Official title: Pilot Cross-Over Trial of Neurally Adjusted Ventilatory Assist (NAVA) and Conventional Flow Triggered Mechanical Ventilation (CMV) in Severe Bronchopulmonary Dysplasia (sBPD)

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Title:	**Pilot Cross-Over Trial of Neurally Adjusted Ventilatory Assist (NAVA) and Conventional Flow Triggered Mechanical Ventilation (CMV) in Severe Bronchopulmonary Dysplasia (sBPD)**
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ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees centigrade
AE	Adverse event
sBPD	Severe Bronchopulmonary Dysplasia
N/IICU	Neonatal & Infant Intensive Care Unit
PICU	Pediatric Intensive Care Unit
NAVA	Neurally Adjusted Ventilatory Assist
CMV	Conventional flow triggered Mechanical Ventilation
Edi	Diaphragmatic Electrical Activity
PEEP	Positive End Expiratory Pressure
PIP	Peak Inspiratory Pressure
cmH_2O	Centimeters of water
Crs	Compliance of the respiratory system
Rrs	Resistance of the respiratory system
Hrs	Hours
ETT	Endotracheal Tube
Vt	Tidal Volume
RR	Respiratory Rate
HR	Heart Rate
BP	Blood Pressure
Tcom	Transcutaneous Carbon Dioxide
$EtCO_2$	End Tidal Carbon Dioxide
MAP	Mean airway pressure
OSI	Oxygen Saturation Index
FiO_2	Fraction of Inspired Oxygen
SpO_2	Oxygen Saturation Percent
PSV	Pressure Support Ventilation

ABSTRACT

Context:
Most research to date in neonatal lung disease has focused on BPD prevention. As a result, insufficient investigation has been performed to define optimal respiratory management strategies for infants and young children with established BPD. Thus, there is no robust evidence base to guide ventilator management to promote lung disease recovery and support neurodevelopment in this population. Neurally adjusted ventilatory assist (NAVA) is an alternative to conventional flow triggered ventilation that has shown promise for improving respiratory gas exchange, patient-ventilator interaction, and work of breathing in preterm neonates. The safety and efficacy of NAVA in infants and young children with established, severe BPD is uncertain.

Objectives:
To compare measures of pulmonary mechanics, respiratory gas exchange, and patient comfort between conventional flow triggered mechanical ventilation and NAVA among prematurely born infants and young children receiving invasive respiratory support for severe BPD.

Study Design:
Prospective, unblinded, pilot randomized cross-over trial of 2 modes of mechanical ventilation.

Setting/Participants:
The trial will take place in the N/IICU and PICU at CHOP and the PICU at Hasbro Children's Hospital. Up to 25 patients will be enrolled in the study to produce up to 20 children with evaluable trial data.

Study Interventions and Measures:
After informed consent, a NAVA catheter will be placed in all enrolled subjects and baseline data will be recorded for 24 hours. After this initial observation period, study participants will be randomized to either continue flow-triggered mechanical ventilation (CMV) (current standard of care) or begin mechanical ventilation with NAVA. This treatment period will last 5 days. After completing the first 5-day treatment period, subjects will crossover to the alternate mode of mechanical ventilation (CMV or NAVA) for a second, 5-day treatment period. The primary study outcome is the median daily, time-weighted oxygen saturation index ([mean airway pressure x FiO2]/SpO_2). Additional measures of respiratory gas exchange, pulmonary mechanics, and patient comfort will also be recorded. The results of all study outcome measures will be compared between the 2 modes of mechanical ventilation with each study participant serving as his/her own control.

PROTOCOL SYNOPSE

Study Title	Pilot Cross-Over Trial of Neurally Adjusted Ventilatory Assist (NAVA) and Conventional Flow Triggered Mechanical Ventilation (CMV) in Severe Bronchopulmonary Dysplasia (sBPD)
Funder	Respiratory Therapy Department and Division of Neonatology and the American Respiratory Care Foundation
Study Rationale	Despite substantial advances in neonatal care, BPD rates are not improving. Most research efforts to date in neonatal lung disease focused on BPD prevention. As a result, insufficient investigation has been performed to define optimal respiratory management strategies for established BPD. Thus, there is no robust evidence base to guide ventilator management to promote lung disease recovering and support neurodevelopment in severe BPD. The pulmonary parenchyma in severe BPD is poorly suited for gas exchange. This in turn leads to patient-ventilator asynchrony, increased respiratory work, and patient discomfort. The NAVA mode of invasive mechanical ventilation is an emerging alternative to CMV that may provide better patient-ventilator interaction, gas exchange, and reduce work of breathing in sBPD. Although NAVA has shown utility in neonatal and pediatric intensive care patients, no randomized studies have explored this mode of ventilation in a cohort exclusively comprised of infants and young children with sBPD. The chronic, heterogeneous lung changes and high ventilator pressures used in sBPD distinguish this illness from other, acute respiratory processes encountered in the neonatal and pediatric intensive care units.
Study Objective(s)	**Primary** To determine whether invasive mechanical ventilation with NAVA, as compared to CMV, improves respiratory gas exchange in prematurely born infants and young children with sBPD. **Secondary** • Compare patient respiratory mechanics and cardiopulmonary stability between the two modes of ventilation • Compare patient comfort between the two modes of ventilation • Compare age and respiratory support at discharge
Study Design	Prospective, unblinded, randomized cross-over trial of 2 modes of mechanical ventilation
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Gestational ages (GA) ≤ 32 weeks 2. Current age between 36 weeks postmenstrual age (PMA) and 2 years corrected age

