TITLE:

Effect of Synchronized vs. Continuous High Flow Nasal Cannula using Neurally Adjusted Ventilatory Assist on Work of Breathing in Infants with Bronchopulmonary Dysplasia

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List of Frequently Used Abbreviations:

- AE- Adverse Event
- ACH- Arkansas Children's Hospital
- ACRI – Arkansas Children's Research Institute
- BPD- Bronchopulmonary Dysplasia
- Edi- Electrical activity of the diaphragm
- HFNC- High flow nasal cannula
- FiO_2- Fraction of inspired oxygen
- GCP- Good clinical practice
- ICH- International Conference on Harmonization
- IRB- Institutional Board Review
- LPM- liters per minute
- NAVA- Neurally adjusted ventilatory assist
- nCPAP- Nasal continuous positive airway pressure
- NICU- Neonatal Intensive Care Unit
- NIPPV- Nasal intermittent positive pressure ventilation
- NIV- Non-invasive ventilation
- PEEP- Positive end expiratory pressure
- RAM- RAM Cannula
- RIP- Respiratory inductance plethysmography
- SAE- Serious adverse event
- TCOM- Transcutaneous oximetry measurement
- UADE- Unanticipated adverse event
- UAMS- University of Arkansas for Medical Sciences
- WOB- Work of breathing

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Background and Rationale:

Affecting between 10,000 and 15,000 infants in the United States each year, bronchopulmonary dysplasia (BPD) is a heterogeneous lung disease seen in formerly premature infants who continue to require ongoing respiratory support at 28 days of life or 36 weeks post menstrual age.[1,2] BPD has been associated with an increased risk for life-long sequelae including asthma, chronic obstructive pulmonary disease, and cerebral palsy, making prevention and treatment of this disease of utmost importance.[3-5] Invasive mechanical ventilation has been identified as a major contributor to the development of BPD in premature neonates, leading to the emergence and more frequent use of various modes of non-invasive ventilation (NIV) for both treatment and prevention of BPD [6,7] Current forms of NIV include: nasal continuous positive airway pressure (nCPAP), nasal intermittent positive pressure ventilation (NIPPV), non-invasive neurally adjusted ventilatory assist (NIV NAVA), and high flow nasal cannula (HFNC). Currently, the gold standard of NIV is nCPAP, which delivers a continuous positive distending pressure through nasal prongs and helps to maintain functional residual capacity within the lung.[8] In nCPAP, airflow is delivered to maintain a set pressure. This differs from HFNC in which heated and humidified air is delivered at a set flow rate without maintaining a set pressure.[9] HFNC supports infants by washing carbon dioxide out of the nasopharyngeal dead space, providing positive distending pressure, and reducing upper airway resistance.[10,11]

HFNC is a form of NIV that is being used more frequently in infants with BPD. Reasons for this increasing use may include a lower incidence of nasal septal breakdown, reduced infant pain scores, improved parent-child bonding, and decreased abdominal distension.[12-14] Osman et al performed an observational cross-over study and found lower premature infant pain profile scores as well as lower salivary cortisol levels in infants receiving HFNC vs. nCPAP.[12] In another study by Klingenberg et al parents reported higher satisfaction with the treatment of their child when he or she was on HFNC rather than nCPAP. Contributing factors for this were increased ability of parents to interact with their child and the perception that their child was more comfortable on HFNC.[13] NCPAP requires larger, tighter fitting nasal interfaces to ensure adequate pressure delivery, whereas HFNC relies on a high flow of gas and the presence of a leak between the patient's nares and the interface to appropriately wash out the nasopharyngeal dead space.[15] This leads to the decreased incidence of nasal septal breakdown seen with the use of HFNC.

