured clinically, i.e. events that cause alarms such as apnea or bradycardia or desaturations outside the clinical limits. These are objective measures that the clinician can incorporate into their decision making if they so choose.

Data to be collected will include heart rate, saturations from the pulse oximeter, and respiratory rate, expired tidal volume, peak pressure and synchronization from the ventilator.
Clinical data will include: birthweight, gestational age, age at study (days of life) and pre-study ventilator settings, Data will be kept in a secure HIPAA compliant database and only study investigators will have access to it.

Analysis: The simultaneous recordings will be scored for: a) Apnea (cessation of breath resulting in no airflow for > 20 seconds or for > 5 seconds if accompanied by bradycardia [HR < 100 bpm] or desaturation [Oximetry < 85%]) b) Bradycardia (hr < 100 bpm for > 5 seconds) c) Desaturation (< 85% for > 5 seconds) d) Synchronicity, measured as average triggering and cycling-off delays for each modality, and total wasted patient respiratory efforts for each modality.

Primary outcome: The number of isolated apneas, bradycardias and desaturations and the number of combined events will be compared by mode of ventilation.

Secondary outcome: a) Synchronicity from the ventilator at the time of an event. This will be analyzed to determine whether asynchronicity is related to increased number of events during the study. b) Overall asynchronicity counts will be determined by ventilator data that can be uploaded and analyzed with software supplied by the manufacturer. c) average mean airway pressure and peak inspiratory pressures required in each mode of ventilation.

There are no well-characterized tools to measure premature infant 'comfort'. There are semi-subjective pain scores that the nursing staff use but we are more likely to have irritation or discomfort from the probe. Thus, this will be an ongoing assessment of a) the infant's state - quiet sleep, quiet awake, agitated, restless, etc. b) new onset tachycardia or tachypnea coincident with applying the probes. c) facial grimaces that are different than baseline as assessed by the nurse caring for the patient

The threshold for an adverse event will be dependent on the baseline level. If the baseline rate is, say, 4-6 events an hour, a 25% increase is 1 event, which is within the patient's variance. On the other hand, in one having no events, just one event is a 100% increase. We have 2 criteria - 1) An event that requires intervention with breathing support such as with more breaths or a bag and mask, 2) an increase from baseline of at least 4-5 events/hr. from baseline

5. **Upload any supporting tables or documents:**

ID: HM20005575 View: SF - Study Activities

Study Activities

1. * **Select which study type best describes the majority of the study. Your response will help determine which IRB panel should review this.**

- (●) **Bio-Medical**
- ( ) Qualitative - Social/Behavioral/Education (SBE)
- ( ) Quantitative - SBE
- ( ) Mixed Method - SBE
- ( ) Mixed Method - Biomedical

2. * **This study will involve (check all that apply):**

- [ ] procedures such as surveys, interviews, field studies, focus groups, educational tests, deception, psycho-physiological testing, any other similar data collection
- [ ] secondary data analysis: procedures such as analysis of information collected for non-research purposes (includes both retrospective and prospectively collected information), or analysis of data previously collected for a prior research study
- [x] **drugs, devices, experimental interventions, biohazards, radiation, other medical or surgical procedures**

ID: HM20005575 View: SF - Bio-Med Project Details

Bio-Med Project Details

1. * **Select all details that apply:**

- [ ] Drugs, Biologics, Supplements, and/or Other Compounds
- [ ] Placebo
- [ ] Washout Period
- [x] **Device Evaluation**
- [ ] Bio-Hazards, Other Toxins, Recombinant DNA/Gene Transfer
- [ ] Radiation Exposure and/or Scans involving radiation (PET, MRA)
- [ ] Stem Cells
- [ ] Expanded Access - Treatment Use of an Investigational Product
- [ ] Other Medical or Surgical Procedures
- [x] **Protected Health Information (PHI)**

ID: HM20005575 View: SF - Bio-Med Device Evaluation Details

Bio-Medical Device Evaluation Details

1. * **Select the type of device evaluation this study will involve:**

- [x] **Marketed Medical Device (including 510k device)**
- [ ] Investigational Medical Device
- [ ] New Use for Marketed Medical Device
- [ ] Other Devices

