# RESEARCH PROTOCOL

## A. SPECIFIC AIMS

Although acute respiratory distress syndrome is a life-threatening and frequent problem experienced by thousands of children each year, little evidence supports best ventilation practices during their critical illness.[1] For over 25 years, pediatric critical care clinicians have debated the risk-benefit ratio of supine versus prone positioning and conventional mechanical ventilation (CMV) versus high-frequency oscillatory ventilation (HFOV).[2-4] This debate has been recently fueled by the completion of the Pediatric Acute Lung Injury Consensus Conference Group (PALICC) guidelines[1] noting the lack of high quality evidence and the publication of three definitive adult-based studies with acute respiratory distress syndrome (ARDS); specifically, one positive prone positioning trial and two adult ARDS HFOV clinical trials -- one neutral and one likely harmful.[5-7] Without pediatric-specific data, the debate of how best to care for children with severe Pediatric Acute Respiratory Distress Syndrome (PARDS) will continue and prevent progress in the field.

Unique maturational differences prevent data generated in adults to be directly applied to children. There are important differences in lung growth and development, immune response and surfactant homeostasis.[3,8] The scientific premise supporting the potential benefits of prone positioning and HFOV are well-grounded. Prone positioning augments ventilation (V) and perfusion (Q) matching along the gravitational axis. Improved V/Q matching reduces the need for potentially toxic levels of delivered oxygen and mean airway pressure.[9,10] HFOV is a mode of ventilation that takes advantage of hysteresis, maintaining the lung open throughout the respiratory cycle, and aims to prevent the injurious effects of volutrauma, atelectrauma and potentially biotrauma that has been linked to multiple organ dysfunction syndrome (MODS).[11,12] It is unknown whether prone positioning and/or HFOV provides a benefit in children with severe PARDS as compared to supine positioning and/or a CMV strategy that delivers small tidal volumes.[13]

The purpose of ***PROSpect*** (**PR**one and **OS**cillation **PE**diatric **C**linical **T**rial) is to provide evidence to support best ventilation practices in critically ill children with *severe* PARDS defined per PALICC guidelines.[1,13,14] We propose a two-by-two factorial, response-adaptive, randomized controlled clinical trial of supine/prone positioning and CMV/HFOV. Approximately 50 pediatric intensive care units (PICUs), about 2/3 U.S. and 1/3 international, with at least 5 years of experience with prone positioning and HFOV that can provide back-up extracorporeal membrane oxygenation (ECMO) support, will participate. Eligible patients with severe PARDS will be randomized within 48 hours of meeting eligibility criteria and within 4 days of endotracheal intubation to one of four groups: supine/CMV, prone/CMV, supine/HFOV or prone/HFOV. Subjects who fail their assigned positional and/or ventilation therapy for either persistent hypoxia or hypercapnia may receive a reciprocal therapy while being considered for ECMO cannulation. Our primary outcome is ventilator-free days (VFD) through day 28, where non-survivors receive zero VFD. We have powered this study to detect a clinically meaningful 2-day improvement in VFD.[15] Up to 1,000 patients will be randomized, stratified by age group (<1; 1-7; 8-17 years) and direct/indirect lung injury. Adaptive randomization will begin after 400 patients are randomized. After the 400$^{th}$ patient has been randomized and every 100 patients thereafter, new allocation probabilities will be computed based on ongoing intention-to-treat trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. *PROSpect* may close enrollment early for efficacy or futility based on pre-specified stopping rules. Subjects will be monitored for safety and followed until hospital discharge or hospital Day 90, whichever occurs first, then evaluated at fixed intervals after PICU

discharge for functional status and health-related quality of life (HRQL). Data will be analyzed per intention-to-treat for the primary analyses and per-protocol received.

**Specific Aims:** In children with severe PARDS:

1. To compare the effects of prone positioning with supine positioning on ventilator-free days.
2. To compare the effects of HFOV with CMV on ventilator-free days.

*Hypothesis:* Children with severe PARDS treated with prone positioning or HFOV will demonstrate more VFD.

**Secondary:** To compare the impact of these interventions on nonpulmonary organ failure-free days.

*Hypothesis:* Children with severe PARDS treated with prone positioning or HFOV will demonstrate more nonpulmonary organ failure-free days.

**Exploratory:** To explore the interaction effects of prone positioning with HFOV on VFD and investigate the impact of these interventions on 90-day in-hospital mortality and, among survivors, the duration of mechanical ventilation, PICU and hospital length of stay and trajectory of post-PICU functional status and HRQL.

## B. BACKGROUND AND SIGNIFICANCE

Pediatric acute respiratory distress syndrome (PARDS) is a manifestation of severe lung injury with a mortality rate of up to 35%.[16-18] The disease is characterized by massive pulmonary inflammation, alterations in surfactant homeostasis and ventilation/perfusion mismatching leading to severe hypoxemia and multiple organ dysfunction.[19,20] Despite the significance of PARDS in critically ill mechanically ventilated children, respiratory management remains largely supportive with no data to support one approach over another.[21-25]

The maximum level of pulmonary function reached during childhood is a crucial determinant for respiratory function throughout life.[26-29] Any event in childhood that causes lung injury and, thereby, reduces the level of pulmonary function may exert a negative impact in adulthood. This may especially be true for lung injurious events during early childhood (i.e., <8 years of age) when the lung is still developing. Although beneficial to many patients with PARDS, numerous studies have shown that mechanical ventilation (MV) induces pulmonary inflammation (biotrauma) that aggravates pre-existing lung injury, known as ventilator-induced lung injury (VILI).[30-32] This inflammation is not limited to the lung as inflammatory mediators enter the systemic circulation to induce organ dysfunction and often failure. As a consequence, patients generally do not die from lung injury but rather from MODS linked to VILI.[33]

Data generated in adults with acute respiratory distress syndrome (ARDS) have shown positive results for prone positioning[7,34] and lung protective ventilation (LPV),[35-37] while demonstrating neutral or negative results for HFOV.[5,6] However, unique maturational anatomic and physiologic differences prevent data generated in adults to be directly applied to children. Specifically, there are important differences in lung parenchyma and airway growth and development, immune response and surfactant homeostasis.[8,38] The immune system of a child <1 year of age is relatively immature, including broad deficits in innate and adaptive immunity. As airway resistance is inversely proportional to the fourth power of airway radius, young children tend to have higher baseline airway resistances compared to adults. Additionally, infants and young children have more compliant chest walls as compared to adolescents and adults due to incomplete ribcage ossification. These factors predispose a young child to greater vulnerability of airway and lung collapse and importantly question the applicability of adult-based ARDS data to children.

In the absence of definitive pediatric-specific data, the management of PARDS remains largely supportive.[1] Critically ill children with PARDS are mechanically ventilated, sedated and often chemically paralyzed until their underlying pulmonary process resolves. Lung protective ventilation, one of the key components of the management of PARDS, comprises the delivery of small tidal volumes (Vt) to avoid volutrauma and positive end-expiratory pressure (PEEP) to prevent alveolar collapse.[13,39] In patients with severe PARDS, such a LPV strategy may be insufficient to provide adequate gas exchange. When this happens, pediatric critical care practitioners resort to unproven alterative interventions, including prone positioning and/or HFOV.

Prone Positioning: Prone positioning is an intervention that improves oxygenation and outcomes from acute hypoxemic respiratory failure in adults and, when applied consistently, has few serious adverse events.[40-44] Several small prospective and retrospective studies in critically ill, mechanically ventilated children with acute lung injury or PARDS confirmed improved oxygenation and a highly favorable safety profile.[45-50] To date, there has been only one pediatric randomized controlled trial (RCT) comparing prone to supine positioning.[4] This study, performed by members of our study group (R01 NR005336), randomized 102 patients with acute lung injury ($PaO_2/FiO_2$ ratio; PF <300 mmHg) to prone positioning for 20 hours each day or to supine positioning. Despite the significant improvement in oxygenation, the study was stopped at the planned interim analysis on the basis of futility. Prone positioning did not exert a beneficial effect on the primary outcome VFD or in the secondary end points, including the proportion of children alive and ventilator-free on day 28, all-cause mortality, time to recovery of lung injury, number of organ failure-free days and cognitive impairment or overall functional health at hospital discharge or on day 28. However, the major drawback of this trial was that it was not limited to pediatric patients with severe PARDS and the use of HFOV was mandated when the child's oxygenation index (OI) was ≥15. Indications that prone positioning might be of benefit in severe PARDS arose from a meta-analysis of primarily adult ARDS patients, showing that the effect of prone positioning was the greatest in patients with severe disease, i.e., a PF <100 mmHg.[34] This conclusion was supported by the adult Proning Severe ARDS Patients (PROSEVA) trial, identifying a 50% reduction in all-cause mortality at 28 days (the primary outcome of the trial) as compared to those who remained in the supine position in patients with severe ARDS defined as PF <150 mmHg.[7] As such, PALICC strongly suggested further investigation of the effects of prone positioning in *severe* PARDS.[51]

| | **PROSEVA** | **Pediatric Prone** | ***PROSpect*** |
|---|---|---|---|
| **Setting** | Only experienced centers | Experience not required | Only experienced centers |
| **Study entry criteria** | PF ratio <150 mmHg, $FiO_2$ ≥0.60, PEEP ≥5; Vt 6 | PF ratio < 300 mmHg | OI ≥16 or OSI ≥12.3* $FiO_2$ ≥0.60 |
| **Timing of Rx** | ARDS ≤ 36H | ALI ≤ 48H | PARDS ≤ 48H |
| **Stabilization period** | 12-24 hours | none | 4 hours |
| **Duration of PP** | 16H/day to day 28 | 20H/day to day 7 | ≥ 16H/day to day 28 |
| **Abdominal restraint** | Restrained | Unrestrained | Unrestrained <8 years, Restrained ≥8 years |
| **Mechanical Ventilation** | Protocolized, LPV | Protocolized, LPV with HFOV | CMV/HFOV randomized |

*OI and OSI includes mPaw

*Scientific Premise*: *PROSpect* will replicate PROSEVA methodology and enroll patients with severe PARDS while controlling the mode of mechanical ventilation. Prone positioning reduces ventral-to-dorsal transpulmonary pressure differences, making ventilation more homogeneous along the vertical axis, decreasing ventral alveolar overinflation and dorsal alveolar collapse, limiting VILI.[10]