HFNC has been investigated and found in some studies to have similar efficacy to that of nCPAP in clinically stable preterm infants.[11,16-18] A meta-analysis published in 2015 by Kotecha et al showed similar efficacy of HFNC when compared with other

forms of NIV.[11] Boumecid et al found no difference between tidal volume generation and thoraco-abdominal asynchrony between nCPAP and HFNC.[16] Saslow et al also demonstrated similar efficacy between nCPAP and HFNC when comparing work of breathing (WOB) using respiratory inductance plethysmography (RIP) to estimate tidal volume.[17] Another study evaluating WOB in twenty preterm neonates found statistically significant but clinically similar results when treated with HFNC vs. nCPAP.[18]

Infants with BPD often have increased WOB which leads to prolonged ventilatory support, increased caloric needs, and prolonged hospitalization. WOB refers to the amount of energy expended to overcome the elastic and resistive forces of the respiratory system during ventilation.[19] Clinical signs of increased WOB include nasal flaring, increased use of accessory muscles (retractions), and paradoxical movements of the rib cage and abdominal wall (thoracoabdominal asynchrony). The measurement of actual WOB is difficult, invasive, and not easily achieved in neonates receiving NIV, however it can be estimated. Swing electrical activity of the diaphragm (Edi) has been used to estimate WOB in neonates and is the difference between the resting tonic activity of the diaphragm (Edi min) and the peak activity of the diaphragm (Edi max) measured by the Edi catheter.[20] Another tool to estimate WOB uses RIP bands to measure the timing of chest and abdominal wall movements. Based on these movements, a phase angle can be calculated, which is reflective of the degree of thoracoabdominal asynchrony. The greater the thoracoabdominal asynchrony, the greater the estimated WOB.[21] A third method estimates WOB using the pressure-time product, which measures the work required for the subject to trigger a breath and is used when no leak is present.[22]

Synchronization of non-invasive respiratory support provides more effective ventilation and reduces respiratory effort but is difficult to achieve with NIV.[23] Synchronization can, however, be achieved using NAVA, in which Edi is measured using an electrode-embedded oro/nasogastric tube called an Edi catheter.[24] The Edi signal is then used to synchronize the rate, timing, and intensity of ventilatory support to the patient's own respiratory effort.[25] NAVA has been shown to have some advantages over unsynchronized respiratory support such as improved patient comfort and reduced WOB.[26,27] Using pressure-time product, Jones et al showed that estimated WOB was reduced in neonatal piglets with lung disease when breaths were given in synchrony with the piglet's respiratory effort using NIV NAVA as opposed to asynchronous delivery of breaths via NIPPV.[27] A study done by Lee et al using swing Edi as an estimate for work of breathing found that NIV NAVA decreased WOB in fourteen preterm neonates when compared to unsynchronized NIV-pressure support.[20] Synchronized HFNC is a novel method of NIV, which has not yet been studied in neonates with BPD. NIV NAVA,

however, is a commonly used mode of support and can potentially be used in a fashion very similar to HFNC to achieve synchronized HFNC. The effect of this novel use of NAVA on WOB has not previously been investigated in infants with BPD.

Innovation:

The proposed study will compare WOB between continuous HFNC and HFNC synchronized using NAVA. To our knowledge, synchronization of HFNC has not been attempted. This study will investigate the feasibility of synchronized HFNC as well as its possible efficacy in decreasing WOB compared to continuous delivery of high flow. This study has special relevance to the care of infants with BPD who continue to require respiratory support. Though decreasing WOB in this population may lead to earlier weaning from respiratory support and earlier discharge from the hospital, the direct and immediate relevance of this trial is the potential for development of technology that can provide synchronized HFNC, should it be shown to decrease WOB.

Hypothesis:

WOB estimated using swing Edi will be less with the use of synchronized HFNC using NAVA compared to continuous HFNC in infants with BPD being treated with NIV.

Specific Aims:

1. The primary objective will be to investigate whether WOB estimated using swing Edi is improved with synchronized HFNC using NAVA over continuous HFNC.