2. * **List devices this study will involve:**

Device	Manufacturer	IDE	IDE Holder	Doc
Servo-i Ventilator	Maquet	N/A	Not Required	Servo-i (0.01)
Servo-i NAVA	Maquet	N/A	Not Required	NAVA brochure(0.01)

3. * **Documents required for upload:**
   - **If the IDE is held by a sponsor-investigator, upload at least one of the following documents for verification of the IDE number:**
     - **Study Protocol including IDE number**
     - **Communication from the FDA with verification of the IDE**
   - **If the IDE is held by the sponsor, upload at least one of the following documents for verification of the IDE number (required if IND held by sponsor):**
     - **Sponsor protocol**
     - **Communication from the sponsor verifying the IDE number**
     - **Communication from the FDA verifying the IDE number**
   - **If evaluating an approved device, upload documentation of the approved use(s).**

ID: HM20005575 View: SF - Data Collection Details

Data Collection Details

1. * **Select all involved in the study:**

- [ ] Specimen/Biologic Sample Collection
- [x] **Protected Health Information (PHI)**
- [ ] Audio/Video
- [ ] Existing Data or Specimens Not From a Registry or Repository
- [ ] Use of Internet for Data Collection
- [ ] Registries/Repositories (Includes Accessing, Contributing or Creating)
- [ ] None of the Above

2. * **Select all identifiers that will be collected as part of this study (including for recruitment, data gathering, data analysis, etc.), even if the data will eventually be anonymized:**

- [ ] Names
- [ ] Geographic Locators Below State Level
- [ ] Social Security Numbers
- [x] **Dates (year alone is not an identifier)**
- [ ] Ages >89
- [ ] Phone Numbers

- [ ] Facsimile Numbers
- [ ] E-mail Addresses
- [x] **Medical Record Numbers**
- [x] **Device Identifiers**
- [ ] Biometric Identifiers
- [ ] Web URLs
- [ ] IP Addresses
- [ ] Account Numbers
- [ ] Health Plan Numbers
- [ ] Full Face Photos or Comparable Images
- [ ] License/Certification Numbers
- [ ] Vehicle ID Numbers
- [ ] Other Unique Identifier
- [ ] No Identifiers
- [ ] Employee V#

3. **If "Other Unique Identifier" was selected above, describe the identifiers:**

4. * **Will participants be able to withdraw their data (paper, electronic, or specimens) from the study if they no longer wish to participate:**
   - ( ) Yes
   - (•) **No**

5. **If yes above, describe how participants will be able to withdraw their data:**

ID: HM20005575 View: SF - HIPAA

HIPAA

1. * **Describe the protected health information that will be obtained or used in this research:**
   MRN, birth dates, date of study. The only data that are needed from the EMR are: gestational age, birth-weight, age at study, medications while on study, ventilator mode and settings at time of study, gender and Apgar scores and head ultrasound results.

2. * **Describe the source(s) of the protected health information:**
   VCU's electronic medical record system

3. * **Explain how the PHI collected or used in this research is the minimum necessary to accomplish this research:**
   The above mentioned data will be needed to evaluate the role of maturity on the outcomes. These variables are either standard clinical descriptors of a neonatal research population (birth-weight, gestational age, gender, Apgar Scores) to inform any reader of an aggregated data publication about whether the study sample is representative of the relevant population, or ones that can influence the outcome variable (medications, ventilator history, evidence of brain bleeds)

4. * **Select all pathways this research will employ to use or access PHI:**

- [ ] De-Identified Data
- [ ] Limited Data Set
- [ ] Waiver of Authorization
- [ ] Partial Waiver of Authorization
- [x] **Signed Authorization Combined with Consent Form**
- [ ] Signed Authorization as Stand-Alone Form

ID: HM20005575 View: SF - Data Confidentiality and Storage

Data Confidentiality and Storage

1. * **Confidentiality refers to the way private, identifiable information about a participant or defined community is maintained and shared. Describe all of the precautions that will be used to maintain the confidentiality of identifiable information, samples or specimens:**
   Subjects will have a study number unique to the subject. The key linking the study number to the patient will be kept in a separate comouter file stored in a password protected computer and file. All other data will be stored in VCU RedCap files.