	3. Severe BPD (as per NIH consensus definition) diagnosed at 36 weeks postmenstrual age 4. Receiving invasive mechanical ventilation for ongoing lung disease 5. Not expected to be ready for extubation within 10 days following enrollment 6. Parental consent **Exclusion Criteria** 1. Severe congenital anomalies 2. Known diaphragmatic defect 3. Current treatment with high frequency mechanical ventilation 4. DNR Status or Futility of Care 5. >10% leak around the endotracheal tube, 6. Treatment with neuromuscular blockade within 72 hours prior to enrollment 7. Acute respiratory instability defined as a ventilator rate increase >15 bpm, PEEP increase >2 cm/H2O, sustained, absolute FiO2 increase >20%, and/or prescribed increase in tidal volume >2 mL/kg within 24 hours prior to enrollment.
Number of Subjects	Up to 25 patients will be enrolled to produce 20 children with evaluable trial data. The N/IICU and the PICU at CHOP and the PICU at Hasbro Children's Hospital will be the only sites for the trial.
Study Duration	Each subject's participation will last until discharge. The active treatment phase of the study will last 11 days. Medical records will be reviewed until hospital discharge. The entire study is expected to last 24 months.
Study Phases **Screening**	Participants will be identified by review of daily census logs in the participating ICU's. Enrollment will be discussed with the patients' primary physician before parents are approached for consent.
24-hour Observation Period	Following informed consent, a NAVA catheter will be placed in all study subjects and baseline data will be recorded for 24 hours.
Study Treatment Period	After the observation period, study participants will be randomized to continue CMV or initiate NAVA. After receiving the randomly assigned mode of mechanical ventilation for 5 days, subjects will crossover to the alternate mode of ventilation for a final 5-day treatment period.
Efficacy Evaluations	Comparisons of primary and secondary outcomes between the two modes of ventilation

Safety Evaluations	Subject safety will be monitored by through assessment of adverse events, vital signs, physical examinations, and laboratory data by the medical and study teams as well as the independent data safety monitoring committee. All study investigators and a core group or respiratory therapists who will care for study infants will be provided training on the Servo I ventilator and the NAVA mode. Clinicians responsible for the care of study subjects receiving the NAVA mode of ventilation will be trained up to the current standard for their role, as is done for clinicians using clinically deployed ventilators. Guidelines for startup and continued management, including troubleshooting techniques of the NAVA mode, will be available for the medical teams and a study investigator will be on call 24/7. Individual subjects will be withdrawn from the study for safety if there is an absolute, sustained increase in FiO_2 by 20% or if the pCO_2/TcO_2 increase by 25 points above baseline or to a level greater than 90 mm Hg, for more than 2 hours while on the NAVA mode. If this occurs, the patient will discontinue NAVA therapy and be transitioned to previous CMV settings. A study investigator will round daily with the clinical team and be available 24/7 for questions. The overall safety of the study will be assessed with interim safety analyses after the completion of every 5 patients (3 times total) and in the event of any serious safety events.
Statistical and Analytic Plan	Summarized values for the primary and secondary outcomes will be compared between the two treatment arms using paired statistical tests (e.g. Wilcoxon signed rank tests, paired t-tests) as appropriate, based on the data distribution. Linear mixed effects models will be used to explore longitudinal change in the study outcomes (as continuous measures) as a function of the treatment arm.
DATA AND SAFETY MONITORING PLAN	Clinical adverse events will be monitored throughout the study period. There will be monthly and as needed ad-hoc study investigator meetings to discuss and monitor trial data and safety. All data will be kept confidential in accordance with HIPPA and CHOP policies. An independent safety monitoring committee inclusive of physicians from each study site will be formed to review any adverse events, adjudicate relatedness to the study procedures, and recommend trial continuation or early closure.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Unblinded Intervention**			
		Observation Phase	**1st Mode Phase**	**2nd Mode Phase**	**Observation**
Study Days		**1**	**2-6**	**7-11**	**12-discharge**
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Demographics/Medical History	X				X
Vital Signs	X	X	X	X	
Ventilator settings/measurements/OSI	X	X	X	X	
Placement of Tcom (if applicable)		X			
Placement of NAVA catheter		X		X	
Randomization		X			
Daily Asynchrony Index		X	X	X	
Daily Salivary Cortisol Levels		X	X	X	
Adverse Event Assessment		X	X	X	X*

*We will monitor for targeted adverse events that may be related to the study procedures for 72 hours after completion of the 2nd mode phase.

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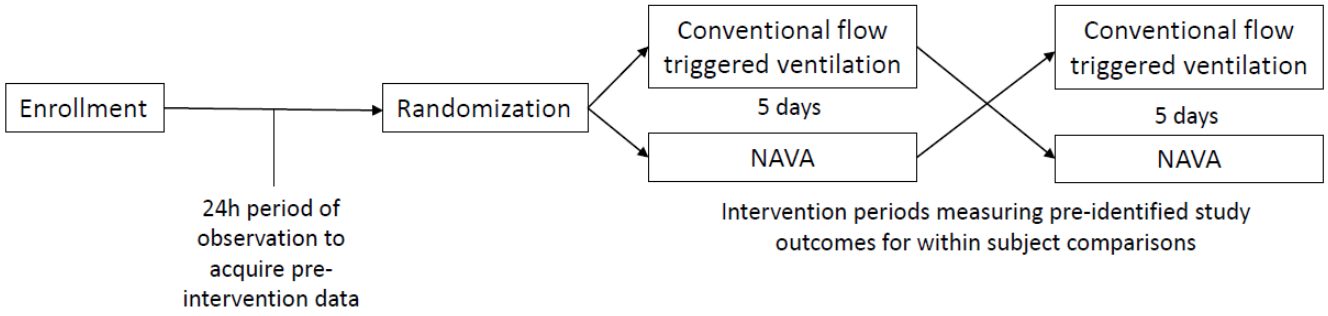
FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Bronchopulmonary dysplasia (BPD) is a leading pediatric cause of death and disability. BPD affects 50% of extremely preterm infants and is a strong predictor of life-long cardiopulmonary and neurodevelopmental impairment.[1-4] Despite substantial advances in neonatal care, BPD rates are not improving. Most research efforts to date in neonatal lung disease focused on BPD prevention. As a result, insufficient investigation has been performed to define optimal respiratory management strategies for established BPD. This is of particular importance for the 5-10% of extremely preterm infants who require prolonged invasive respiratory support. For this population, that comprises an increasing number of the infants cared for in tertiary, referral centers, there is no robust evidence to guide ventilator management to promote lung disease recovery and support neurodevelopment.