High-Frequency Oscillatory Ventilation: From a theoretical perspective, HFOV is an ideal LPV mode given its very small tidal volumes and change in pressure at the alveolar level.[2] With HFOV, a continuous distending pressure is generated to maintain adequate lung volume, with superimposed small oscillations in a frequency range of 5-15 Hz allowing for gas exchange. In an international cross-sectional study of pediatric acute lung injury, ranging from mild to severe, 16% of patients were managed with HFOV.[52] To date, there has been only one pediatric RCT comparing HFOV to conventional mechanical ventilation (CMV) in 70 children with diffuse alveolar disease and/or airleak syndrome.[53] This study showed that HFOV using an aggressive volume recruitment strategy resulted in a significant improvement in oxygenation and a decreased requirement for supplemental oxygen at 30 days. However, 30-day mortality was not changed and the control group did not utilize a lung protective approach to ventilation. A meta-analysis of all six pediatric and adult clinical trials demonstrated improved mortality in patients randomized to HFOV.[54] However, two large randomized studies in adults with moderate to severe early ARDS launched the recent discussion on HFOV in PARDS.[5,6] Whereas in the OSCillation for ARDS (OSCAR) trial no difference in 30-day mortality was observed, the OSCILLation for ARDS Treated Early (OSCILLATE) trial was prematurely stopped (after the 500 patient analysis) because of higher in-hospital (47% versus 35%) and 60-day mortality (47% versus 38%) in the HFOV group. It should be noted that approximately half of the subjects enrolled in the OSCILLATE trial were septic requiring vasoactive agent support. Such a population would be anticipated to do poorly when exposed to the high mean airway pressures (mPaw) as directed by the protocol. The "one size fits all" approach of OSCILLATE did not allow for ventilator management to be titrated according to a patient's unique pathophysiology, a conclusion also noted by Malhorta and Drazen in their editorial entitled "High-frequency oscillatory ventilation on shaky ground."[55] Furthermore, a post-hoc data analysis of pediatric patients enrolled in a protocolized sedation trial performed by members of our study group (Randomized Evaluation of Sedation Titration for Respiratory Failure, *RESTORE,* U01 HL086622)[56] showed similar mortality rates but prolonged duration of MV among patients managed with HFOV compared to CMV after adjusting for risk category. The current management of pediatric patients with HFOV may not be superior than that with CMV, supporting PALICC's call for a pediatric RCT to examine the role of HFOV in PARDS.[57]

| | **OSCAR** | **OSCILLATE** | **PROSpect** |
|---|---|---|---|
| **Device and setting** | Novalung, little experience in participating centers | Sensormedics, only experienced centers | Sensormedics, only experienced centers |
| **I:E ratio** | 1:1 (higher distal pressures) | 1:2 | 1:2 |
| **Study entry criteria** | PF ratio < 200, PEEP > 5 | PF ratio < 200<br>PEEP > 10 | OI ≥16 or OSI ≥12.3, $FiO_2$ ≥0.60 |
| **Recruitment** | Not allowed | Sustained inflation 40 cmH2O for 40 seconds | Staircase mPaw recruitment maneuver |
| **Initial mPaw** | 5 cmH2O above plateau pressure | 30 cmH2O after recruitment | Dependent on "optimal" mPaw during recruitment |
| **Initial frequency** | Low | Low | High (8 – 12 Hz) |
| **pH adjustment** | Cycling volume | Frequency | Frequency |
| **mPaw adjustment** | Not specified | mPaw/$FiO_2$ table | Individualized mPaw maneuver Q12H |
| **Control group** | Not protocolized, local practice | Protocolized | Protocolized |

*Scientific Premise*: *PROSpect* will use a more physiologic-based approach to HFOV with individualized mPaw titration and higher frequencies to maximize lung volume and deliver the smallest tidal volume. HFOV maintains the recruited and stabilized alveoli due to the delivery of a constant mPaw.[2,58-60] Data from our team show that such an approach is safe in terms of hemodynamics and feasible in terms of oxygenation and ventilation. Furthermore, this approach is very different from the approach to HFOV in the two adult trials. Both OSCAR and OSCILLATE employed low frequencies (thereby delivering larger tidal volumes) and used a protocolized "one size fits all" mPaw titration, which led to the application of high pressures and subsequent hemodynamic compromise.

## C. SUPPORTING DATA

### C.1 Pediatric Acute Lung Injury Consensus Conference

A panel of 27 international pediatric experts met over two years to develop a taxonomy to define PARDS and make recommendations regarding treatment and research priorities.[1] The experts developed and voted on recommendations addressing: 1) Definition, prevalence and epidemiology; 2) Pathophysiology, comorbidities and severity; 3) Ventilator support; 4) Pulmonary-specific ancillary treatment; 5) Non-pulmonary treatment; 6) Monitoring; 7) Noninvasive support; 8) ECMO support; and 9) Morbidity and long-term outcomes. Additional data recently supported the PALICC PARDS definition noting that severe PARDS was associated with high mortality (37%), particularly if present 24 hours after diagnosis.[61]

### C.2 Pediatric Prone Trial

From 2001 to 2004, we conducted a multi-center, randomized, controlled clinical trial, testing the hypothesis that at the end of 28 days children with acute lung injury (PF <300 mmHg) treated with prone positioning would have more VFD than those treated with supine positioning.[4] We enrolled 102 pediatric patients, aged 2 weeks to 18 years, from 7 U.S. PICUs. Patients were randomized to either supine or prone positioning within 48 hours of meeting acute lung injury criteria, with those patients in the prone group being positioned within 4 hours of randomization and remaining prone for 20 hours each day during the acute phase of their illness for a maximum of 7 days, after which they were positioned supine. Both groups were managed using a low tidal volume/PEEP strategy, extubation readiness testing and sedation, hemodynamic, nutrition and skin care guidelines. The use of HFOV was mandated when a subject's OI was ≥15. Ninety percent of the patients randomized to the prone arm showed improved oxygenation (PF ≥20 mmHg or OI ≥10% decrease). The trial was stopped at the planned interim analysis on the basis of the pre-specified futility stopping rule. There were no differences in the number of VFD between the 2 groups (mean [SD], 15.8 [8.5] supine vs 15.6 [8.6] prone; mean difference, −0.2 days; 95% CI, −3.6 to 3.2; P=0.91). After controlling for age, Pediatric Risk of Mortality III score, direct vs indirect acute lung injury and mode of mechanical ventilation at enrollment, the adjusted difference in ventilator-free days was 0.3 days (95% CI, −3.0 to 3.5; P=0.87). Prone positioning did not significantly reduce VFD or improve other clinical outcomes in pediatric patients with acute lung injury.

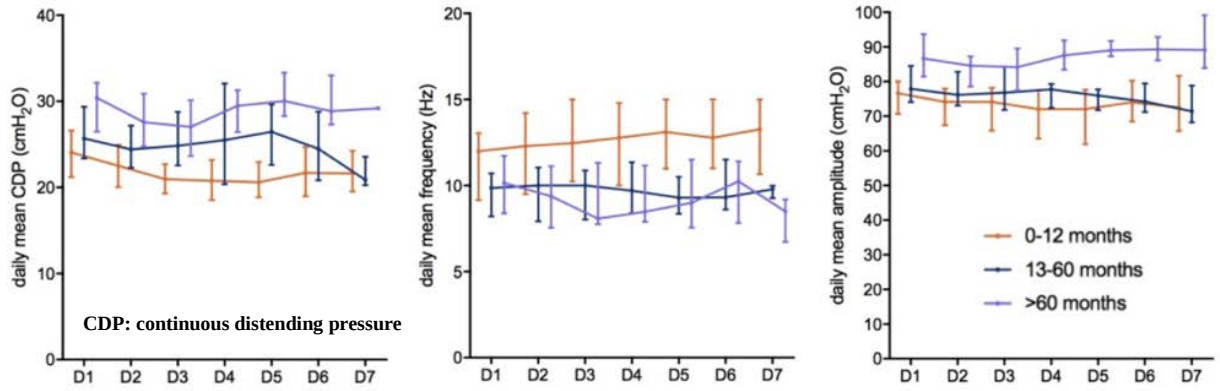
### C.3 *RESTORE* HFOV Propensity Score Analysis

In the absence of pediatric trials, we conducted a propensity score analysis of data from the *RESTORE* study to compare the outcomes of patients with acute respiratory failure managed with HFOV within 24-48 hours of endotracheal intubation with those receiving CMV and/or late HFOV.[57] Among 2,449 patients enrolled in *RESTORE*, 353 patients (14%) were ever supported on HFOV, of which 210 (59%) had HFOV initiated within 24-48 hours of intubation. The

propensity score model predicting the probability of receiving early HFOV included 1,064 patients (181 early HFOV vs 883 CMV/late HFOV) with significant hypoxia (OI ≥8.0). The degree of hypoxia was the most significant contributor to the propensity score model. After adjusting for risk category, early HFOV use was associated with a longer duration of mechanical ventilation (hazard ratio, 0.75; 95% CI, 0.64–0.89; P=0.001) but not with mortality (odds ratio, 1.28; 95% CI, 0.92–1.79; P=0.15) compared with CMV/late HFOV. These analyses make supporting the current approach to HFOV less convincing.[62]

### C.4 Physiologic Approach to HFOV

We will use an individualized mPaw titration algorithm and higher frequencies than traditionally practiced, thereby maximizing lung volume while delivering the smallest tidal volume. Data from our team show that such an approach is safe in terms of hemodynamics and feasible in terms of oxygenation and ventilation. Between 2014 and 2016, 115 non-cardiac patients with acute hypoxemic respiratory failure, of whom 53% met the criteria for PARDS (40% severe PARDS) were oscillated. Indications for HFOV included Peak Inspiratory Pressure (PIP)/Pressure Plateau (Pplat) >28 cm $H_2O$, PEEP >8 cm $H_2O$, $FiO_2$ >0.60 and increase in oxygenation index on three consecutive measurements one hour apart from each other. All patients underwent a staircase incremental-decremental mPaw titration. An open-lung strategy was employed, targeting frequency >9 Hz and amplitude 70-90 cm $H_2O$. Analysis within three age groups (<12 months, 13-60 months and >60 months) showed that this approach was feasible irrespective of age. Also, there were no significant negative effects on heart rate or blood pressure, indicating that the open-lung strategy did not result in hemodynamic instability. Also, both oxygenation and




ventilation were feasible; the pH was always >7.15 without severe or refractory hypercapnia.