2. Secondary objectives will be to evaluate the effect of NAVA-synchronized vs. continuous HFNC on thoracoabdominal asynchrony (using RIP bands to calculate phase angle), uncalibrated tidal volume (using RIP bands), FiO2 requirement, neural respiratory rate, oxygen saturation, and transcutaneous O_2 and CO_2 levels.

Investigational Device(s)

- **Pneumotachograph** (Hans-Rudolph, Shawnee, KS, USA) will be inserted into the inspiratory limb of the ventilator circuit and flows will be recorded on the data acquisition system.
- **RAM cannula** (RAM cannula, Neotech, Valencia, CA, USA) is intended to be used for preterm and term neonates, infants, and pediatric patients who require supplemental oxygen, respiratory support, or assistance in breathing in an ambulatory, hospital, or institutional environment. In this study it will be used to provide both continuous and NAVA-synchronized HFNC.
- **Servo-u ventilators and Servo Tracker Software** (Maquet Critical Care, Solna, Sweden) is cleared (K15814). It is being used as intended and will provide monitoring of the subjects' respiratory drive, to improve synchrony between the ventilator system and patient when the electrical signal to from the brain to the diaphragm is active.
- **NAVA-Edi catheter** (Maquet Critical Care, Solna, Sweden) is cleared (K153688). It will be used to detect electrical signal from the diaphragm and will be used to calculate swing Edi (difference between the resting tonic activity of the diaphragm and the peak activity of the diaphragm) to be used as an estimate of WOB.
- **Transcutaneous monitor** (TCM4, Radiometer, Brea, CA, USA) will be used to measure CO2 and O2 levels.
- **RIP bands** (SleepSense, MFI Medical San Diego, CA) are cleared (K173868) and will be placed around the chest and abdomen to measure breathing movements and relative tidal volume.
- **Pulse oximeter probe** (MasimoSET, Irvine, CA, USA) is cleared (K061204). It will be used to measure oxygen saturations and heart rate.
- **MP100 Biopac data acquisition** (Biopac Systems Inc., Goleta, CA, USA) will be used to collect data from the monitoring devices.

Study Population:

Up to thirty subjects at Arkansas Children's Hospital (ACH) will be consented to retain twenty-four participants in the study. Inclusion criteria will include:

- Chronological age greater than 28 days
- Gestational age at birth less than 33 weeks as documented in the subjects' initial history and physical

- A diagnosis of BPD, defined for this study as having received supplemental oxygen for greater than or equal to 28 days from birth
- Currently receiving NIV in the form of nCPAP, NIV NAVA, NIPPV, or HFNC

Exclusion criteria will include:

- Post-menstrual age (gestational age plus chronological age) of greater than 50 weeks 0 days
- Oxygen requirement greater than 40% at the time of enrollment
- Transcutaneous CO2 measurements > 80
- Currently receiving invasive ventilation
- Major congenital anomalies of the heart and/or lungs
- Bilateral phrenic nerve palsy
- Major gastrointestinal malformations, including gastroschisis, omphalocele, and congenital diaphragmatic hernia
- Currently receiving treatment for pneumonia or suspected/confirmed sepsis

Study Design/Procedures:

Parental consent will be obtained prior to study. Synchronized HFNC is not an option on current HFNC devices, which provide only a constant flow of gas. NAVA devices only provide pressure measurements during NAVA in intubated patients, or NAVA using non-invasive nasal prongs (NIV NAVA). Nonetheless, many neonatal intensive care units (NICUs), including the ACH NICU, use nasal cannulas designed for low or high flow, but not approved for nasal CPAP, to attempt provision of nasal CPAP and NIV NAVA. For our study, we will use the cannula currently in use at ACH (RAM cannula, Neotech, Valencia, CA, USA) and as currently FDA approved, and set the NAVA ventilator so that it responds similarly to a HFNC. The RAM cannula will be used to provide both continuous and NAVA-synchronized HFNC.