The pulmonary parenchyma in severe BPD (sBPD) is poorly suited for gas exchange. The lung architecture often consists of large, air-trapped cystic expansions that increase dead space with adjacent areas of focal lung collapse and interstitial fibrosis. Small airway malacia, which further contributes to air trapping, directly impairs the ability of most flow-sensing ventilators to appropriately support patient-initiated breathing. This in turn leads to patient-ventilator asynchrony, increased respiratory work, and patient discomfort.[5,6] In practice, clinicians often rely on frequent doses of narcotic sedatives to suppress patient respiratory effort and/or high positive end-expiratory pressures (PEEP) to overcome lung intrinsic PEEP and enable sufficient inspiratory air flow to trigger the ventilator.[7] Patient-ventilator asynchrony can exacerbate air trapping and impair the ability to wean ventilator settings, resulting in prolonged exposure to invasive mechanical ventilation.[8] In infants, the ventilator is traditionally triggered when an alteration in flow in the ventilator circuit is sensed. At times, infants are either unable to generate the required flow change to trigger the ventilator or the insufficient airflow results in a significant delay in breath delivery. Greater ability to identify and support patient triggered ventilation is expected to improve patient-ventilator synchrony, gas exchange, and comfort.

1.2 Name and Description of Investigational Intervention

The Maquet Servo I ventilator has a proprietary mode of ventilation approved for use in infants and children called Neurally Adjusted Ventilatory Assist (NAVA). This mode utilizes a breath trigger based on the electrical activity of the diaphragm (Edi) instead of a flow or pressure trigger used by traditional modes of conventional mechanical ventilation (CMV). NAVA utilizes a specialized nasogastric tube imbedded with four electrode sensors that detect Edi. The Edi signal is used to trigger the ventilator and determine the level of inflationary support provided by the ventilator. This allows the ventilator to match, breath to breath, the inspiratory time and respiratory rate of the patient. The ventilator matches the support it provides based off the Edi level (i.e. higher Edi leads to more support provided). The peak inspiratory pressure is determined by both the ventilator pressure selected by the clinician and value termed the NAVA level. The NAVA level is calculated as the The maximum Edi detected minus the minimum Edi detected. PIP is calculated as the NAVA level plus the PEEP: [PIP = (Edi_{max} – Edi_{min})+PEEP. The delivered PIP is determined for each individual breath according to these paremeters.[9] Importantly, NAVA doesn't simply

replace flow-triggered technology used by standard conventional ventilators, but rather adds an additional means of detecting patient respiratory effort. NAVA works on the principal of "first serve first" in which the ventilator triggers each breath using either the neural trigger or the standard flow trigger, whichever it senses first.[9] A key safety feature of the NAVA mode is mandated clinician input of back-up ventilator settings. In the event that the patient stops breathing or the electrical diaphragm signal is lost, the ventilator will automatically switch from the NAVA mode to the mode and settings selected for back-up ventilation by the clinicians. These settings can be entered to match the infant's settings employed on the Draeger ventilator. In this manner, NAVA ventilations adds to standard conventional mechanical ventilation with traditional ventilation as an ever-present safeguard.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Clinical Studies

1.3.1.1 Clinical Studies in Adults

Studies conducted in adults have demonstrated safety and efficacy of the neural trigger used in NAVA compared to the pneumatic trigger[10] and in critically ill patients showed improved work of breathing[11,12] and reduced asynchrony.[13] These early studies, however, only assessed the use of NAVA for short time frames (e.g. up to 3 hours) and did not include patients with chronic lung disease.

Spahija et al, explored the use of NAVA compared to pressure support ventilation (PSV) in subjects with COPD and saw improvement in patient-ventilator synchrony.[14] This study, however, also utilized a short study time frame of only 10 minutes in each mode. Coisel et al, compared NAVA and PSV in subjects who underwent abdominal surgery and monitored each mode for 24 hours.[15] As seen in other studies, they reported an increase in variability of the respiratory pattern, with NAVA mode, as well as increased oxygenation.