   The data on the laptop is non-identifiable. It will consist of real-time data from the ventilator and apnea monitor, without any identifiers. It will be analyzed for events, without identifiers. Only the event numbers (number and duration of apneas, bradycardias, etc. and synchronicity) will be linked to the subject when stored in VCU Redcap files.The signed consent form will be stored in a locked filing cabinet in a locked office in the VCU Children's Pavilion.

2. * **Who will have access to study data:**
   Named investigators

3. * **If applicable, describe the process for assigning codes to the data including :**
   - how codes will be assigned
   - whether there will be a key linking identifiable information to the data
   - where the key will be stored
   - who will have access to the key
   - when the key will be destroyed
   Each subject will get a study number (1, 2, 3, etc) as they are identified/consented to the study. The code will be kept separately as above and access limited to study investigators. The key code will be destroyed upon completion of tfe study and analysis. The key linking the study number to the patient will be kept in a separate computer file stored in a password protected computer and file. Only the 4 investigators named in this study (Moores, Xu, Sirota and Rozycki) will have access to the key.

4. * **Will the sponsor or investigator obtain a certificate of confidentiality for this study:**

- (●) **No - CoC will not be Obtained**
- ( ) Yes - CoC has been Obtained
- ( ) Yes - CoC Request is Pending
- ( ) Yes - Plan to Submit CoC Request

5. **If the Certificate of Confidentiality has been obtained by the PI, upload it here:**
6. * **What will happen to the research records when the research has been completed:**

- ( ) Stored indefinitely with identifiers removed
- ( ) Stored indefinitely with identifiers attached
- (●) **Destroyed at the end of study once the minimum time required for data retention has been met per VCU Data Retention Policy and/or sponsor retention requirements**
- ( ) Destroyed when notified by sponsor but not less than the minimum time required for data retention per VCU Data Retention Policy
- ( ) Other

7. **If Other, explain:**
8. **If "stored indefinitely with identifiers attached", explain why identifiers are necessary:**

ID: HM20005575 View: SF - Types of Sites

Types of Sites

1. * **Select which of the following accurately describes this study:**

- (●) **Not Multicenter Study**
- ( ) Multicenter Study - VCU Lead
- ( ) Multicenter Study - Non-VCU Lead

2. * **Select all sites where study interventions or interactions will occur and/or identifiable data will be held:**

- [x] **VCU Site**
- [ ] Non-VCU Site (VCU Investigators are conducting/overseeing the conduct of the study)

3. * **Is there a community partner in this research study:**
   - ( ) Yes
   - (●) **No**

ID: HM20005575 View: SF - VCU Site Details

VCU Site Details

1. * **Select all VCU sites that will be utilized in this study:**

- [ ] Clinical Research Services Unit (CRSU)
- [ ] Massey Cancer Center
- [x] **VCU Health System**
- [ ] VCU Qatar
- [ ] Other VCU Site

2. * **Provide details regarding each VCU Site including:**
   - what clinics / facilities will be used
   - resources that are available for the conduct of this study:
   Site - NICU on CCH6
   Study involves normal care practices - normal care and monitoring by personnel will continue during the study period.

ID: HM20005575 View: SF - VCU Health System

VCU Health System

1. * **The PI has reviewed and agrees to comply with the Conduct of Clinical Research in VCU Health System Patient Care Areas policy:**
   - (●) **Yes**
   - ( ) No
2. * **Explain how you will notify and obtain support from patient care providers in the units where the study will be conducted:**
   Investigators will brief and inform clinical personnel of study design by poster in break room, email and personal interactions before first enrollment.