## D. EXPERIMENTAL APPROACH

### D.1 Design and Rationale

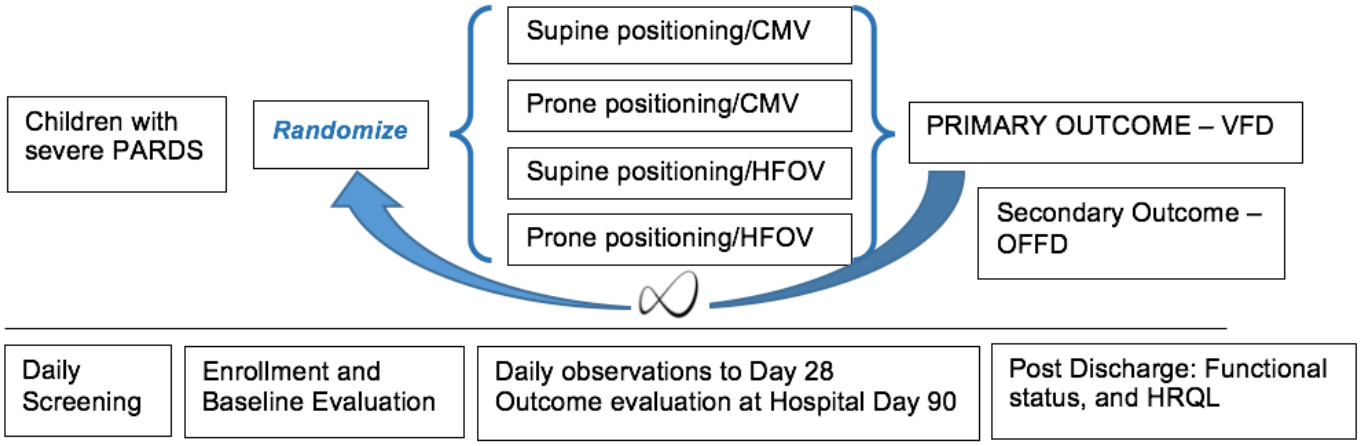
This is a two-by-two factorial, response-adaptive multi-center randomized controlled clinical trial that tests whether pediatric patients with severe PARDS randomized to supine versus prone positioning and to conventional mechanical ventilation versus high-frequency oscillatory ventilation exhibit more ventilator-free days over a 28-day period. Our primary research hypothesis is that children with severe PARDS randomized to either prone positioning or HFOV will demonstrate more ventilator-free days. We hypothesize that a superior treatment would improve VFD by at least 2 days, a clinically meaningful difference.[15] Our secondary research hypothesis is that these two interventions will demonstrate more nonpulmonary organ failure-free days. The rationale for our research hypotheses is that prone positioning and HFOV will provide better support for the failing lung without causing harm as evidenced by a more rapid

recovery and return to unsupported breathing. Improvement in VFD will be considered within the context of patient safety; specifically, patients must also exhibit a similar safety profile.

Up to 1,000 patients will be randomized. Randomization will be stratified by age group (<1; 1-7; 8-17 years) and direct/indirect lung injury. Adaptive randomization will begin after 400 patients are randomized. After the 400$^{th}$ patient has been randomized and every 100 patients thereafter, new allocation probabilities will be computed based on ongoing intention-to-treat trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. *PROSpect* may close enrollment early for efficacy or futility based on pre-specified stopping rules.

Enrolled subjects will be followed from endotracheal intubation until hospital discharge or hospital Day 90, whichever occurs first. After PICU discharge, we will complete telephone-based family interviews at 1, 3, 6 and 12 months to assess the subject's functional status and health-related quality of life (HRQL). Data will be analyzed per intention-to-treat for the primary analyses and per-protocol received.

**Study Scheme:**




**Rationale:**

Two-by-two factorial study design. This study will address two major research questions with one clinical trial, saving time and resources. In addition, pediatric practice commonly uses prone and supine positioning with both ventilation strategies (CMV and HFOV), and though we are not anticipating significant interaction effects between positioning and ventilation strategies, this study will allow an evaluation of potential synergistic effects.

Response-adaptive randomization. This design will improve trial efficiency. Data generated during the course of the trial will be used to modify randomization allocation, thereby randomly assigning more subjects to a more efficacious intervention(s).

Randomization stratification by age group and lung injury type. We are stratifying by age group (<1; 1-7; 8-17 years) because in infancy, chest wall compliance is nearly three-times that of the lung. By the second year of life, the increase in chest wall stiffness is such that the chest wall and lung have similar compliance as in adults. By eight years of age, the height of the chest wall is similar to that of an adult. It is possible that the increased chest wall compliance and the consequent increase in alveolar excursion for the same transpulmonary pressure may place the infant at greater risk for ventilator associated lung injury. It is also possible that chest wall stiffening relative to the lung may improve the infant's ability to maintain adequate end-

expiratory lung volume, an important determinate of lung unit patency in dependent lung regions. When evaluating the impact of age on prone positioning we will search for nonlinear relationships; specifically, does the effect of prone positioning vary in different age groups.

We are also stratifying by direct/indirect lung injury because there may be a differential lung recruitment response to prone positioning and HFOV; specifically, prone positioning may be more effective in patients with indirect lung injury whereas HFOV may be more effective in direct lung injury. Direct lung injury is operationally defined as lung injury originating from pulmonary disease (e.g., pneumonia) and indirect lung injury originating from non-pulmonary disease (e.g., sepsis).[63]

### D.2 Study Population

**Participating Centers:** Approximately 50 PICUs with at least 5 years of experience with prone positioning and HFOV that can provide back-up ECMO support have been recruited to participate. Consistent with the PROSEVA study, experienced centers are those with at least a 5-year history of using the therapies.[7] Our rationale for including experienced centers diminishes the need for fundamental training in study interventions and will allow our team to focus training on the *PROSpect* protocols. Requiring ECMO backup optimizes patient safety since all enrolled subjects will have severe PARDS and would not easily tolerate an inter-hospital transport for ECMO if study interventions failed.

We modeled our anticipated enrollment rate based on our experience with the *RESTORE* trial; specifically, 761 *PROSpect*-eligible *RESTORE* patients (31% of 2449 *RESTORE* patients) were enrolled over a total of 1309 months from 31 U.S. PICUs (of varying size with unequal start/stop times) at a rate of 0.58 patients per site per month. Assuming that the *PROSpect* consent rate will be approximately 60% (lower than the *RESTORE* intervention group consent rate of 72%; yet higher than the 50% rate in *HALF-PINT*), the enrollment rate becomes 0.58×(60%/72%) = 0.58×83% = 0.48 patients per site per month.[56,64] To enroll 1,000 *PROSpect* patients, it would take approximately 2083 months or, in total, approximately 44 sites 48 months each.

To ensure that *PROSpect* ends fully enrolled and on-time with results that can be generalized throughout the field, we have designed *PROSpect* to include one-third international sites.[52] PICUs in Asia, Australia/New Zealand and Western Europe have volunteered, augmenting existing U.S. resources. All PICUs are active in pediatric critical care research, members of their national research societies and engaged in each other's work through the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS). The clinical practices of the international PICUs are known by the Principal Investigators and all are English-competent.

All PICUs provided letters of support outlining their organizational, leadership and interprofessional team support for *PROSpect*. All have reviewed and agreed to follow our research protocols (http://www.prospect-network.org). All have equipoise on the topic, can enroll a minimum of 6 subjects/year and are aware of the expectation that at least a quarter of our sites must be ready to enroll in our UG3 year. In addition, all domestic sites have agreed to engage in a reliance agreement with the University of Pennsylvania and international sites will complete local human subjects review processes. We used external data from either the *RESTORE* database and/or the Pediatric ARDS Incidence and Epidemiology (PARDIE; http://pardie.palisi.org) database to validate each PICU's reported available population.

**Patient Eligibility and Recruitment:** Site co-investigators or their designee will screen their PICUs daily for eligible patients. Screening logs will be used to facilitate the screening process and provide an auditable record of potentially eligible patients. Patient eligibility criteria focus on pediatric patients with severe PARDS occurring within 4 days of endotracheal intubation. Enrolling subjects within 48 hours of meeting criteria for severe PARDS occurring within 4 days

of endotracheal intubation allows us to enroll a more homogenous group of subjects with potentially recruitable lung disease.

**Inclusion Criteria:** Pediatric patients (≥2 weeks of age and ≥42 weeks post gestational age and <18 years of age) intubated and mechanically ventilated with **severe PARDS** for <48 hours per PALICC guidelines, that is, **chest imaging consistent with acute pulmonary parenchymal disease and OI ≥16 or, if an arterial specimen is not available, oxygen saturation index (OSI) ≥12.3 while receiving an $FiO_2$ ≥0.60** (OI: [$FIO_2$ × mPaw]/$PaO_2$ × 100; OSI: [$FIO_2$ × mPaw]/$SpO_2$ × 100). We will require two consecutive blood gases meeting severe PARDS criteria separated by at least 4 hours. Requiring two consecutive blood gases avoids enrolling transiently hypoxemic patients who are responsive to conventional measures to improve hypoxemia. To facilitate early identification of PARDS, the OSI may be used in lieu of the first blood gas in the absence of a functional arterial line.

**Exclusion Criteria:** Exclusion criteria focus on patients in whom prone positioning or HFOV is contraindicated. Patients will be excluded if they are/have any of the following at the start of mechanical ventilation:

- Perinatal related lung disease
- Congenital diaphragmatic hernia or congenital/acquired diaphragm paralysis
- Respiratory failure explained by cardiac failure or fluid overload
- Cyanotic heart disease
- Cardiomyopathy
- Unilateral lung disease
- Primary pulmonary hypertension
- Intubated for status asthmaticus
- Obstructive airway disease (e.g., bronchiolitis or disease characterized by hypercapnia and/or evidence of increased resistance visible on the flow – time scalar and/or presence of intrinsic PEEP)
- Active air leak
- Bronchiolitis obliterans
- Post hematopoietic stem cell Transplant
- Post lung transplant
- Home ventilator (including noninvasive) or home oxygen dependent
- Neuromuscular respiratory failure
- Critical airway (e.g., post laryngotracheal surgery or new tracheostomy) or anatomical obstruction of the lower airway (e.g., mediastinal mass)
- Facial surgery or trauma in previous 2 weeks
- Head trauma (managed with hyperventilation)
- Intracranial bleeding
- Unstable spine, femur or pelvic fractures
- Acute abdominal process/open abdomen
- Obesity (2w-24 months: WHO weight-for-length/height z-score ≥+3; ≥2 years: WHO body mass index (BMI)-for-age z-score ≥+3)
- Received either prone positioning or HFOV with current illness
- Supported on ECMO during the current admission
- Family/medical team not providing full support (patient treatment considered futile)
- Previously enrolled in current study
- Enrolled in any other critical care interventional clinical trial concurrently
- Known pregnancy

### D.3 Interventions

Once randomized, subjects will be transitioned to their allocated intervention(s) within 4 hours. Receiving the allocated intervention(s) after this time will be considered a protocol violation.