1.3.1.2 Clinical Studies in Children

Although NAVA has been studied in term and preterm infants and compared with CMV modes, a 2017 Cochrane review of NAVA in pre-term infants found only 1 valid trial with endpoints examining rates of BPD, other morbidities, and mortality.[16,17] This single trial showed that NAVA was associated with lower PIPs compared with CMV in preterm infants with RDS, but did not show differences in mortality or morbidity. A number of small cross-over trials looked at NAVA in a range of patients, from premature infants at high risk of developing BPD to patients with established BPD. In all of these previous studies, NAVA was shown to decrease the PIP. Studies have also demonstrated better patient ventilator synchrony and a decrease in work of breathing, FiO_2 and $PaCO_2$ with NAVA compared to CMV.[16-20]

Observational and interventional trials have also been performed in the pediatric ICU. Comparison of PSV and NAVA in a multiple cross-over study in the post-operative cardiac surgical population showed an improvement in patient-ventilator synchrony and decreased peak inspiratory pressures[21]. Alander et al, compared the different types of conventional triggers (flow and pressure) with NAVA in both pediatric and neonatal patients[22]. Each trigger type was assessed for 10 minutes. There was a significant difference in short-term patient-ventilator synchrony but no difference in oxygenation parameters. The interaction

between the patient and ventilator was investigated by Bordessoule, et al in ten infants. This study showed that 4.6% & 7.7% of patient efforts did not result in ventilator support during pressure control and PSV, respectively. There were no wasted efforts (non-supported patient initiated breaths) with NAVA[23]. Kallio et al, also showed an improvement in PIP and oxygenation with a reduction in need for sedative medication for non-surgical patients[24]. In contrast, Duyndam, et al did not see a difference in comfort in relation to sedation needs or COMFORT scores.[25] The currently available literature for the use of NAVA in children is limited to preterm infants with RDS with very little research concentrating on sBPD. These studies are also limited to short time frames for comparisons lasting no longer than 12 hours and commonly comparing NAVA to PSV, a weaning mode of mechanical ventilation, and not to a ventilator mode providing moderate support.

1.4 Relevant Literature and Data

The NAVA mode of invasive mechanical ventilation is an emerging alternative to conventional pressure or flow triggered ventilation that may provide better patient-ventilator interaction, comfort, and gas exchange in severe BPD (sBPD). There is only one study that looks specifically at NAVA use in infants with sBPD. Lee et al performed a retrospective review of infants born prematurely that underwent tracheostomy and required mechanical ventilation for > 6 months.[26] 14 infants over a 6 year period met their definition of prolonged mechanical ventilation and only 9 were supported with NAVA. In these nine infants, compared to the 5 infants supported with other modes, they saw a decreased use of sedation in children and fewer cyanotic events once patients were switched to the NAVA mode. Although no studies raised safety concerns with the use of NAVA in infants there are no prospective randomized controlled trials comparing NAVA to other modes on mechanical ventilation for safety and efficacy in sBPD.

As part of our evaluation, we will compare daily salivary cortisol levels and median daily State Behavioral Scale (SBS) and Withdrawal Assessment Tool (WAT-1) between the two modes of ventilation to evaluate patient stress and comfort levels. Salivary cortisol has been shown to increase in response to stress in both pre-term and term infants in multiple studies[27] and stay elevated in response to persistent stress in multiple different disease processes[28]. The well described adult diurnal pattern of cortisol release is absent in full term infants less than a month and begins to approximate the adult circadian rhythm in pre-term infants by 3-6 month, but may remain attenuated until age 4[28,29].

1.5 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, CFR Parts 50, 54, 56, and 812. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to establish pilot data on the safety and efficacy of NAVA during invasive mechanical in infants and young children with established, severe BPD

2.1 Primary Objective

To determine whether invasive mechanical ventilation with NAVA, as compared to CMV, improves respiratory gas exchange in prematurely born infants and young children receiving invasive respiratory support for severe BPD.

The primary study outcome is the median, time-weighted daily oxygen saturation index ([mean airway pressure x FiO2]/SpO2). Secondary measures of respiratory gas exchange that will be evaluated are the daily median transcutaneous pCO_2 levels (measured hourly) and the daily frequency of intermittent hypoxemic events (SpO_2 < 80% for ≥ 10 seconds and less than 3 minutes) recorded by continuous SpO_2 measurement.

We hypothesize that NAVA compared with conventional mechanical ventilation will result in statistically significant reductions ($p<0.05$) in the median daily oxygen saturation index.

2.2 Secondary Objectives

To determine whether NAVA as compared to CMV, improves measures of pulmonary mechanics and patient comfort in prematurely born infants and young children receiving invasive respiratory support for severe BPD (see section 6.2 for a list of secondary study outcomes).

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

We propose a prospective, randomized cross-over trial comparing NAVA mechanical ventilation to CMV. After a 24-hour observation period to collected baseline Edi data, enrolled preterm infants and young children requiring invasive ventilation for sBPD will undergo two consecutive 5-day treatment periods, one while receiving CMV and the other while receiving NAVA (Figure 1). The treatment order will be determined by randomization. For each study site, the ventilator used for the observation phase and CMV phase of the study will be the standard flow triggered ventilator platform primarily used at each institution for routine clinical care. At CHOP, this is the Dräger V500 ventilator and at Hasboro, this is the Servo U ventilator. Edi will be continuously monitored, recorded, and displayed for all phases of this trial by the servo I or U ventilators, as it has the capability to monitor, record, and display these data while in standby mode.

3.1.1 Screening Phase

Potential subjects will be screened using daily census logs and the protocol inclusion and exclusion criteria. Male and female children born ≤32 weeks' gestation, who are ≥36 weeks PMA and < 2 years of age at enrollment, and expected to continue receiving invasive mechanical ventilation for at least 11 days after enrollment will be eligible for the study.

3.1.2 Study Observation Phase

Prior to beginning the initial treatment phase, all subjects will undergo a 24-hour period of observation with an Edi catheter in place while receiving CMV as ordered by the primary medical team. This period will be used to establish baseline Edi (Edi peak and Edi min), positive inspiratory pressure (PIP), and transcutaneous pCO_2 levels that will be employed in the study treatment phase.