ID: HM20005575 View: SF - Study Funding

Study Funding

1. * **Have you applied for funding:**
   - ○ Yes
   - ◉ **No**

2. **If so, is this study already funded:**
   - ○ Yes
   - ◉ **No**

ID: HM20005575 View: SF - Study Population

Study Population

1. * **Provide the total number of participants you expect to enroll in this study under the VCU IRB:**
   15

2. **If this is a multi-Center Project, what is the total anticipated number of subjects across all sites:**

3. * **Provide justification for the sample size:**
   Sample Size

   Based on published data, monitored events occur at an average frequency of 9.2 over a 4-hour period. The degree of variability is not known but assuming an SD of 50%, a sample size of 10 subjects would have an 0.8 power for a 50% reduction in events at an alpha of 0.05. A similar study to ours comparing NIPPV and flow-synchronized NIPPV (2) had 19 participants and achieved statistically significant differences between the two modalities. Based on this, we are anticipating a need for 15 subjects

4. * **List the study inclusion criteria:**
   1. < 1501 grams (VLBW infant)
   2. Patient must be receiving daily caffeine therapy for apnea
   3. On non-invasive ventilation, either NIPPV or non-invasive NAVA

5. * **List the study exclusion criteria:**
   1. No concerns for acute sepsis (i.e., blood cultures, if drawn, have been negative for 48 hours, and no active signs/symptoms of sepsis).
   2. No history of meningitis or seizures
   3. No signs of increased intracranial pressure, including bulging fontanelle, presence of ventricular shunt device, or ventriculomegaly by most recent ultrasound.
   4, Presence of Grade III or IV intraventricular hemorrhage
   5. No cyanotic heart defects or clinically significant congenital heart disease. Will allow PDA, PFO, and mild to moderate ASD/VSD as determined by pediatric cardiology.
   6. Non-English speaking legal representatives (parents)

6. * **Check all participant groups that are likely to be involved in this study. If it is possible that a regulated vulnerable population (children, pregnant women, prisoners) COULD BE involved in the study, be sure to check them:**

- ☐ Healthy Volunteers
- ☑ **Children**
- ☐ Emancipated Minors
- ☐ Pregnant Women
- ☑ **Fetuses, Neonates, Fetal Material or In-Vitro Fertilization**
- ☐ Prisoners
- ☐ Decisionally Impaired Adults
- ☐ When cancer is integral to the research - cancer Patients, Family Members, Healthcare Providers or Prevention
- ☐ VCU Health System Patients
- ☐ Non-VCU Patients
- ☐ VCU/VCUHS Students or Trainees
- ☐ VCU/VCUHS Employees
- ☐ Individuals with Limited English Proficiency
- ☐ Active Military Personnel
- ☐ When researching in a K-12 environment - populations Within School Districts or Other Learning Environments

7. **If you are either targeting, or excluding, a particular segment of the population / community, provide a description of the group/organization/community and provide a rationale:**
   The decreased ability to explain the technical aspects of the study to LEP parents through either medically-approved translation service or a medically-certified informed consent form in other languages makes it difficult for these parents to be fully informed to make a decision in the best interests of their child.

8. * **Select the age range(s) of the participants who may be involved in this study:**

- ☑ **< 1 Year**
- ☐ 1 - 6 Years
- ☐ 7 - 12 Years
- ☐ 13 - 17 Years
- ☐ 18 - 20 Years
- ☐ 21 - 65 Years
- ☐ > 65 Years

ID: HM20005575 View: SF - Children

Children

1. * **Check all of the childrens categories that apply to the study:**

- ☐ 45 CFR 46.404 Research involving no greater than minimal risk to children, with adequate provisions for soliciting the assent of the children and permission of their parents or guardians, as set forth in Sec. 46.408
- ☑ **45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to individual participants**
- ☐ 45 CFR 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition
- ☐ 45 CFR 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. (Research in this category must be reviewed and approved by the Secretary of the Department of Health & Human Services)

2. * **Will this study involve participants who could be wards of the state:**
   - ○ Yes
   - ◉ **No**

3. * **Describe how children will be assented to participate in the study:**
   Not applicable - this study is recruiting newborn infants only

4. * **Describe how you plan to obtain permission of parents or guardians:**
   Parents of stable infants receiving non-invasive ventilation will be approached in their private single patient NICU rooms and presented with layman-term information about the study. They will be given a copy of the consent form, all of their questions will be answered and they will have the opportunity to take the information home to review.