**Protocol highlights are as follows** (Full protocol included in the Appendix):

**All groups:**

- The goal is adequate oxygenation and ventilation:
  Oxygenation: Pulse oximeter oxygen saturation ($SpO_2$) 88-92%
  Ventilation: pH 7.15-7.30 (irrespective of $PaCO_2$)
- Monitoring will include an arterial line.
- Neuromuscular blockade administered for first 24 hours, then as clinically indicated.
- Subjects will be placed in their allocated position (supine or prone) first, then converted to their allocated ventilation strategy (CMV or HFOV). This will avoid multiple consecutive recruitment maneuvers.

**Supine Positioning:** Patients randomized to supine positioning will remain supine. Supine repositioning includes a Q2H rotation from full supine to right lateral/supine to full supine to left lateral/supine to full supine.

**Prone Positioning:** Patients randomized to receive prone positioning will be positioned prone ≥16 hours/day for a maximum of 28 days. Prone repositioning includes a Q2H rotation from full prone to right lateral/prone to full prone to left lateral/prone to full prone. For safety, clinicians will use the positioning checklist and Standard Operating Procedure (SOP) for all turns. Failure to do so will be considered a protocol violation.

Criteria for stopping prone positioning includes (1) improved lung function consistent with resolving PARDS; specifically, spontaneous breathing and OI <8 in the supine position for at least 4 hours after the end of a prone session or (2) treatment failure where the subject demonstrates a three-day pattern of decreased PF ratio of at least 20% or an increase in OI of at least 10% post supine-to-prone positioning.

Prone positioning is immediately interrupted in an emergency: e.g., non-scheduled extubation, main-stem bronchus intubation, ETT obstruction, hemoptysis, cardiac arrest, bradycardia or hypotension for more than 5 minutes and any other life-threatening event. Evolving clinical situations that may also preclude daily prone positioning, that is, acute abdomen or Stage III pressure injuries that cannot be managed in the prone position.

**Conventional Mechanical Ventilation (CMV):** The CMV arm will use a lung-protective ventilation strategy consistent with PALICC recommendations. This includes: (1) low tidal volume to obtain exhaled Vt (Vte) of 5-7 ml/kg (ideal body weight [IBW]); (2) PIP goal limited to ≤28 cm $H_2O$ (may allow up to 32 cm $H_2O$ for subjects with poor chest wall compliance); (3) lung recruitment maneuver to identify best PEEP then maintained per PEEP-$FiO_2$ grid; and (4) use of synchronized intermittent mandatory ventilation (SIMV) or assist control (AC), Pressure Control Ventilation (PCV) or Pressure Regulated Volume Control (PRVC or equivalent). The protocols delineate ongoing CMV support, escalation of support and weaning of support. Monitoring will include Vte and percent ETT airleak measured at the airway. Criteria for failed CMV include a 4-hour pattern of either persistent hypoxia ($SpO_2$ <85%) with $FiO_2$ 1.0 and max PEEP per grid or persistent hypoventilation (pH <7.15) with PIP >35 cm $H_2O$ and a respiratory rate that does not cause intrinsic PEEP.

**High-Frequency Oscillatory Ventilation (HFOV):** The HFOV arm will use a lung-protective ventilation strategy consistent with PALICC recommendations. HFOV management is based on physiologic principles of gas delivery. To optimize the high-frequency approach, high rates (≥8 Hz) will be used knowing that increased amplitudes will be required for adequate ventilation.

Given the known attenuation of pressure amplitude across the endotracheal tube and along the natural airways, pressure amplitude and tidal volume delivery will remain within typical parameters for HFOV at the alveolar level. The HFOV strategy includes use of a frequency at 8-12 Hz, an amplitude (delta-P) 60-90 and a mPaw recruitment maneuver. The protocols delineate ongoing HFOV support, escalation of support, weaning of support and conversion to CMV. Criteria for failed HFOV include a 4-hour pattern of either persistent hypoxia ($SpO_2$ <85%) at $FiO_2$ 1.0 and mPaw >40 cm $H_2O$ or persistent hypoventilation (pH <7.15) with max power/amplitude at a frequency <8 Hz.

For reproducibility across centers we will restrict the HFOV ventilator to the SensorMedics 3100A (patient <35 kg) or 3100B (patient ≥35 kg). The SensorMedics, compared to other HFOV ventilators, allows manipulation of the inspiratory-to-expiratory time ratio, provides an active exhalation phase, can be used across the enrolling age groups, is FDA-approved for this application and is available in each of the proposed clinical sites.

**Failed Management:** Clinicians may consider a reciprocal therapy (supine to prone; prone to supine; CMV to HFOV; HFOV to CMV) in a sequence based on their clinical judgment while considering ECMO cannulation. Reciprocal treatments, when used, will be managed per *PROSpect* protocols. Subjects cannulated for ECMO will be discontinued from further study treatments and followed so that ventilator management can be described and for study outcomes.

**Co-Interventions (all groups)**, managed per PALICC recommendations.[13,51,65]

- **Endotracheal tube (ETT) suctioning:** Performed with an unexplained, rapid increase in $PaCO_2$ and/or decrease in chest movement. Routine suctioning is not recommended.
- **Hemodynamic management guidelines:** Subjects will be managed using a fluid conservative strategy based on the subject's mean arterial blood pressure percentile for age, net fluid balance and urine output.[66]
- **Sedation guidelines:** The care team will prescribe a target comfort level each day. Adjustment of sedatives to achieve target comfort levels will be guided by a nurse-implemented goal-directed sedation protocol.
- **Enteral nutrition:** Monitoring, advancement and maintenance managed by a goal-directed protocol that is collaboratively established by the interprofessional team. The 2017 ASPEN nutrition guidelines recommend that critically ill pediatric patients receive a minimal protein intake of 1.5 gm/kg/day to achieve positive nitrogen balance.[67]
- **Skin care and pressure injuries guidelines:** A skin assessment will be performed and recorded daily. Pressure injuries will be staged and managed according to National Pressure Injury Advisory Panel (NPUAP) guidelines.[68]
- **Extubation Readiness Test (ERT):** This standardized test will be implemented twice daily at 07:00 ± 2H and 16:00 ± 2H in subjects who are spontaneously breathing with an OI ≤6.[69] Since our primary outcome is VFD, failure to complete an ERT on an eligible subject will result in a protocol deviation.[56]
- The use of **inhaled nitric oxide (iNO)** and systemic **steroids** will be monitored but not protocolized. Per the PALICC guidelines, iNO should only be used for patients with documented pulmonary hypertension and/or right ventricular failure, and there are no data supporting the routine use of systemic steroids.

### D.4 Primary, Secondary and Exploratory Outcome Measures

**Primary Outcome: Ventilator-free days (VFD) through Day 28.** VFD is defined as the number of days within 28 days that a subject is alive and free of mechanical ventilation.[70] It is the inverse equivalent of the 28-day hospital mortality-adjusted duration of mechanical ventilation. While mortality is an ideal primary outcome, the cause of death in PARDS is

multifactorial. Mortality-adjusted duration of mechanical ventilation is a well-accepted alternative way to evaluate outcomes of treatments for PARDS.[71] VFD appropriately reflect both improved survival and shorter duration of ventilation and avoid potential biases caused by shorter duration of ventilation as a result of early mortality. In computing VFD, we will consider day 0 as the time of endotracheal intubation or, in subjects with tracheostomies, the time of initiation of assisted breathing. Duration of mechanical ventilation continues until the first time the endotracheal tube is continuously absent for at least 24 hours or, in subjects with tracheostomies, the first time pressure support is <5 cm $H_2O$ (continuous or bi-level) for at least 24 hours. Subjects will be assigned 0 VFD if they remained intubated or were transferred to another PICU or died prior to day 28 without remaining extubated for more than 24 hours. Subjects cannulated for ECMO will also be assigned 0 VFD. To accommodate the use of noninvasive ventilation, we will also compute the total duration of assisted breathing to the first time pressure support is <5 cm $H_2O$ (continuous or bi-level) for at least 24 hours.

**Secondary Outcome: Nonpulmonary organ failure-free days (OFFD) through Day 28.** Nonpulmonary OFFD is defined as the number of days within 28 days that a subject is alive and free of clinically significant non-pulmonary organ failure. Nonpulmonary organ failure-free days will be calculated for the clinically important nonpulmonary organ systems (neurologic, cardiovascular, renal and hematologic) using nonpulmonary PEdiatric Logistic Organ Dysfunction-2 (PELOD-2) scores to Day 28.[72] Slutsky and Tremblay postulate that ventilator-induced lung injury (VILI) may play a pivotal role in the initiation and/or propagation of a systemic inflammatory response leading to multisystem organ failure.[30,73,74] In animal models, the strategy of mechanical ventilation influences the local release of inflammatory mediators from the lung and preventing volutrauma and atelectrauma reduces the release of these mediators. Effective lung protection strategies that limit VILI may lead to a modification of the systemic inflammatory response and development of MODS. Thus, nonpulmonary OFFD is a relevant secondary outcome of interventions posited to limit the inflammatory milieu in the lung.

**Exploratory Outcome: Interaction effects between the positioning and ventilation strategies.** We will evaluate possible interaction effects of prone positioning with HFOV on VFD, which will allow us to probe for potential differential effects when these two interventions are used concurrently.

**Exploratory Outcome: 90-day in-hospital mortality.** 90-day in-hospital mortality is a critical measure of treatment safety and considers death beyond 28 days. Deaths from all causes will be monitored through hospital discharge or day 90 (whichever occurs first). The primary and secondary causes of death (as specified on the death certificate) will be recorded to allow us to probe the cause of death in PARDS.

**Exploratory Outcome: Duration of mechanical ventilation (among survivors).** Duration of mechanical ventilation provides a prospective evaluation of ventilator support independent of mortality. As above, duration of mechanical ventilation is defined as the time from day 0 to the first time the endotracheal tube is continuously absent for at least 24 hours. For subjects with tracheostomies, duration of mechanical ventilation is defined as the time of initiation of assisted breathing to the first time pressure support is <5 cm $H_2O$ (continuous or bi-level) for at least 24 hours. Duration of mechanical ventilation will be considered to be 28 days for subjects still intubated on day 28, and will be calculated for subjects who survive to hospital discharge or day 90 (whichever occurs first).

**Exploratory Outcome: PICU and hospital length of stay (among survivors).** PICU and hospital length of stay (LOS) provide proxy measures of resource utilization. PICU LOS is defined as the time from day 0 to the time of PICU discharge, while hospital LOS is defined as the time from day 0 to the time of hospital discharge. PICU and hospital LOS will be considered

to be 90 days for subjects still in the PICU/hospital on day 90, and will be calculated for subjects who survive to hospital discharge or day 90 (whichever occurs first).