At the end of the 11-day treatment phase, a second observation phase will begin and will be limited to medical record review. This phase will continue until the child is discharged in order to ascertain age and respiratory support needs at discharge.

3.1.3 Study Treatment Phase (start of the study intervention)

Computer generated randomization by will be performed by the study team to determine the initial ventilator mode. The randomly assigned mode of ventilation will be initiated in accordance with accepted standardized ventilation practices for conventional mechanical ventilation by the BPD consult teams at each center. These guidelines include a tidal volume of $\geq$ 8 ml/kg and an inspiratory time sufficient to allow full inspiratory cycle as assessed by flow time scalars on the ventilator. Data will be collected to fulfill the primary and secondary objectives. After 5 days the subject will be switched to the second ventilator mode. During each phase, the ventilator will be managed by the clinical team, but with close consultation from the study team and application of study guidelines for patient management.

3.2 Allocation to Treatment Groups

The initial mode of ventilation will be randomly assigned using a computer-generated sequence. Investigators and clinicians will not be blinded to the ventilator mode as it is essential for medical management. Every subject will be placed in both ventilator modes during the study to serve as their own controls.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The duration of the interventional phase of the study will be up to 11 days per subject, with 1 day in observation, 5 days in the initial ventilator mode, and 5 days in the second ventilator mode. All subjects will be followed until discharge for safety and assessment of the postmenstrual age and respiratory support administered at discharge.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted in two intensive care units at CHOP (NI/ICU and PICU) and the PICU at Hasbro Children's Hospital.

Recruitment will stop when 20 subjects successfully complete the trial. It is expected that approximately 25 subjects will be enrolled to produce 20 evaluable subjects.

3.4 Study Population

3.4.1 Inclusion Criteria

1) Gestational ages (GA) ≤ 32 weeks
2) Current age between 36 weeks postmenstrual age (PMA) and 2 years corrected age
3) Severe BPD (as per NIH consensus definition) diagnosed at 36 weeks postmenstrual age
4) Receiving invasive mechanical ventilation for ongoing lung disease
5) Not expected to be ready for extubation within 11 days following enrollment
6) Parental consent

3.4.2 Exclusion Criteria

1) Severe congenital anomalies
2) Known diaphragmatic defect
3) Current treatment with high frequency mechanical ventilation
4) DNR Status or Futility of Care
5) >10% leak around the artificial airway,
6) Treatment with neuromuscular blockade within 72 hours prior to enrollment
7) Acute respiratory instability defined as a ventilator rate increase > 15 bpm, PEEP increase > 2 cm/H2O, sustained FiO2 increase > 20%, and/or prescribed increase in tidal volume > 2 mL/kg within 24 hours prior to enrollment will be excluded.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening and Commencement of Study

The following evaluation will be done prior to the study:

- Informed Consent
- Medical Record Review

4.2 Unblinded Ventilator Mode Crossover Phase

Observation phase and Ventilation Mode crossover phases will have the same study procedures performed on a daily basis or less frequently as indicated.

- Placement of NAVA catheter. Catheter will be placed prior to the baseline monitoring phase and will be replaced before going into the 2nd ventilator mode on day 7 of the study.
- Placement of transcutaneous CO_2 monitor (Tcom) (if not already in use) will occur prior to the monitoring phase and remain throughout the 11 days of data collection.
- Salivary cortisol samples will be collected three times per day using a swab placed in the patient's mouth to collect pooled saliva. Samples will be collected at the same time each day and independently analyzed for cortisol values. The 3 cortisol values will be averaged for the 24 hour time frame.
- Asynchrony index will be calculated as the number of asynchrony events divided by the sum of the ventilator cycles and ineffective efforts for 1 minute. This will be determined two ways: first by physical assessment by the respiratory therapist with their patient/ventilator assessments every four hours and second by assessment of time delay or complete miss of neural trigger compared to ventilator trigger from ventilator waveforms.
- Download of data from the ventilators and clinical monitoring equipment as well as extraction of information from the electronic medical record will be done for data normally documented as part of routine clinical care.

4.3 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator or attending physician to protect the subject for reasons of safety or for administrative reasons. If the withdrawal occurs during the NAVA mode phase of the trial, each site will return the subject to a ventilator platform that is routinely used at their site, selected at the discretion of the treating physician. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF. Specific subject and study stopping rules are outlines in section 5.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

- Date of birth
- Gender
- Race/Ethnicity
- Current Dosing Weight
- Gestational age
- Corrected gestational age at entry into study
- Corrected gestational age at discharge
- Birth weight

- Current medications
- SBS and WAT-1 Score
- Respiratory support required at discharge

5.1.2 Physical Examination

Cardiorespiratory assessment including respiratory rate, auscultation, symmetry, retractions, nasal flaring, and asynchrony index.

5.1.3 Vital Signs

Vital signs for the study will be recorded from the electronic medical record and continuous multiparameter clinical monitors. Any vital signs seen outside the ranges considered clinically normal for each subject will be reported to the medical team as standard practice. All bedside care team members will be aware that the subject is enrolled in the study. BP will be monitored using the standard automated device and cuff that is being used currently. HR, Pulse oximetry, Tcom will be monitored continuously as is the standard of care for ventilated children in the N/IICU and PICU.