ID: HM20005575 View: SF - Children: Direct Benefit [45 CFR 46.405]

Children: Direct Benefit [45 CFR 46.405]

1. * **Explain briefly how the risk is justified by the anticipated benefit to participants:**
   While both modes of non-invasive ventilation are currently approved and used in the US and in the VCU NICU, it is not known which may be better. Hence, there is a possibilty that one mode may be inferior to the other. Currently, a clinician picks one mode and then watches for clinical signs to determine if they picked the right one. By participating in this study, the subject gets exposed to both in a brief period of time, and the efficacy and superiority of one over the other can be assessed. In normal care, this side by side assessment is not done.

2. * **Explain briefly how the relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches:**
   The alternative approach is to not participate. Study participants will be far more intensely monitored for how the ventilation mode is working than non-participants. Non-participants depend on nursing observation (a nurse may have 1-2 other patients) and historic data from the monitor. Participants will have an investigator watching their respiratory status continuously for four hours on each mode, so be better able to assess which one is better for the subject. This information will be shared with the clinical team who may use it to potentially select a better mode of non-invasive ventilation for that patient.

ID: HM20005575 View: SF - Pregnant Women, Fetuses, Neonates and Post-Delivery Material

Pregnant Women, Fetuses, Neonates and Post-Delivery Material

1. * **Check all of the following categories that apply to this research:**

- ☐ 45 CFR 46.204 Research involving pregnant women or fetuses.
- ☐ 45 CFR 46.205(a) and (b) Research involving neonates of uncertain viability.
- ☐ 45 CFR 46.205(a) and (c) Research involving nonviable neonates
- ☑ **45 CFR 46.205(d) Research involving viable neonates.**
- ☐ 45 CFR 46.206 Research involving, after delivery, the placenta, the dead fetus, or fetal material.
- ☐ 45 CFR 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

ID: HM20005575 View: SF - Neonates: Viable [45 CFR 46.205d]

Neonates: Viable [45 CFR 46.205d]

If research data is collected on a neonate (newborn, after delivery) that is VIABLE, the regulations for special protections for children apply (Subpart D). Therefore, in addition to selecting Viable neonates here, Children must be selected in Study Population.

If research data is collected on pregnant women, or the viability of the neonate is questioned, other sections may apply.

ID: HM20005575 View: SF - Potential Subject Identification and Recruitment

Potential Subject Identification and Recruitment

1. * **Choose all recruitment methods that may be used:**

- ☐ E-mail Campaign
- ☐ Phone Solicitation
- ☐ Flyers, Letters or Newspaper/TV/Radio Ads

- [ ] Website
- [x] **Direct Contact**
- [ ] Psychology Research
- [ ] Participant Pool (SONA)
- [ ] VCU TelegRAM announcement
- [ ] Word of Mouth
- [ ] Other

2. **If Other, please describe:**

3. * **Select the methods used to obtain names and contact information for potential subjects:**

- [x] **Pre-Existing Relationship with Participants**
- [ ] Selected from Pre-Existing VCU Records
- [ ] Selected from Pre-Existing Non-VCU Records
- [ ] Selected from Publicly Available Records
- [ ] Referred by Health Care Provider or Other Health Professional
- [ ] Recruited from Database or Registry
- [ ] Identified through Community Based Organization (Schools, Church Groups, etc.)
- [ ] Self Referred (Flyer/Ad)
- [ ] Other

4. **If Other, please describe:**

5. * **Describe specific details for identifying and recruiting participants, including but not limited to:**
   - Specific locations where recruitment materials will be displayed
   - How contact information is obtained for any direct contact with potential participants
   - Who will approach and/or respond to potential participants:
   Inpatient babies in the Neonatal Intensive Care Unit (NICU) will be screened for inclusion and exclusion criteria by investigators, who work in the NICU.
   Families of potential subjects will be approached by one of the investigators for consent.