**Exploratory Outcome: Post hospital discharge functional status and HRQL.** Not all pediatric patients who survive PARDS return to their previous level of health. These outcomes will allow us to explore the trajectory and quality of patient survival. Functional status will be assessed using the Pediatric Cerebral Performance (PCPC), Pediatric Overall Performance Category (POPC),[75] and Functional Status Scale (FSS) score[76]. HRQL will be assessed using the chronological age-appropriate Pediatric Quality of Life Inventory (PedsQL™; Version 4.0 Generic Core Scales for subjects 2-19 years; Infant Scales for subjects <2 years; http://www.pedsql.org).[77,78] These measures will be obtained through interviews with the parent/legal guardian. See section D.8 for information on the timing of assessments.

### D.5 Measurement of Study Variables During Hospital Course

**Methods of Data Collection:** Site co-investigators will be trained in data collection methods by the DCC Project and Data Managers prior to enrolling subjects.

Baseline assessments will be completed on all subjects to allow group comparison. This includes demographic and socioeconomic data, medical history information, primary cause for acute respiratory failure, pre-enrollment chest X-ray (CXR; de-identified digitized file), baseline PCPC, POPC,[75] and FSS,[76,79] and the PRISM III-12 score.[80,81]

**Schedule of clinical and laboratory evaluations:**

| Data Collection Schedule | Screening | Baseline | Daily PICU to Day 28* | Post PICU discharge to Day 28 |
|---|---|---|---|---|
| Demographic Data | X | X | | |
| Past and present medical history, pre-enrollment CXR | X | X | | |
| PCPC, POPC, FSS score | | X | | Hospital discharge |
| Admission PRISM III-12 score | | X | | |
| Vital signs, vasopressor use | | X | X | |
| Ventilator parameters; arterial blood gases | | X | X | |
| If CMV: $ETCO_2$ ($NM_3$) dead space/volumetric capnography evaluation | | X | X | |
| NMB, iNO, systemic steroids | | X | X | |
| Comfort status/agents | | X | X | |
| Skin assessment | | X | X | |
| PELOD-2 | | X | X | |
| Pre-specified; Unanticipated adverse events | | X | X | |

Daily data, extracted from existing documentation at 08:00±2H

* Daily measurements will be assessed in both CMV/HFOV groups when the subject is supine. Comfort status includes pain, sedation, delirium and iatrogenic withdrawal syndrome (IWS) scores. Exposure to sedative medications includes total dose and length of exposure.[56]

### D.6 Study Safety

Subjects will be prospectively monitored daily for the occurrence of pre-specified adverse events. Potential risks associated with prone positioning include unplanned extubation, vascular line/invasive tube removal, plugging/obstruction of the endotracheal tube with secretions and/or blood, main-stem bronchus intubation, transient hemodynamic instability or cardiac dysrhythmias, hypercarbia (unresponsive to ventilation protocols), clinically significant agitation (State Behavioral Scale; SBS +1/+2 for 2 consecutive hours), facial and eyelid edema, pressure injuries (any dependent surface), and corneal abrasions. Potential risks associated with the ventilation protocols include hemodynamic instability, airleak (e.g., pneumothorax, pneumomediastinum) and cardiac dysrhythmias related to increased mPaw, mucous plugging/airway obstruction, and clinically significant agitation and pressure injuries (occipital/auricular). Most specified events should be tracked in the PICU only and not the Ward, with the exception of clinically significant iatrogenic withdrawal (IWS) for subjects receiving ≥ 5 days of opioids or benzodiazepines, ventilator associated pneumonia through 24 hours after PICU discharge, catheter-associated bloodstream infection (if the line was inserted in the PICU) through 24 hours after PICU discharge; and new tracheostomy through hospital discharge or Study Day 90 (whichever occurs first). If an adverse event overlaps the positioning and ventilation protocols (e.g., agitation), attribution will be assigned based on the clinical judgment of the bedside team. See also section F.7 for information about event severity and relatedness classifications and reporting procedures,

### D.7 Biorepository

We will collect blood samples for future studies of genomics, proteomics and metabolomics of PARDS. Such studies will provide objective measures of PARDS, intermediate outcomes for clinical trials and allow for early interventions and prevention of PARDS. While performance of these studies will be beyond the scope of this clinical trial, *PROSpect* provides a unique and low-cost opportunity to collect biomarker samples in conjunction with a wealth of clinical data for further study. Blood samples will be obtained on Study Day 0, 1, 2, 3, 5, 7, 10, and 14 processed locally, then shipped to Children's Hospital of Philadelphia for bio-banking.

### D.8 Follow-up Procedures

We base these procedures on our experience with the *RESTORE* and *RESTORE*-cognition (R01 HD074757) studies. Prior to hospital discharge, all U.S. parents/legal guardians will be assisted in entering their full contact information plus two alternative contacts into a REDCap database that is separate from the *PROSpect* clinical database. All emails and telephone numbers will be verified by the local investigators so that data entry errors can be identified and rectified prior to hospital discharge. Parents/legal guardians will also be given a refrigerator magnet to remind them to contact the CCC if their contact information changes.

Approximately two weeks after PICU discharge, the CCC will call or email parents/legal guardians and confirm their preferred method of communication for follow-up. Options include phone interview plus completion of instruments online or by mail. Contacting the family at this time will provide us another contact point with families. A trained Spanish-speaking interviewer will contact Spanish-only speaking families. If the parents are unable to be reached at 2 weeks we will contact the participating site to see if any further contact occurred (e.g., readmission or clinic visit) and attempt to locate families using people-finding software (LexisNexis™) and/or social media before considering the family lost to follow-up.

At 1, 3, 6 and 12 months post-PICU discharge, we will contact parents/legal guardians based on their stated preference. If a child is still hospitalized or re-hospitalized during the data collection period, all data collection will be held until the child returns home and we will resume data

collection per schedule based upon the PICU discharge date. If re-hospitalized, parents will be asked to obtain or give permission to allow the PENN team to obtain a copy of the child's discharge summary, so the readmission can be generally described.

We will reassess functional status using the PCPC, POPC[75] and FSS[76] and assess HRQL using the chronological age-appropriate Pediatric Quality of Life Inventory (PedsQL™; Version 4.0 Generic Core Scales for subjects 2-19 years; Infant Scales for subjects <2 years; http://www.pedsql.org).[77,78] The surveys will take 7 to 20 minutes to complete, depending on the age of the subject. In addition to the parents/legal guardians, children ≥8 years who are cognitively capable (discharge PCPC ≤3) will be asked to self-report their HRQL. We will compensate each family $50 for their participation. We are interviewing families over time to better understand the trajectory of their recovery. We will not follow our international subjects because of potential language barriers, time-zone differences, inability to systematically locate subjects lost to follow-up and the questionable validity of our instruments in all countries enrolling in *PROSpect*.

We will implement tools for maximizing patient cohort retention for longitudinal long-term outcomes research studies.[82-84] Establishing a rapport with families enhances successful follow-up as well as 1) collection of extensive and verified family contact information, 2) telephone contacts at regular intervals not greater than Q3 months (considered to be positive encounters by families), 3) regular contact with families by mail and email (if desired by family), 4) managing follow-up in one location (CCC), 5) flexibility in accommodating family schedules. We will also assist families in obtaining referrals for medical and psychiatric services if requested. We will develop a public study website and a study Facebook page to enhance study enthusiasm. The website will include study information, a private portal for subjects to update their contact information, provide contact preferences, schedule telephone interviews and links to internet resources for parents.

## E. STATISTICAL CONSIDERATIONS

The overall objective of this study is to identify the best positional and/or ventilation practice that leads to improved patient outcomes in critically ill children with severe PARDS. The study design is a two-by-two factorial, response adaptive, randomized controlled clinical trial of supine positioning vs. prone positioning and conventional mechanical ventilation vs. high-frequency oscillatory ventilation. The primary outcome for this study is ventilator-free days (VFD) through day 28. The Biostatistics and Data Coordinating Center in the Department of Cardiology at Boston Children's Hospital, led by DCC PI Wypij, will function as the independent *PROSpect* Data Coordinating Center (DCC). The DCC PI and Biostatistician will be responsible for all statistical analyses, including the analysis of post-discharge outcomes, and will collaborate with Berry Consultants for the response adaptive randomization.

### E.1 Study Design

The design evaluates four arms in a two-by-two factorial structure, crossing supine positioning vs. prone positioning and conventional mechanical ventilation (CMV) vs. high-frequency oscillatory ventilation (HFOV). Eligible children will be randomly assigned to one of the four possible treatment options. Thus this study will address two major research questions with one clinical trial. The sample size selected (up to 1,000 patients in total; see section E.6) provides high power to detect a clinically meaningful two-day difference in our primary outcome (VFD) between groups to address both of our research questions. In addition, pediatric practice commonly uses supine and prone positioning with both ventilation strategies, and though we are not anticipating significant interaction effects between positioning and ventilation strategies, this study will allow an evaluation of potential synergistic or antagonistic effects.

The design utilizes response adaptive randomization, which will improve trial efficiency. Data generated during the course of the trial will be used to modify randomization allocation, thereby randomly assigning more patients to a more efficacious arm(s).

### E.2 Analysis Data Sets

Data sets for DSMB reports, randomization update analyses and final data analyses consist only of data for which all queries have been resolved. In addition to the data management steps described in section F to reduce error in data acquisition and entry, a biostatistical cleaning will focus on inconsistencies, missing data and outliers in variables related to the derivation of key outcomes. These activities will be ongoing throughout the study and will involve the DCC Data Managers and Biostatistician. Preplanned construction of new variables will be conducted in accordance with the study hypotheses and analysis plans. Variable transformations may be required for interpretive and statistical purposes.

**Intention-to-treat Analysis Data Set:** The intention-to-treat data set consists of all randomized subjects. Subjects will be classified according to the treatment randomized regardless of actual treatment received. The ITT data set will be used for analysis of the primary outcome, including DSMB reports, randomization update analyses and final data analyses (see Sections E.3 and E.5). Missing data during the hospital stay is expected to be minimal, as patients have severe respiratory disease, and we expect minimal parental withdrawal during patient hospital stays. If the primary outcome is not known, the worst possible outcome (i.e., zero ventilator-free days) will be assigned.

**Per-Protocol Analysis Data Set:** The per-protocol data set consists of all randomized subjects, except subjects who never received the intervention, subjects withdrawn from the protocol during the first 24 hours post-randomization by a clinician or parent/legal guardian and subjects whose parent/legal guardian withdrew full consent for the protocol and data collection. The per-protocol dataset will be used for analysis of all primary, secondary and exploratory outcomes, including DSMB reports and final data analyses. Only subjects included in the per-protocol data set will be eligible for follow-up.