5.1.4 Laboratory Evaluations

- Salivary cortisol samples will be collected three times per day using a swab placed in the patient's mouth to collect pooled saliva. Samples will be collected at the same time each day and independently analyzed for cortisol values. The 3 cortisol values will be averaged for the 24 hour time frame. The samples will be labeled with study ID#, date and time of collection and stored at -20C prior to being shipped for analysis.
- Samples will be shipped on dry ice to Salimetrics SalivaLab, Attn: Kelly Henning 5962 La Place Court, Suite 275 Carlsbad, CA 92008.
- Salivary Cortisol testing: Samples will be thawed to room temperature, vortexed, and then centrifuged for 15 minutes at approximately 3,000 RPM (1,500 x g) immediately before performing the assay. Samples will be tested for salivary cortisol using a high sensitivity enzyme immunoassay (Cat. No. 1-3002). Sample test volume is 25 µl of saliva per determination. The assay has a lower limit of sensitivity of 0.007 µg/dL, a standard curve range from 0.012-3.0 µg/dL, and an average intra-assay coefficient of variation of 4.60%, and an average inter-assay coefficient of variation 6.00%, which meets the manufacturers' criteria for accuracy and repeatability in Salivary Bioscience, and exceeds the applicable NIH guidelines for Enhancing Reproducibility through Rigor and Transparency. 10% of the samples will be run in duplicate to report an intra-assay variability.
- Blood gas values order by the medical team for clinical care will be documented and trended.

5.1.5 Ventilatory Parameters

The following parameters will be collected and trended from the ventilator:

- FiO_2
- RR

- Vt
- MAP
- PIP
- PEEP
- Dynamic Lung Compliance (Crs)
- Dynamic Lung Resistance (Rrs)
- NAVA level
- Edi peak and min - measured from the Edi Catheter that will remain in place during the 11 days of data collection
- Pressure waveform data

5.2 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations, and laboratory data by the medical and study team as well as the independent safety monitoring committee.

Clinicians responsible for the care of study subjects receiving the NAVA mode of ventilation will be trained up to the current standard for their role, as is done for clinicians using clinically deployed ventilators (as listed in section 8.4.2). Guidelines for startup and continued management, including troubleshooting techniques, of NAVA mode will be available for the medical teams and a study investigator will round with the clinical team daily to provide expertise on the device/mode as well as be on call for assistance 24/7. Individual subjects will be withdrawn from the study for safety if an absolute increase in FiO_2 by 20% or if the pCO_2/TcO_2 increase by 25 points or greater than 90 mm Hg, which ever is achieved first, for more than 2 hours from baseline while on NAVA mode, The NAVA arm of the study will be discontinued and the patient will be transitioned to previous CMV settings. Study investigators will be available 24 hours day when a patient is on the trial.

The overall safety of the study will be assessed with interim safety analysis after the completion of every 5 patients (3 times total) and upon any serious safety events occurring.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Outcome

The mean daily oxygen saturation index ([mean airway pressure x FiO2]/SpO2) compared between NAVA and conventional mechanical ventilation will be the primary study outcome. Oxygen saturation index is a reliable surrogate measure for oxygenation index in children with moderate to severe lung disease that is used clinically and in research when arterial blood gas PaO_2 levels are not routinely available.

6.2 Secondary Outcome

The following secondary study outcomes will be compared between NAVA and conventional mechanical ventilation treatment periods. All outcome measures will be taken

from nursing and respiratory therapy charting in the EPIC or downloaded directly from the machines.

Measures of cardiorespiratory mechanics and stability:

(1) Measures of respiratory mechanics: hourly mean PIP, MAP, tidal volume, respiratory rate, FiO_2, Edi (peak and min), and NAVA level. The NAVA catheter will be in place for the entire study (24 hour baseline and both crossover groups) for a consistent Edi measurement for both treatment arms and all over measures are comparable across machines and modes of ventilation.

(2) The daily number of intermittent ($SpO_2 < 80\%$ for ≥ 10 seconds and less than 3 minutes) and prolonged ($SpO_2 < 80\%$ for ≥ 60 seconds) hypoxemic events recorded by continuous pulse oximetry.

(3) Median hourly transcutaneous pCO_2 levels

(4) Median daily Q4-6 hour OSI

(5) Dynamic lung compliance.

Patient Comfort and sedation exposure:

(1) Median daily State Behavioral Scale (SBS) and Withdrawal Assessment Tool (WAT-1) scores. Both scoring systems are validated measures of subject comfort and sedation requirements used in the CHOP intensive care units.

(2) Daily frequency and total daily dose (mg/kg) of sedation medications.

(3) Mean daily asynchrony index calculated as the number of asynchrony events divided by the sum of the ventilator cycles and ineffective efforts.

(4) Salivary cortisol will be collected three times per day and averaged by the respiratory therapist. The daily average will be assessed and compared as a marker for patient stress on the different ventilator modes.

Long Term Outcomes

(1) Postmenstrual age at discharge

(2) Respiratory support required at discharge

6.3 Statistical Methods

6.3.1 Analysis Plan

Subject demographic and clinical characteristics will be summarized with standard descriptive statistics. Summarized values for the primary and secondary outcomes will be compared between the two treatment arms using paired statistical tests (Wilcoxon signed rank tests, paired t-tests) as appropriate based on the data distribution. Crossover treatment trials traditionally have a washout phase with no treatment in order to determine if all outcome measures are reflective of the current treatment and not remnants of the prior treatment. Ventilation studies are not able to have a washout phase, as it is not possible to stop providing ventilator support for a set timeframe. In addition, the timeframe needed for

a washout is unknown for change in ventilation modes. For the primary analysis, all data will be included in the analysis. As a secondary analysis we will selectively exclude the first 4, 8, and 12 hours of data to determine what washout phase may make a difference in data analysis. This timeframe will be considered a washout out phase to ensure all data collected for each mode of ventilation is related to this mode and not residual effect of the prior mode. Linear mixed effects models will be used to explore longitudinal change in the study outcomes (as continuous measures) as a function of the treatment arm. These models are well suited for repeated measurements in longitudinal studies and are capable of handling unbalanced data if present (e.g. due to drop-out). Random effects terms for both the intercept and slope will be evaluated to account for potential subject specific deviation from the cohort's overall average baseline (intercept) and change over time (slope). Model fit will be assessed using the Akaike Information Criterion.