6. **Describe any special recruitment procedures for vulnerable populations:**

7. **Upload all recruitment materials including ads, flyers, scripts, letters, email invitations, TelegRAM announcements, and postcard reminders:**

8. * **Before potential participants consent to the study, will screening questions be asked or will any screening procedures/tests be done that would not otherwise be done as standard of care:**
   No

9. **If Yes, will identifiable information about individuals be recorded during screening:**
   - ( ) Yes
   - ( ) No

ID: HM20005575 View: SF - Privacy

Privacy

1. * **Privacy is an individual's right to control how others view, record, or obtain information about them. When privacy is violated it can involve such things as being asked personal questions in a public setting; being publicly identified as having a particular characteristic or diagnosis; being photographed, videotaped or observed without consent; or disclosing personal information.**

   Describe how participants' privacy will be protected during:
   - identification,
   - recruitment,
   - screening,
   - the consent process,
   - conduct of the study, and
   - data dissemination:

   The NICU is a single bed room design. All work including obtaining consent, and performing the study will be done in the private single bed room.
   Data will only be reported in aggregate, not by individuals. No data will be linked to any information that could identify the subject

ID: HM20005575 View: SF - Costs to Participants

Costs to Participants

1. **Select all categories of costs that participants or their insurance companies will be responsible for:**

- [x] **Participants will have no costs associated with this study**
- [ ] Study related procedures that would be done under standard of care
- [ ] Study related procedures not associated with standard of care
- [ ] Administration of drugs / devices
- [ ] Study drugs or devices
- [ ] Other

2. **If Other, explain:**

3. * **Provide details of all financial costs to the participant, other than time and transportation. Additional details regarding standard of care costs will be requested on another screen, if applicable.**
None

4. **If applicable, upload a Cost Analysis form here:**

ID: HM20005575 View: SF - Compensation

Compensation

1. * **Describe any compensation that will be provided including:**
- items such as parking/transportation
- total monetary amount
- type (e.g., gift card, cash, check, merchandise, drawing, extra class credit)
- how it will be disbursed:
None

2. **If compensation will be pro-rated, explain the payment schedule:**

ID: HM20005575 View: SF - Risks, Discomforts, Potential Harms and Benefits

Risks, Discomforts, Potential Harms and Benefits

1. * **Describe the risks to participants associated with this study:**
- physical, psychological, social, legal, financial, and other risks
- seriousness of given risks
- probability or likelihood of given risks
1. For some participants, the nasograstric tube may need to be replaced before the study begins. There is very very small risk of trauma, bleeding or a transient drop in heart rate when a new tube is placed. Note that tubes are placed and replaced routinely in this population.
2. Even though both modes of non-invasive ventilation are currently used clinically, it is possible that one mode will not be as well tolerated as the other, or that it will take longer than one hour to adjust the settings. The subject might have more apnea/bradycardia/desaturation events. While these are common and are, in fact, why the patient is being treated clinically with one of the two modes under investigation, a significant increase in the events. If this occurs, the study will be stopped and the clinical team notified. Any needed interventions will be under the direction of the clinical team. The most likely outcome will be to place the subject back on the ventilation mode that he/she was on prior to the study.
3. The adverse events are the outcomes that will be affected by/measured for the interventions. Both NIPPV and NAVA are used to treat/prevent these events. The study is seeking to answer which mode is better at preventing them. Since we don't know this yet, it is possible that one of the modes will be worse, which is why it will be monitored as an adverse event, and if one mode does cause more events, the study will be stopped. Plus this info will be given to the clinician to use when selecting a mode for the patient in the future.