### E.3 Randomization and Randomization Update Analyses

After verifying the patient's eligibility status with the potential subject's attending physician, the parent or legal guardian will be introduced to the site co-investigator or their designee by a member of the clinical team. The site co-investigator or their designee will provide information about the study and alternatives to participating in the study. Based on our previous studies, we have found that these introductions respect the primacy of the bedside team and acknowledge local support for the clinical trial.[85,86]

After informed consent is obtained and the subject has been stabilized from a hemodynamic perspective, patients will be randomized to one of four groups: supine/CMV, prone/CMV, supine/HFOV or prone/HFOV. The DCC will manage the randomization process centrally, as centralized randomization is necessary for the adaptive randomization.

For the first 400 randomized subjects (intention-to-treat population), allocation will be 1:1:1:1 among the four treatment arms, stratifying by age (<1; 1-7; 8-17 years) and by direct/indirect lung injury (6 strata in total). Stratification by age and type of lung injury will allow us to balance potentially important subgroups among the four intervention groups (see also section D.1). Randomization will occur in permuted blocks with random block sizes of 4 and 8.

**Randomization Update Analyses:** Randomization update analyses will first occur after the 400$^{th}$ patient has been randomized and every 100 patients thereafter. At each randomization update analysis, new allocation probabilities are computed based on ongoing intention-to-treat

trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. Randomization update analyses will consider each of the 2x2 treatment strategies as separate arms.

Using Supine/CMV as the base strategy, we define $HR_{Prone/CMV}$, $HR_{Supine/HFOV}$ and $HR_{Prone/HFOV}$ as the hazard ratios for duration of ventilation among those with non-zero VFD, comparing these three strategies to Supine/CMV. We utilize a linear model structure, with

$$\text{Log } HR_{X/Y} = \beta_{Prone}\, I(\text{Positioning=Prone}) + \beta_{HFOV}\, I(\text{Ventilation=HFOV}) + \beta_{Interaction}\, I(\text{Positioning=Prone, Ventilation=HFOV}).$$

We place uniform priors $\beta_{Prone}$ and $\beta_{HFOV}$, with an informative prior on $\beta_{interaction}$ focused on values near 0. The model will assume additivity unless it is clearly contradicted in the data.

Let the baseline probability of VFD=0 be equal to $\pi$, for which we place a Jeffreys Beta(0.5,0.5) prior. The baseline distribution of duration of ventilation among those with non-zero VFD in the Supine/CMV strategy is modeled as a Gamma($\alpha$,$\beta$) distribution using the noninformative Jeffreys prior.

After fitting this model we obtain posterior distributions for all the parameters, which induces a joint distribution over the median duration of ventilation for each strategy. Define

$M_{X/Y}$ = Pr(strategy$_{X/Y}$ has the lowest median duration of ventilation)

We construct new allocation probabilities beginning with defining

$$r_{X/Y} = \frac{\sqrt{M_{X/Y} SE(Median_{X/Y})}}{N_{X/Y}}$$

These $r_{X/Y}$ values are normalized to sum to 1. If, after renormalization, any value is under 5%, those values will be truncated to 0 and the remaining $r_{X/Y}$ values renormalized. This process results in the new allocation probabilities $p_{Supine/CMV}$, $p_{Prone/CMV}$, $p_{Supine/HFOV}$ and $p_{Prone/HFOV}$ that will be used until the next randomization update analysis. For example, if $p_{Supine/CMV}$=0, $p_{Prone/CMV}$=0, $p_{Supine/HFOV}$=0.4 and $p_{Prone/HFOV}$=0.6, this would indicate that the CMV arms have been temporarily eliminated from consideration for poor performance (allocation is 0), and that all subjects until the next randomization update analysis would be allocated with a probability of 40% for Supine/HFOV and 60% for Prone/HFOV. Balance among the age and lung injury strata will be maintained in the response adaptive randomization phase by the method in Saville and Berry.[87]

This formula is driven by the probability that each strategy has the lowest median. The square root results in moving the probability closer to equal randomization to limit the aggressiveness of the responsive adaptive randomization, and the standard error component acts to avoid strong imbalances in the data. This responsive adaptive randomization is hence quite conservative compared to others in the literature, maintaining closer to equal randomization unless the data strongly prefer one positioning strategy or one ventilation strategy.

### E.4 Consideration of Early Stopping of the Trial

The DSMB may elect to stop the trial if there are concerns regarding safety, low patient accrual, protocol performance/compliance, data quality, futility or efficacy. Early stopping rules for futility and efficacy are described below.

**Stopping Early for Futility:** Early stopping for *futility* will be considered at DSMB meetings after the 400$^{th}$ patient is randomized. At these times, in an intention-to-treat analysis of the primary outcome variable, we will calculate four Bayesian predictive probabilities at the

*maximum* sample size, namely that prone is declared superior to supine, that supine is declared superior to prone, that HFOV is declared superior to CMV and that CMV is declared superior to HFOV. If at any of these times, *all four* of these predictive probabilities are <10%, then we would stop the trial for futility. Effectively, even with the maximum number of subjects, there would be little possibility that any arm is identified as better than any other arm.

**Stopping Early for Efficacy:** Early stopping for *efficacy* will be considered at DSMB meetings after the 400$^{th}$ patient is randomized. At these times, in an intention-to-treat analysis of the primary outcome variable, we will calculate these same four Bayesian predictive probabilities but at the *current* sample size. If at any of these times, *any* of these predictive probabilities are >95%, then we would consider stopping some or all of the arms for efficacy. If the Bayesian predictive probability that prone is declared superior to supine (or else the reverse) is >95%, then we would declare prone (or else supine) as the better positioning strategy and stop randomizing prone vs. supine. However, it would still be important to evaluate comparisons between HFOV and CMV. If the *other* Bayesian predictive probabilities (that HFOV is declared superior to CMV, or else the reverse) are both <50% and do not increase by more than 10% from the current sample size to the maximum sample size, we would stop study accrual for efficacy of prone (or else supine) positioning but for futility of HFOV vs. CMV strategies, follow all previously randomized subjects for their outcomes and then stop. Otherwise, we would continue to randomize patients to HFOV vs. CMV using the better positioning strategy. An analogous plan would be implemented if the Bayesian predictive probability that HFOV is declared superior to CMV (or else the reverse) is >95%.

### E.5 Statistical Analyses

**Analysis of the Primary Outcome:** The primary outcome for this study is ventilator-free days (VFD) through day 28, which is the inverse equivalent of the 28-day hospital mortality-adjusted duration of mechanical ventilation. In practice, we will model this inverse equivalent (e.g., 28 – VFD). There are two primary outcome analyses, one for positioning strategy and one for ventilation strategy. For positioning strategy, analysis of the primary outcome will be performed on an intention-to-treat basis using proportional hazards regression models adjusting for ventilation strategy. Similarly, for ventilation strategy, analysis of the primary outcome will be performed on an intention-to-treat basis using proportional hazards regression models adjusting for positioning strategy.

At the conclusion of the trial, we will report descriptive statistics on VFD and 28-day hospital mortality-adjusted duration of mechanical ventilation in supine vs. prone positioning subjects and CMV vs. HFOV subjects with 95% credible intervals for medians and for pairwise differences in medians. We will also report the probability that each therapy offers the highest and lowest medians. We will also make graphical comparisons using boxplots and Kaplan-Meier survival curves.

We will also evaluate possible interaction effects between the positioning and ventilation strategies, which will allow us to probe for potential differential effects when these two strategies are used concurrently. Although we may have low power to detect possible effect modification between positioning and ventilation strategies, we will explore for them using interaction terms in regression models. If a significant interaction is found, a separate analysis will be conducted comparing all four combination strategies separately.

Analysis of the primary outcome will also be performed on a per-protocol basis. In addition, we will explore adjustment for age group (<1; 1-7; 8-17 years) and lung injury type (direct; indirect).

**Analysis of the Secondary Outcome:** Similar to the analysis of the primary outcome, analysis of the secondary outcome, nonpulmonary organ failure-free days, will also use proportional

hazards regression models. This analysis will be performed on a per-protocol basis and will control for age group and lung injury type.

**Analysis of the Exploratory Outcomes:** Analyses of exploratory outcomes will use logistic regression for binary outcomes (90-day in-hospital mortality), proportional hazards regression for time to event outcomes (durations of mechanical ventilation, PICU stay and hospital stay among survivors) and linear regression for continuous outcomes. For non-normal continuous outcomes, data transformations or nonparametric methods will be considered, as appropriate. These analyses will be performed on a per-protocol basis and will control for age group and lung injury type.

We will use appropriate methods for longitudinal outcomes, including random effects models or generalized estimating equations, to model repeated measures outcomes from the follow-up study, including PCPC, POPC, FSS and PedsQL scores.

Descriptive statistics will be calculated, including means, standard deviations, medians, interquartile ranges and ranges for continuous variables and frequency counts and percentages for categorical variables. Data will be examined for skewness, outliers and systematic missing data. Throughout, residual analyses and model fit assessments will be performed to assess the appropriateness of modeling assumptions and check for outlying or overly influential observations.

Other differences between treatment groups will be considered statistically significant if the two-tailed p-value is <0.05. Careful assessment of the results from exploratory analyses will be made, though no formal multiple comparisons procedures are planned. Data analyses will be performed using SAS® (Version 9.4, SAS Institute, Inc., Cary, NC) or similar statistical packages.

**Additional Analyses:** PARDS is a complex disease having many causes and, among PARDS patients, responses to any intervention may be heterogeneous. The net benefit for an individual patient likely depends on the amount of potentially recruitable lung. Thus, we will perform a post-hoc analysis of responders, defined as patients who exhibit an increase in $PaO_2/FiO_2$ ratio of at least 20 or a decrease in oxygenation index [OI = ($FiO_2$ × mean airway pressure × 100)/$PaO_2$] of at least 10% within 24 hours of starting an intervention. In addition, we will tabulate the number of subjects who switch to the reciprocal therapy (i.e., treatment failures),

We will also examine for time trends on outcome measures or treatment group effects (due to seasonal variation or learning effects) for primary or secondary outcome measures. If necessary, we will adjust for time in regression models. We do not expect effects of sex/gender or racial/ethnic group on outcome variables or treatment group differences, but we will carefully examine for them. We will perform stratified analyses in subgroups and assess statistical interactions in the total sample. If necessary, we will present sex- and/or race-specific results. We will assess whether adjustment for site through the use of mixed effects or generalized estimating equations models or for region (e.g., North America, Europe, Australia, southeast Asia) through the use of fixed effects affects study inferences. We will also assess whether varying levels of protocol compliance result in varying levels of intervention effects using regression methods.