The provision of continuous HFNC with displayed flow rates and Edi signal will be done using the Servo ventilator and the recently developed HFNC software for this ventilator. To more accurately record flow rates, a pneumotachograph (unheated, calibrated, 0-10 liters per minute (LPM), Hans-Rudolph, Shawnee, KS, USA) will be inserted into the inspiratory limb of the ventilator circuit and flows will be recorded on the data acquisition system. The pneumotachograph will also be used to translate pressure settings into flow settings for the synchronized HFNC portion of the study.

During NAVA-synchronized HFNC, the NIV NAVA mode will be set in such a way that synchronized HFNC will be provided. A minimal end-expiratory flow of 2 LPM will be provided using the positive end expiratory pressure (PEEP) setting in the NIV NAVA

mode on the ventilator. The PEEP setting corresponding to 2 LPM via the pneumotachograph will be used. In order to deliver the desired peak flow rate with each neurally-triggered breath, a NAVA level of 15 $cmH_2O/\mu V$ will be set, then the maximum pressure setting that corresponds to the desired flow rate using the pneumotachograph will be used for the study. The subject will thus be provided with "synchronized HFNC".

This contrasts with the constant-flow trials when subjects will receive a constant and non-synchronized flow using the HFNC software on the ventilator.

WOB for this study will be calculated by a computerized program utilizing a process which has been used in a previously published study.[28] Edi signal analysis will also be performed by a specifically developed computer program.

Prior to the study period each subject will have the following monitoring equipment placed (if not already present): Edi catheter, transcutaneous monitor (TCM4, Radiometer, Brea, CA, USA) to measure CO_2 and O_2 levels, pulse oximeter probe (MasimoSET, Irvine, CA, USA) to measure oxygen saturations and heart rate, and RIP bands (SleepSense, MFI Medical, San Diego, CA, USA) around the chest and abdomen to measure breathing movements and relative tidal volume.

Each subject will be randomized on the day the study is to occur to begin with either NAVA-synchronized or continuous HFNC before crossing over to the other mode to serve as his/her own control. The same RAM cannula will be used in both study arms and will provide a leak of 60-80% as recommended by the product manual. The delivery of high flow during both synchronized and continuous HFNC will be given at two commonly provided levels of high flow: 6 LPM and 8 LPM, given in the same order in each mode (6 LPM then 8 LPM). Each subject will receive 15-minute trials of each mode-level combination, for a total of four trials performed in succession. During each trial, the first 10 minutes will be used for stabilization, and the last 5 minutes will be used for data collection, as has been done in previous trials.[20, 27-28] There will be approximately one to two minutes between each trial to adjust ventilator settings. Thus, the mode-level combinations of the trials will be as follows: for subjects randomized to begin with synchronized support: synchronized-6 LPM, synchronized-8 LPM, unsynchronized-6 LPM, unsynchronized-8 LPM. For subjects randomized to begin with unsynchronized support: unsynchronized-6 LPM, unsynchronized-8 LPM, synchronized-6 LPM, synchronized-8 LPM.

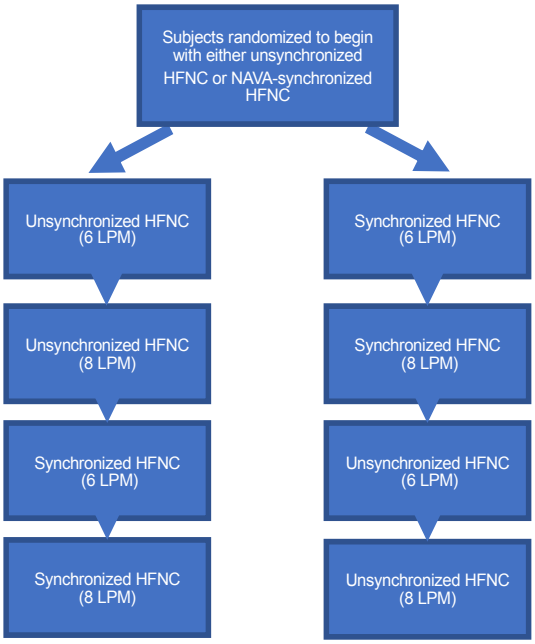

Figure 1. Flowchart depicting order of trials based on initial randomization.