6.4 Sample Size and Power

We will enroll up to a total of 25 subjects to generate 20 subjects will have adequate evaluable data, during a proposed 24 month study period. The **Table** shows the number of patients required, with 80% power and α=0.05, to detect a range of within subject differences in mean oxygen saturation index (at various within subject standard deviation [SD] levels) between the two treatment periods. As shown, the proposed sample size of 20 subjects will provide sufficient power to detect a range of clinically meaningful differences in oxygen saturation indices with statistical significance.

Table. Minimal detectable difference in mean oxygen saturation index

	Detectable difference			
SD	1	1.5	2	3
0.25	**4**	**3**	**3**	**3**
0.5	**7**	**5**	**4**	**3**
1	**18**	**10**	**7**	**5**
1.5	38	**18**	**11**	**7**
2	65	30	**18**	**10**
3	144	65	38	**18**

6.5 Interim Analysis

Interim analysis for safety will be performed after every 5 subjects are completed to determine the safety and validity of the ventilator management guidelines by the safety monitoring committees at each site.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.2 Adverse Event Reporting

Study procedures that are greater than minimal risk are the use of the servo I ventilator and the NAVA mode at CHOP. While the servo ventilator is approved for clinical care at CHOP, the NAVA mode is not widely used and may be unfamiliar to some of the medical staff. Section 5.2 and 8.4.2 more explicitly discuss the risks and mitigation of these risks. Targeted adverse event monitoring will occur from study start to 72 hours after the intervention phase has concluded.

Although no SAEs are expected, if any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8 STUDY ADMINISTRATION

8.1 Treatment Assignment Methods

8.1.1 Randomization

Computer generated randomization will determine the initial mode of mechanical ventilation. There will be 1 randomization scheme for the entire study (to be used by both sites) to ensure equal allocation of each ventilation mode as the starting mode. Investigators and clinicians will not be blinded to the mode of ventilation as this information is essential for patient management and is easily discovered. However, blinded data analysis will be performed.

8.2 Data Collection and Management

The information collected will be entered into the password protected computerized database REDCap and house on the CHOP server. Confidentiality will be ensured from abstraction through analysis by utilizing the HIPPA functions in REDCap. To ensure security, a copy of the data collected will be saved in a Research share drive on the CHOP server with only study team members having access. Data will be downloaded from the ventilators and monitoring devices and saved to the research share drive by study ID number. All Identified data will be maintained and destroyed in compliance with CHOP Policy A-3-9.

Saliva specimens transferred for analysis of cortisol levels will be done under material transfer and data use agreements. Saliva specimens will only be marked with study ID number and day of sample. No identifiable information will be transferred with the specimens.

8.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset.

8.4 Regulatory and Ethical Considerations

8.4.1 Data and Safety Monitoring Plan

Clinical adverse events will be monitored throughout the study period. There will be monthly and as needed ad-hoc meetings among the study investigators to discuss and monitor data and safety. All data will be kept confidential in accordance with HIPPA and CHOP policies. An independent safety monitoring committee (DSMC) will be formed to review any adverse events that occur and determine if they are related to the study or the natural course of this critical illness. The DSMC will have a representative make up of 3 physicians represented by each specialty involved with these patients (neonatologist, pediatric intensivist, and pediatric pulmonologist). The DSMC will meet as needed to discuss patient specific concerns as well review data at the planned interim analysis after every 5 patients.

CHOP PI will monitor and review the study progress, subject safety, and the accuracy and security of the emerging data at CHOP, and will report any adverse events in accordance with the FDA regulations and IRB policies.

8.4.2 Risk Assessment

The risks in this study associated with passing a second tube into the esophagus (the NAVA catheter) for research purposes is minimal, with a low probability of associated harm. The risk of inserting this tube for research purposes is no greater than inserting a feeding tube or temperature catheter. The insertion of these devices for clinical purposes is performed by nursing staff and is done frequently in the NI/ICU and PICU for almost every patient. The risk of esophageal perforation from the catheter used for Edi measurements is the same as that for routine insertion of feeding tubes done at the bedside and is extremely rare. The treatment for this complication consists of withdrawal of the tube and a course of antibiotics as the perforation heals naturally.

The proper positioning of the NAVA catheter will be confirmed with a positioning identification software on the Servo I ventilator. There will be continuous monitoring of vital signs throughout the study in accordance with unit standards. A respiratory therapist specially trained in NAVA mode will care for the study patient 24 hours a day and a study physician will be available for consultation throughout the study to ensure safety and comfort of the patient and consultation for any ventilator adjustments. NAVA is an FDA approved mode of ventilation for subjects currently available and used commonly in children with other disease processes routinely at other hospitals. This mode is commonly used at other hospitals for sBPD and other diseases; however, the efficacy of its use compared to conventional ventilation has not been adequately studied.

To measure the transcutaneous CO_2, a probe is placed on the skin in a fleshy area of the body and it heats the skin. Often times a temporary red mark is left when the probe is removed and there is a small chance of burning of the skin if the probe is left in place for too long. For this reason, nursing and respiratory therapy staff routinely rotate the position of the probe.