### E.6 Sample Size Justification

We base our sample size calculations on patient data from the *RESTORE* trial. Of 2,449 *RESTORE* patients, 712 patients met *PROSpect* eligibility criteria (severe PARDS with bilateral disease by the fourth day of intubation, not intubated for asthma/reactive airways disease or bronchopulmonary dysplasia and not supported on extracorporeal membrane oxygenation). The

mean VFD for these 712 patients was 16.0 days with 14.2% patients assigned zero VFD (died or still intubated by day 28). We powered for a clinically meaningful 2-day improvement in VFD[15] by either intervention alone (i.e., the other intervention had no effect; Scenario 1) or a 4-day improvement (e.g., 2-day improvement for each intervention when both interventions showed a 2-day improvement; Scenario 2).

We shifted the data from these 712 patients, creating two new datasets from which to sample patients during simulations. First, we reduced the percentage of patients assigned zero VFD to 12.1% and increased the VFD for other patients to create a new dataset with mean VFD of 18.0 (2-day improvement). Second, we reduced the percentage of patients assigned zero VFD to 10.0% and increased the VFD for other patients to create a new dataset with mean VFD of 20.0 (4-day improvement). In Scenario 1, where there is a 2-day improvement in VFD by one intervention alone (e.g., prone) and the other intervention had no effect (e.g., HFOV), we sampled from the original dataset (for the supine/CMV and supine/HFOV groups) and the first new dataset (for the prone/CMV and prone/HFOV groups). In Scenario 2, where there is a 2-day improvement in VFD by each intervention, we sampled from the original dataset (for the supine/CMV group), the first new dataset (for the prone/CMV and supine/HFOV groups) and the second new dataset (for the prone/HFOV group).

Based on 1,000 total patients with fixed randomization (250 per group), simulation results (based on 10,000 simulations) estimate that we would have approximately 91% power for Scenario 1 and 93% power for each intervention for Scenario 2. Using response-adaptive randomization, we would obtain similar power to fixed randomization, specifically 90% for Scenario 1 and 93% power for each intervention for Scenario 2. However, with response-adaptive randomization we would expect to allocate more study patients to the superior intervention (or interventions). For example, for Scenario 1, we estimate that approximately 60% patients would be assigned to the more efficacious treatment (mean 593 patients, range 531-660, based on 10,000 simulations and no early stopping) and approximately 40% to the less efficacious treatment (mean 407, range 340-469). When the interventions have the same mean VFD, the mean sample size would be 500 per treatment (either positioning or ventilator strategies, range 435-565 for both).

The sample size chosen has power over 90% to detect a combined difference of 2% on mortality and an average gain of 2 days VFD in the survivor population.

### E.7 Dissemination Plan and Data Archiving

The results of this clinical trial will be critically important to disseminate to critical care clinicians, both pediatric and adult. The *PROSpect* Publications and Presentations Committee will develop a strategic plan for the comprehensive dissemination of the study findings. Together, the Principal Investigators will work expeditiously to submit the primary paper within 6 months of the last subject providing primary outcome data. Major secondary papers will also be completed within the following 2 years. Abstracts, papers for presentation and podcasts will be targeted for the annual meetings of American Thoracic Society (ATS), Critical Care Medicine (CCM) and the American Association of Critical Care Nurses (AACN) and the biennial meeting of the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS). Members of the *PROSpect* Integration Committee will provide the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) network, the Australian and New Zealand Intensive Care Society (ANZICS), the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) and the Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN) updates on the clinical trial yearly to maintain disciplinary interest in the study. It is anticipated that the results of this study will impact the professional training of numerous disciplines and will inform clinicians on the long-term outcomes of severe PARDS survivors. In addition to several primary publications

targeted for simultaneous presentation and publication in high impact journals, we anticipate numerous secondary publications as well.

Per NHLBI policy, we will provide a deidentified dataset and all the data-related documentation necessary to utilize the study data (dictionary, calculated variables and standard operating procedures) to the NHLBI no later than 3 years after the final follow-up interview or 2 years after the primary paper has been published, whichever comes first. We will submit this dataset to the NHLBI Data Repository managed by the BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center). In addition, analyses of the primary, secondary and pre-specified exploratory outcomes will be reported on ClinicalTrials.gov.

## F. DATA MANAGEMENT AND QUALITY CONTROL

The *PROSpect* DCC and will manage all data for the study, including post-discharge data.

### F.1 Development of Electronic Case Report Forms (eCRFs) and Manual of Operations (eMOO)

The *PROSpect* DCC will collaborate with the CCC in electronic case report form (eCRF) and manual of operations (eMOO) development to ensure the highest possible data quality. Forms design features include the selection of valid, reliable measurements that are least burdensome, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open-ended questions) and smooth flow in question patterns to reduce missing data. The detailed eMOO will ensure efficient and accurate data collection and ease of communication and its web-based format will allow updating as needed. Members of the Executive Committee will sign off on eCRFs and the eMOO before implementation.

### F.2 Data Management System

The DCC will develop a web-based data management system (DMS) for *PROSpect* using the InForm™ electronic data capture system (Version 6.1, Oracle Health Sciences, Redwood Shores, CA) with access via a secure website at www.prospect-network.org. According to programmed workflow logic, the DMS will generate eCRFs as needed for each patient (e.g., daily forms, study discharge form). The DMS will accommodate use of both US and non-US measurement units (e.g., glucose values could be entered in mg/dL or mmol/L). The DMS allows for the data to be viewed in real-time by the DCC staff and certified data entry personnel at the clinical sites. Many logic and range checks and cross-form validations will be programmed to ensure data quality. Automated queries will be generated as data are entered and the DCC Data Managers and Biostatistician will also generate queries as they review data. The system supports source data verification and maintains a complete audit trail of transactions to ensure data integrity and regulatory compliance. Furthermore, the DMS provides staff with a variety of reports to assist project management and study data may be readily exported for use in Microsoft Excel®, SAS® or other software.

The DCC will be supported by the Boston Children's Hospital Clinical Research Information Technology team, who have supported more than 25 clinical trials that used InForm™ and who will help the DCC with database releases, upgrades and troubleshooting.

### F.3 Data Coordination

The InForm™ DMS includes standard reports about enrollment and queries and custom reports can be easily programmed. The DCC will provide weekly reports to the PIs about enrollment, consent rates and adverse events. The DCC will also provide monthly reports to site co-

investigators regarding data entry accuracy and timeliness and query resolution. The DCC will have two full-time Data Managers available to assist site personnel on all DMS-related issues during the data collection phase.

### F.4 Data Entry, Editing and Audit Trails

All clinical data will be entered into the InForm™ DMS by certified clinical site personnel to ensure accurate record keeping. The DMS data capture screens closely resemble the appearance of a paper CRF. The DMS allows data entry personnel to easily view which eCRFs are complete, incomplete with missing required fields highlighted or incomplete with open queries. Context-specific help and logic and range checks reduce the number of errors and assist the data entry process. As data are being entered, the DMS generates queries about out-of-range or illogical values. The query may give the range of valid responses or reference responses to other related questions that make the current entry invalid. In addition, the Data Managers or Biostatistician may issue queries as they review data. In response to a query, the system user may confirm an out-of-range value, correct a data entry error or temporarily bypass the error and continue with data entry. The DMS contains a complete audit trail of all original values and all edits.

### F.5 Data Confidentiality, Security and Back-up

To ensure data safety and reliability, server back-up procedures will be executed daily to back up all electronic study-related materials, which include the database, Word® documents, statistical programs and files. Access to the DMS requires user authentication. Authorized users include the DCC staff and certified data entry personnel at each site. Identifiable patient data, such as contact information and medical record numbers, will not be tracked in the DMS. A Patient Study ID paper log containing the Patient Study ID Number, patient initials and the last 3 digits of the Medical Record Number (MRN) will be stored separately and securely at the clinical sites and will not be shared with the DCC.

### F.6 Firewalls

All DCC application software and data are hosted securely on the BCH network. The BCH network is protected by several firewalls and security is monitored and audited regularly by the BCH Information Services Department (ISD). All application and database software will enforce access rules through user authentication and authorization schemes established by the DCC and ISD. The DCC will ensure that no data are compromised or shared inappropriately by maintaining strict security procedures between personnel, data and all other study investigators. For example, Drs. Curley, Cheifetz and Kneyber and their research staffs will have limited access to status reports within the database and they will be unable to view or change any of the study participant data, except at their own study sites (for Drs. Cheifetz and Kneyber).

### F.7 Study Monitoring

**Remote Site Monitoring:** The DCC will coordinate the remote site monitoring process, and the CCC advanced practice pediatric critical care nurse will serve as the study monitor. If an international site's medical record system is in a foreign language, a bilingual registered nurse not affiliated with the study will be recruited to serve as an unbiased assistant to the study monitor. Remote site monitoring sessions will commence after a site enrolls their third subject and will occur at least yearly or more frequently if performance thresholds are of concern to either the Executive Committee or DSMB. Specific triggers for additional site monitoring may include variation in site performance metrics, variation in reporting of *PROSpect*-specified events or the occurrence of an unanticipated problem. In addition, international sites will

demonstrate competence in the International Conference on Harmonisation's Guideline for Good Clinical Practice (ICH-GCP) standards by remote site monitoring.

Prior to a remote site monitoring session, study sites will complete a Site Self-Assessment Checklist, which includes verifying the accuracy, completeness and security of regulatory documents, study logs and informed consent documents. Next, the study monitor will conduct the remote monitoring process using a data-encrypted web conferencing system to review patient-specific data. The monitor will compare the source documentation to a printout of patient-specific data downloaded from the InForm database by the DCC. Via remote monitoring, the primary outcome will be 100% source verified on all subjects. A random selection of data elements on a subset of subjects will also be also source verified, including inclusion/exclusion criteria, secondary and exploratory outcomes and adverse events. An attempt will be made to schedule remote site monitoring sessions for when a *PROSpect* subjects is on study so that the study monitor can audit, in real-time, positional and ventilation practices/protocol adherence.

A report is generated after completion of the remote monitoring review. Members of the Steering Committee will review these reports. The site co-investigators are responsible for correcting deficiencies, if any, to the satisfaction of the Steering Committee.