The flows described in the NAVA-synchronized trials refer to the peak flow provided during inspiration. A baseline flow rate of 2 LPM will be provided expiration in these trials (using the PEEP setting corresponding to the appropriate flow rate). During the unsynchronized trials, the continuous high flow rate will be provided (as is common practice with the use of HFNC). During the NAVA-synchronized HFNC trials, the Edi trigger will be set to 0.5 microvolts, apnea time to 5 seconds, back up rate to 10 breaths per minute, and backup pressure settings will be set to provide an estimated peak flow of 6 or 8 LPM according to the designated trial (again, using the pressure setting corresponding to the appropriate flow rate).

Servo-u ventilators and Servo Tracker Software (Maquet Critical Care, Solna, Sweden) will be used in order to track Edi signal. The MP100 Biopac data acquisition (Biopac Systems Inc., Goleta, CA, USA) will be used to collect data from the monitoring devices. HFNC will be delivered using appropriately sized RAM cannula to allow for air leak around the subject's nares. Persistent (>20 seconds) bradycardia (less than 100 beats per minutes), desaturation (<85%), or hypercarbia (transcutaneous CO_2 >70) will result in cessation of the study.

Risks and Benefits:

Infants often have gagging and may have vomiting when a gastric tube, such as the NAVA catheter, is removed or replaced. Rarely, patients could have a gastric tube go into a place besides the stomach or coil in the esophagus. We should be able to detect if this occurs using the placement screen on the ventilator because the NAVA catheter has electrodes on it that detect the electrical activity of the heart and diaphragm, which can be used to determine the location. In extremely low birth weight infants, transcutaneous monitors (TCOMs) can cause skin burning. These effects are not seen in larger infants like those included in this study. There is a small risk of loss of confidentiality inherent in all research. We will do everything possible to protect the subjects' confidentiality.

There may or may not be direct medical benefit to the subjects involved in this study. The subjects will have continuous carbon dioxide and oxygen monitoring during the study and if any subject has any problems we will be able to detect and respond to this quickly. If a subject shows apparent improvement while using particular HFNC settings, we may be able to suggest to the treatment team that these settings be continued or the current settings adjusted accordingly. If a subject was already performing well on NIV, there may or may not be an improvement during the study. Subjects performing well on NIV will still undergo the trials of settings and interfaces if enrolled in this study. If using synchronized HFNC improves WOB in the subjects included in this study, then we hope the information learned from this study will benefit other infants with BPD needing respiratory support in the future.

Data Handling and Recordkeeping:

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. Each subject will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in a research office. Only the principal investigator and sub-investigators will have access to the code and information that identifies the subject in the study. Demographic and clinical information, such as gestational age, date of birth, gender, race/ethnicity, pregnancy complications, and clinical diagnoses, will be obtained from the medical record and kept on a password protected computer. All data will be de-identified after analysis is complete by destroying the code key. De-identified data will be maintained as per UAMS and ACRI policy (currently all data will be kept until the last subject is 21 years of age plus 2 years) and destroyed per institutional guidelines.

Data Analysis:

The primary hypothesis is that WOB estimated by swing Edi will be less during synchronized HFNC compared to continuous HFNC. Statistical analysis will be performed in conjunction with the Arkansas Children's Research Institute (ACRI)/ University of Arkansas for Medical Sciences (UAMS) Department of Pediatrics Biostatistics program. A randomization list of synchronized vs. continuous HFNC will be provided by the biostatistics team.