2. * **Describe how the risks / harms will be minimized:**
1. The nasogastric tubes will be placed by experienced NICU personnel who place nasogastric tube every day.
2. The subjects will be monitored contiuously by: cardiorespiratory monitor, 2 pulse oximeters and by direct observation by study personnel during the set-up phase and each four hour observations. If , during the first trial, the event number or severity increases beyond what which would be considered safe in normal clinical care, the mode will be considered a failure. The clinical team will be informed and the clinical team (not the investigators) will decide if, in their judgment, the alternate mode should be used for the second trial. If the increased event number or severity occurs during the second trial, the mode will be considered a failure, the clinical team will be informed and the clinical team will determine further care decisions.
3. The events are ones that are monitored as part of the usual care, and this will continue during the study period. These babies are always connected to monitors which are linked to nursing phones as well as central telemetry. The investigator doing the study will be present to assess/intervene, and as back-up, the clinical team will provide their routine care for such events.

3. **If the disclosure of any of the information obtained during the study would place the individual at risk for harm (legal, reputation, emotional etc.) and the information will be recorded so that the individual could be identified, explain the protections that will be put in place to decrease the risk of disclosure:**
Not applicable

4. * **The Code of Virginia requires that most medical personnel and all employees of institutions of higher education report suspected child/elder abuse or neglect. Is it likely investigators could discover information that would require mandatory reporting by the investigators or staff:**
Yes
No

5. * **Is it likely investigators could discover a participant's previously unknown condition (eg disease, suicidal thoughts, wrong paternity) or if a participant is engaging in illegal activities:**
Yes
No

6. **If yes, explain how and when such a discovery will be handled:**

7. * **Describe any potential risks or harms to a community or a specific population based on study findings:**
None anticipated

8. * **Describe criteria for withdrawing an individual participant from the study; such as safety or toxicity concerns, emotional distress, inability to comply with the protocol, etc.:**
If, between consent and study, the subject no longer meets inclusion criteria or does meet exclusion criteria.
If the number/severity of events becomes a clinically relevant safety concern, the study mode will be considered a failure. The clinical team will be informed and they will have the authority to stop the study.

9. * **Summarize any pre-specified criteria for stopping or changing the study protocol due to safety concerns:**
The exact number/severity of events that might define a safety concern is subject dependent based on prior event history. A subject who normally has 0-1 events an hour may have a clinical safety concern at 4-5 events/hr while in one who is normally having 3-4 events/hr, the same rate of 4-5 events would not be significant. Clinically, a change in event rate is judged against baseline rate. However, events that require significant intervention, i.e. mechanical breathing support from ventilator or bag and mask, will be an absolute stopping indication.
The threshold for an adverse event will be dependent on the baseline level. If the baseline rate is, say, 4-6 events an hour, a 25% increase is 1 event, which is within the patient's variance. On the other hand, in one having no events, just one event is a 100% increase. We have 2 criteria - 1) An event that requires intervention with breathing support such as with more breaths or a bag and mask, 2) an increase from baseline of at least 4-5 events/hr. from baseline.

10. **Where appropriate, discuss provisions for ensuring necessary medical, professional, or psychological intervention in the event of adverse events to the subjects:**
Current protocols in place in NICU.

11. * **Describe any potential for direct benefits to participants in this study:**
Observational results will be shared with the clinical team. These may include infant's comfort level on each mode of non-invasive ventilation; pressure levels on each mode, general frequency of apnea/bradycardia/desaturation events. Based on this information, the clinical team may choose to change the mode of ventilation.
There are no well-characterized tools to measure premature infant 'comfort'. There are semi-subjective pain scores that the nursing staff use but we are more likely to have irritation or discomfort from the probe. Thus, this will be an ongoing assessment of a) the infant's state - quiet sleep, quiet awake, agitated, restless, etc. b) new onset tachycardia or tachypnea coincident with applying the probes. c) facial grimaces that are different than baseline as assessed by the nurse caring for the patient.

12. * **Describe the scientific benefit or importance of the knowledge to be gained:**
Information derived from analysis of study data may determine which mode of non-invasive ventilation is better in short term use for VLBW infants by examining outcome data with more depth and precision than is currently done clinically. This will help clinicians to better choose the optimal mode.