For CHOP site only (as Hasboro site already used Servo U ventilators and the NAVA mode): There is a risk to the introduction of a less familiar mode of ventilation that is not widely used at CHOP. Lack of knowledge and expertise by the clinical team on the use of this mode can lead to decompensation in the respiratory status of the patient (i.e. reduction in SpO_2, increase in CO_2, increased heart rate, increase in work of breathing, and cardio respiratory arrest, and death). The risk of use of this mode is the same as the use of any of the modes of ventilation that are not widely used but on the multitude of ventilation devices available at CHOP. Each ventilator has approximately 12 modes of ventilation that can be used with only about 4 or 5 that are widely used. As an example, The Drager V500 ventilator, the primary ventilator platform at CHOP, has 14 modes and only 6 of them are commonly used in all ICU's. To assist in minimizing this risk to subjects, all clinical staff members that will care for these subjects will be trained on the use of the Servo I ventilator in accordance with the standards of ventilator training for their role. The current standard for each roll is:

- Nursing – in-servicing and hands on training limited to modes, reading of settings and monitoring parameters, adjustment of FiO_2, and alarm silence
- Physicians/FLC's – in-servicing on modes, reading of setting and monitoring parameters, and ordering
- Respiratory Therapists – in-servicing on modes, ventilator functionality, patient set-up, setting of parameters and alarms, reading of monitoring parameters, troubleshooting, and cleaning completed with competency check off

Only trained and certified respiratory therapists will be assigned to care for patient on study 24/7. Guidelines for escalation and de-escalation of care will be available at the bedside of all subjects. A study investigator will provide a physical assessment of the subject and round daily with the clinical team to provide expertise on the mode of ventilation as well as be available 24/7 for questions. Additionally, when the subject is in the NAVA mode arm of the study, the Drager ventilator will remain in the patient room and be ready for immediate use if needed. The medical team will always have the option for safety or preference reasons to transition the subjects back to the standard Draeger ventilator used for routine clinical care. An additional safety feature of the NAVA mode is the mandated input of back-up ventilation settings as described in section 1.2 of the protocol.

Collection of salivary cortisol presents no more than minimal risk as it is less invasive than the mouth care these children receive on a daily basis

8.4.3 Potential Benefits of Trial Participation

There are no direct benefits to the subject for participating in the study. There are benefits for future patients with BPD to assist with determining the most effective ventilatory strategies for children with sBPD.

8.4.4 Risk-Benefit Assessment

The risk of participation in the study is a slight increase over minimal risk. The participants will be closely monitored for any potential adverse effects of the different ventilation mode by clinicians with experience using the servo ventilator and NAVA at other institutions. The children will not receive any direct benefit, however this study will assist us in gaining a

better understanding of what role, if any, NAVA can play in the treatment of children with severe BPD in the future.

8.5 Recruitment Strategy

All subjects will be recruited from the CHOP N/IICU and PICU and Hasboro Children's Hospital PICU. Unit census documents will be reviewed weekly to identify possible subjects. For subjects likely to be eligible, attending and respiratory therapist records will be further reviewed to assess for eligibility (only the number of subjects screened for eligibility and no specific subject level data will be recorded prior to informed consent). The Investigator or a designated study team member will confirm eligibility with the potential subject's attending physician and request permission to approach the parent(s) or guardian(s). If appropriate, the parent(s) or guardian(s) of eligible subjects will be approached and details of the study will be discussed. If interested, the parent(s) or guardian(s) will be invited to participate. Study personnel will then review the information in the consent form, answer any questions, and obtain informed consent. Only 2 participants will be allowed in the trial at the same time due to the number of Servo I ventilators available or use.

8.6 Informed Consent/Assent and HIPAA Authorization

After determining eligibility and obtaining permission from the attending physician, a study team member will contact a potential participant's parent(s) or guardian(s) to obtain informed consent and HIPAA authorization. The consent discussion will be conducted in the NICU in a private setting (e.g. at the bedside, in a private meeting room) where possible, or via telephone or video conference. A study team member will describe the goals and procedures involved in the study. Parent(s) or guardian(s) will be provided the opportunity to ask questions about the study and to discuss the study with their family, friends, and/or other medical professionals. Before any study procedures take place, the consent form must be signed by a legally acceptable surrogate and the investigator-designated research professional obtaining the consent. The consent form will be signed in paper copy form or electronically in REDCap. The parents will be permitted to take as much time as they need to make a decision. The investigators will be available to answer any questions or concerns about the study and to ensure that the parent/guardian signing the consent document comprehends the nature of the study, the study procedures and the risks and benefits of participation. Entry into the study will not be coerced. Study procedures will not proceed without documentation of consent. Also, HIPAA Authorization will be included as a combined consent-authorization document. The Part 11 compliant version of REDCAP eConsent will be used for consenting.

Parents/guardians with limited English proficiency will utilize a consent process that includes verbal consent conversation with a translator of their primary language and the use of one of the approved short forms. LEP subjects with a short form available in their preferred language may provide consent in person. The study PI is familiar with the IRB stipulations related to this process for obtaining consent. The ORC job aid process for consenting will be followed.

8.6.1 Waiver of Assent

Assent is to be waived under 45 CFR 46.408, as the capability of all of the children is so limited that they cannot reasonably be consulted.

9 PUBLICATION

The study investigators plan to publish the findings of this study in a peer-reviewed journal. Any results shared at conferences or in papers will not contain identifiable patient information.

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