Data collected will be checked for outliers and extreme values, as well as distributional assumptions of the parametric statistical tests. Paired sample t-test will be used to compare the primary and secondary outcomes, as well as safety data, under the two NIV methods when such assumptions are met. When necessary, multivariate analysis that may be more powerful in the presence of high correlation between the outcomes will be conducted for both primary and secondary outcomes. When significant deviation from assumptions is encountered, nonparametric alternatives such as Wilcoxon signed-rank test will be used. Statistical analyses will be performed using SAS (Version 9.4, SAS Institute, Cary, NC, USA) statistical software.

Sample size and power calculation:

We plan to recruit twenty-four neonates being treated for BPD with NIV. Based on the previous study conducted by Lee et al, using swing Edi to estimate WOB with NIPPV vs NIV NAVA, a 20% reduction in the primary outcome is expected.[20] A sample size of twenty-four subjects achieves 81% power to detect a 20% change in the primary outcome. This sample size is based on a two-sided alpha of 0.05. Randomized subjects that do not complete the study will be replaced and will not be included in data analysis. Potential reasons for withdrawal from the study include:

- Serious adverse effects believed to be related to the investigational device
- Intolerable side effects of the study procedures
- Investigator believes it is in the best interest of the subject to discontinue study participation
- Parents request withdrawal from the study

Adverse Event:

An adverse event (AE) is any medical occurrence that develops or worsens in severity during the course of the study, whether or not it has a causal relationship to the study treatment. Concurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures, including abnormal laboratory values, are considered AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event (SAEs):

An adverse event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be subjects), or requires intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include

- death
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

An investigator should immediately report to the Sponsor **ANY** serious adverse event, whether or not considered device related, including those listed in the protocol or device manual, along with an assessment of whether there is a reasonable possibility that the device caused the event.

Although an event may be considered 'Serious' based on previous criteria and should be reported to ORRA immediately, not all SAEs meet Expedited Reporting criteria.

To avoid confusion, as the terms "serious" and "severe" are not synonymous, the following clarification is given: The term "severe" is often used to describe the

intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is *not* the same as "serious," which is based on subject/event *outcome* or *action* usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. *[ICH-E2A(II)(B)]*

Related:

An event is "related" if more likely than not it was caused by the research activity.

Unexpected:

An event is "unexpected" when its specificity, nature, severity or incidence is not accurately reflected in the consent form, protocol, or investigator's brochure previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

Study Period:

All Adverse Events (AE) will be recorded by the Investigator from the time the consent is signed through the end of the last use of the study device. All AEs will be recorded on the AE log. All relevant historical medical conditions that are known/diagnosed prior to the use of the study device are to be recorded as medical history.

Unanticipated Adverse Device Effects (UADEs):

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

Monitoring, Recording and Reporting of AEs:

All Adverse Events (AE) will be recorded by the Investigator from the time of consent through the end of the last use of the device. All AEs will be recorded on the AE log. Assessments may include monitoring the subjects' clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures. If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an

AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates or exacerbates at any time during the study, it will be recorded as an AE. **Pre-existing conditions should be recorded as adverse events only if the frequency, intensity, or the character of the condition worsens during the study.** The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately to the Sponsor.

AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual continuing review to the IRB. Certain AEs must be reported in an expedited fashion to allow for timelier monitoring of subject safety and care.

The reporting of these events depends on the characteristics of the event:

1. Seriousness (grading of event)
2. Relatedness to study therapy (An event is "related" if more likely than not it was caused by the research activity)
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:

1. Determine whether the adverse event is related to the investigational device. Attribution categories are as follows:
   - Unrelated
   - Unlikely
   - Possible

- Probable
- Definite

2. Determine expectedness of event. Expected events are those previously identified resulting from administration of the device. An adverse event is considered unexpected when the type or severity of the event is not listed in:

- Protocol
- Device manual
- Consent form

Note: This includes all events that occur within 30 days of the last use of the protocol treatment or device. Any event occurring more than 30 days after the last use of the device that is possibly, probably, or definitely attributable to the investigational device must be reported according to the instructions above.