13. **If applicable, describe alternatives (research or non-research) that are available to potential participants if they choose not to participate in this study:**
They will be maintained on their current clinically chosen mode of ventilation

14. * **Indicate if this study will have a Data Safety Monitoring Board (DSMB) or a Data Safety Monitoring Plan (DSMP): [Required for all Full Review studies]**

- [ ] DSMB Review Required
- [x] **DSMP Required**
- [ ] Not Required

ID: HM20005575 View: SF - DSMP Details

DSMP Details

1. * **Describe your Data Safety Monitoring Plan for monitoring the data collected to ensure the safety of participants:**
At 5 subject intervals, data on the number of failures, and the frequency/severity of events will be provided to Dr. Karen Hendricks-Munoz, MD, MPH who is Chair of Neonatal Medicine at VCU. She will assess the study for safety. Her opinion about whether the study should continue is final.
The DMSP is the chief of the service. We will submit outcomes and adverse event data to her after every 5 subjects. It is an expectation that the DMSP assessment of whether to stop or continue will be made in writing to the PI within 28 days, and a copy will be forwarded to the other investigators, the device sponsor and the IRB each time.

ID: HM20005575 View: SF - Consent Qualifiers

Consent Qualifiers

1. * **Are you submitting your study as exempt and therefore no consent is required:**
- ( ) Yes
- (•) **No**

ID: HM20005575 View: SF - Consent Groups

Consent Groups

1. * **List all consent groups:**

Group	Types	Waivers	Roles	Roles - Other	Consent	Coercion	Decision	Status Change
VLBW infants on non-invasive ventilation	Written/Signed Consent by Parent/Guardian (for child) or Legally Authorized Representative (for adult)	No Waivers Requested	Principal Investigator Co/Sub-Investigator Trainee/Student		In the subject's private room when the parents/guardians are visiting	Preference will be given to having one of the investigators not currently caring for the potential subject as person to obtain consent. The alternative of not participating, with no effect on care, will be emphasized during review of the consent form Several of the investigators take one week turns on the clinical service where the study participants will be cared for. Since only the investigators will be obtaining consent, it is very likely that an investigator who is not directly caring for the patient will be available to explain the study and obtain consent. Since the subjects are usually in the NICU for weeks, during which they often meet the criteria to participate, it would be very unusual for the clinician caring for the subject to need to get consent	Parents/guardians may have up to 24 hours to consent. This may be renewed if the subject continues to receive non-invasive ventilation	

2. **Upload any consent / assent documents:**

ID: HM20005575 View: SF - Documents

Documents

[redacted]

ID: HM20005575 View: SF - Protocol Complete

Section Complete:
SUMMARY

End of Application:
IRB HUMAN SUBJECTS STUDY

Click Continue Below

[redacted]

[redacted]

ID: HM20005575 View: Bio-Med Devices

Bio-Medical Devices

1. * **Name:**
   Servo-i Ventilator
2. * **Manufacturer:**
   Maquet
3. * **Provide the IDE number for any investigational devices or new use of a marketed device:**
   N/A
4. * **Select who holds the Investigational Device Exemption for the device:**

   - ○ External to VCU Sponsor or Investigator
   - ○ VCU Sponsor-Investigator
   - ○ VCU Sponsor who is not the Investigator
   - ◉ **Not Required**

5. **If evaluating an approved device, upload documentation of the approved uses:**
   Servo-i (0.01)

   Describe use of the device in the methods section.

ID: HM20005575 View: Bio-Med Devices

Bio-Medical Devices

1. * **Name:**
   Servo-i NAVA
2. * **Manufacturer:**
   Maquet
3. * **Provide the IDE number for any investigational devices or new use of a marketed device:**
   N/A
4. * **Select who holds the Investigational Device Exemption for the device:**

- ○ External to VCU Sponsor or Investigator
- ○ VCU Sponsor-Investigator
- ○ VCU Sponsor who is not the Investigator
- ◉ **Not Required**

5. **If evaluating an approved device, upload documentation of the approved uses:**
   NAVA brochure(0.01)

   Describe use of the device in the methods section.