Expedited Reporting of AE:

Institutional Review Board Reporting

Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other adverse events should be recorded and reported to the UAMS IRB at continuing review.

Sponsor Reporting:

The Sponsor will be promptly notified of all potential UADEs by the investigator/study staff using the FDA MedWatch 3500A.

The Sponsor will evaluate all potential UADEs and report these evaluations to FDA in accordance with 21CFR812.

All other serious adverse events not expeditiously reported to FDA will be reported to the Sponsor in the Annual Progress Report and the IRB at continuing review.

Deaths that are related to research will be reported to the Sponsor immediately upon notification of the Investigator. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21CFR812.

Deaths:

The investigator will notify the Sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator will attempt to determine, as conclusively as possible, whether or not the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related will be described in a written report.

Deaths that are related to research will be reported to the Sponsor immediately upon notification of the investigator. A death due to a terminal condition of the research subject would be considered anticipated if not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21CFR812.

Monitoring:

Clinical site monitoring will be conducted by the UAMS Office of Research Regulatory Affairs to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirements.

Monitoring specialists from the UAMS Office of Research Regulatory Affairs will conduct periodic on-site, comprehensive monitoring as determined by a protocol specific monitoring plan, which will be provided by the Monitoring Unit of ORRA.

A medical monitor has been identified and will serve as an independent, non-biased decision maker regarding protocol changes, evaluation of adverse events, and enrollment of subjects not meeting protocol requirements. The medical monitor will

monitor reports of SAEs in real time to ensure good clinical practice and to identify safety concerns quickly. He may also suggest protocol modifications to prevent the occurrence of particular AEs and may serve as a resource to the clinical investigators for advice about management of SAEs, but will not be involved in other aspects of the trial. Meetings may be held with the primary investigators and the monitor on a quarterly basis to ensure the trial is being safely and efficiently run.

Protocol Deviations and Violations:

A Protocol Deviation is any unintentional change, divergence, or departure from the study design or procedures defined in the protocol. A Protocol Violation is an event clearly occurring outside the approved research protocol that is considered serious non-compliance and often may affect the rights, safety and/or welfare of subjects.

Protocol Deviations/ Violations will be tracked and compiled in a Protocol Deviation Log. Deviations that potentially cause concern for the subject's health, safety, or rights will be reported to the Sponsor as soon as possible for guidance on reporting and any corrective actions that may be needed.

If an emergency occurs that requires a deviation from the protocol in order to protect the welfare of a subject, the PI will attempt to contact the IRB prospectively if time allows. If circumstances do not allow, the IRB will be notified as soon as possible.

If the protocol deviation does not represent a significant alteration in the approved protocol and/or does not affect the rights, safety or welfare of the subject, it will be reported to the UAMS IRB at the time of Continuing Review. If the protocol deviation/ violation represents a significant alteration in the approved protocol and/or if it affects the rights, safety or welfare of the subject, it must be reported to the Sponsor and the UAMS IRB immediately.

Ethical Considerations:

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study. The formal consent of each subject, using the IRB-approved consent form, will be obtained from the

parent(s) before that subject is submitted to any study procedure. All parents will be provided a consent form describing this study and providing sufficient information in language suitable for them to make an informed decision about participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room or by phone, and parents of potential subjects may take as much time as needed to make a decision about their participation. Phone consent will be obtained with a witness and consent will be faxed, e-mailed, or otherwise transmitted to parent(s) who will then transmit it back to the Arkansas Children's Hospital Neonatal ICU. The person conducting the consent process will then sign the form, and a signed copy of this form will be given/sent to the mother or father/LAR. Phone consent will only be obtained in the event that the parents are unable to be present in the NICU.

Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the parent and the individual obtaining the consent. A copy of the signed consent will be given to the parent, and the informed consent process will be documented in each subject's research record. No research-related activities will be performed until the signed consent form is obtained by study personnel.

Dissemination of Data:

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a subject. The study will be listed on Clinicaltrials.gov in accordance with FDA requirements.

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