**Support for Study Safety Monitoring:** Subjects will be monitored daily for the occurrence of events defined as any undesirable experience or unanticipated benefit. A description of all adverse events will be recorded in the study database. The relationship of the *PROSpect* protocol to the event will be classified as not, remotely, possibly, probably or highly probably related by the bedside team. The severity of an adverse event will be classified as mild, moderate or severe by the bedside team. All study-related serious adverse events (SAE) and unanticipated problems (UP) will be reported within 24 hours to Dr. Curley (or the PI on call), the CCC and the DCC. The site co-investigator, CCC and DCC will work together to prepare a detailed description of the SAE/UP, an explanation of the basis for determining that the event presents a SAE/UP and a description of any corrective actions that are proposed in response to the SAE/UP. Within 72 hours, the DCC will send the full narrative report to the DSMB Chair and NHLBI Executive Secretary. The CCC will report the SAE/UP to the University of Pennsylvania IRB and to each international clinical center for submission to their IRB. Recommended protocol modifications will be implemented immediately. Non-serious events will be submitted to the DSMB and NHLBI on a schedule determined by the DSMB.

### F.8 Data Management for the Follow-up Procedures

For the follow-up procedures, the DCC will assist the CCC in developing two web-based databases that are separate from the InForm clinical database. These databases will be housed at the University of Pennsylvania-based CCC. The first database, built in Qualtrics, will be used to collect contact information for subjects and their families. Once contact information data collection and entry has started, the DCC will no longer have access to this database. The second database, built in REDCap, will be used to collect follow-up data on functional status and health-related quality of life. The DCC will continue to be able to access this database and will monitor and analyze these follow-up data.

The DCC will closely monitor follow-up rates. The Data Manager will generate monthly reports to track the number of contact attempts and follow-up interviews and will create data-driven benchmarks to identify monthly follow-up goals and progress towards reaching these goals. Also on a monthly basis, the DCC will clean the follow-up data and issue queries to the CCC. Upon the completion of follow-up data collection, the DCC Biostatistician will export necessary follow-up data to address specific needs of the proposed analyses. These data will be merged with the main study data as needed to perform any additional analyses.

### F.9 Strategies to Optimize Enrollment and Protocol Adherence

We will implement the following activities to optimize enrollment and protocol adherence:

1. Understanding local practices and structure: Site co-investigators will complete an Organizational Assessment yearly to identify all research team members and *PROSpect* Champions and delineate their roles and responsibilities, levels of expertise, communication expectations and readiness for training. Sections include information on the hospital, unit, medical staff, nursing staff, respiratory therapy staff, unit-based practices, routine competency testing and quality metrics.
2. Training tool-box: The CCC will take the lead in developing a tool-box of training materials that will include discipline-specific voice-over slide sets, positioning and ventilation videos, self-learning packets, post-tests, pocket cards and bedside research binders. All study tools will contain the *PROSpect* Logo but accommodate local individualization to facilitate unit-based adoption.
3. Train-the-trainer methodology and certification: All site co-investigators will be required to undergo a competency-based training program and certification process. The site co-investigators will then train all clinicians (physicians, nurses, respiratory therapists [if utilized]) involved in the clinical management of intubated, mechanically ventilated patients. In addition to the core physician-nurse-RT team, each PICU will identify additional multidisciplinary "Champions" to serve as unit-based resources on *PROSpect* protocols. This Champion team will allow clinical staff access to a *PROSpect* expert 24/7 and will also accommodate the monthly training schedules of new staff/orientees. Prior to caring for a study patient, clinical staff must complete a self-learning packet by passing a scenario-based post-test. Any subject cared for by a non-certified clinician will be considered a protocol deviation. If this occurs, an improvement plan will be required prior to enrolling a subsequent subject.
4. Project management training: Training will be coordinated with the DCC who will be responsible for certifying all research assistants in study-related activities that include screening and data management. The Principal Investigators will train site co-investigators in best-practices in obtaining informed consent.[85,88]
5. Web-based electronic manual of operations (eMOO): The CCC and DCC will develop and maintain an eMOO that will include all study materials: study protocols, Standard Operating Procedures (SOP) for screening, consenting, enrolling subjects, electronic Case Report Forms (eCRFs), form completion guidelines, training materials, Q&A bank, quality control (QC) tools and reports.
6. Virtual start-up meetings: Prior to enrolling subjects, all sites will participate in a start-up virtual call with the CCC-DCC teams to verify the completion of all regulatory, training and study coverage requirements.
7. Monthly Steering Committee (SC) calls: These monthly calls will be held to review clinical and administrative issues and study metrics.
8. Audit and feedback (study metrics):
    - We will prospectively monitor <u>treatment fidelity</u> by embedding an auditing function into eCRFs and implementing daily *PROSpect* walk rounds. During the *PROSpect* walk rounds the site co-investigator or *PROSpect* Champion will provide bedside clinicians with real-time protocol support and log the extent to which *PROSpect* protocols are implemented as designed (if not implemented, capturing the rationale: e.g., training issue, concerns about patient safety). These data will be summarized monthly and these reports will constitute a standing agenda item on our SC calls. We will pair high and low adherent sites to allow cross-PICU learning. We will also implement random remote site monitoring when subjects are on study to audit, in real time, protocol adherence.

- Our weekly enrollment reports (site and total) will include: (1) screening and enrollment; (2) enrollment rate; (3) summary of reasons eligible patients were not enrolled (ENE); (4) parent/legal guardian consent rate; (5) language involved in failure to consent issues; (6) hours the parent/legal guardian were unavailable (physically or emotionally) to consent; (7) enrollment graph plotting number of subjects enrolled over our 4-year enrollment period.
- Our weekly safety reports will include (1) pre-specified events; (2) tracer events (e.g., documented episodes of $FiO_2$ 1.0); (3) unanticipated events; and (4) protocol deviations.
- Monthly data quality reports will include timely data entry, accurate data entry (per form completion guidelines), open queries, time to resolution of open queries and usable subjects.
- We will conduct dashboard calls with each enrolling PICU after 3 subjects are enrolled and once/year thereafter. The calls will review all site metrics identifying strengths and opportunities for improvement.

## Protection of Human Subjects

This is an NIH-Defined Phase III Clinical Trial.

### 1. Risks to Human Subjects

#### a. *Human Subjects Involvement and Characteristics, and Design*

***PROSpect*** (**PR**one and **OS**cillation **PE**diatric **C**linical **T**rial) is a two-by-two factorial, response-adaptive, randomized controlled clinical trial of supine positioning/prone positioning and conventional mechanical ventilation (CMV)/high-frequency oscillatory ventilation (HFOV) in children with *severe* Pediatric Acute Respiratory Distress Syndrome (PARDS). Our primary outcome is ventilator-free days (VFD), where non-survivors receive zero VFD. We hypothesize that children with severe PARDS treated with either prone positioning or HFOV will demonstrate ≥2 more VFD. Improvement in VFD will be considered within the context of patient safety; specifically, patients must also exhibit a similar safety profile. Our secondary outcome is nonpulmonary organ failure-free days. We will also explore the interaction effects of prone positioning with HFOV on VFD and also investigate the impact of these interventions on 90-day in-hospital mortality and, among survivors, the duration of mechanical ventilation, PICU and hospital length of stay and post-PICU functional status and health-related quality of life (HRQL).

Approximately 50 pediatric intensive care units (PICUs), about 2/3 U.S. and 1/3 international, with at least 5 years of experience with prone positioning and HFOV in the care of pediatric patients with severe PARDS, that can provide back-up extracorporeal membrane oxygenation (ECMO) support will participate. Approximately 50 PICUs will enroll up to 1,000 pediatric patients (≥2 weeks of age and ≥42 weeks post gestational age and <18 years of age) intubated and mechanically ventilated with severe PARDS for <48 hours per Pediatric Acute Lung Injury Consensus Conference Group (PALICC) guidelines, that is, chest imaging consistent with acute pulmonary parenchymal disease and oxygenation index (OI) ≥16 or oxygenation saturation index (OSI) ≥12.3. We will require two consecutive blood gases meeting severe PARDS criteria (separated by at least 4 hours during which time the clinical team is working to recruit lung volume and optimize the patient's hemodynamic status per PALICC guidelines). Exclusion criteria focus on patients in whom the length of mechanical ventilation is unlikely to be altered by positional or ventilation management and in those for whom prone positioning or HFOV is contraindicated. The clinical sites are all PICUs who normally manage patients with PARDS within this age group and are specifically trained in the clinical, including ventilatory, management of critically ill infants, children and adolescents.

Eligible patients with severe PARDS will be randomized within 48 hours of meeting eligibility criteria and within 4 days of endotracheal intubation to one of four groups: supine/CMV, prone/CMV, supine/HFOV or prone/HFOV. Subjects who fail their assigned positional and/or ventilation therapy for either persistent hypoxia or hypercapnia may receive the reciprocal therapy while being considered for ECMO cannulation. Randomization will be stratified by age group (<1; 1-8; 8-17 years) and direct/indirect lung injury. Adaptive randomization will begin after 400 patients are randomized. After the 400$^{th}$ patient has been randomized and every 100 patients thereafter, new allocation probabilities will be computed based on ongoing intention-to-treat trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. *PROSpect* may close enrollment early for efficacy or futility based on pre-specified stopping rules. Data will be analyzed per intention-to-treat for the primary analyses and per-protocol received.

Enrolled subjects will be followed from endotracheal intubation until hospital discharge or hospital Day 90, whichever occurs first. Approximately two weeks post-PICU discharge, the Clinical Coordinating Center (CCC) will call or email the family and confirm their preferred method of communication for their follow-up contacts. Options include phone interview plus completion of instruments online or by paper mail. At 1, 3, 6 and 12 months after PICU discharge, we will contact the family to complete the follow-up interview, scheduled at their convenience, to assess the subject's functional status and HRQL. All U.S. parents/legal guardians will be invited to participate as well as cognitively capable (Pediatric Cerebral Performance Category ≤3) subjects ≥8 years of age. All interviews will be coordinated and conducted by trained personnel from the CCC at the University of Pennsylvania.

**b. *Sources of Materials***

Sources of research material will include: (1) subject's medical record, (2) arterial blood samples for blood gas analysis, (3) blood samples for bio-banking, (4) family contact information and (5) follow-up interviews with parents/legal guardians and with cognitively capable children ≥8 years of age to assess functional status and HRQL.

Site co-investigators (or their designee) will be trained by the Data Coordinating Center (DCC) to collect data using electronic study case report forms (eCRF). A web-based electronic Manual of Operations (eMOO) describing Standard Operating Procedures (SOP) for data collection will be prepared to ensure consistent decision-making across centers.

Each site will maintain an enrollment log that will link each patient to a unique study number. All data collection forms will contain this unique study number. Enrollment logs will be maintained by the site in a locked filing cabinet in a locked office accessible to study staff only. All data received at the DCC in Boston will be de-identified. All family contact data received at the CCC in Philadelphia for subject follow-up will be entered into a Qualtrics database that is separate from the DCC database. Only Dr. Curley and her CCC team will have access to individually identifiable private information about human subjects.

The follow-up data will only be collected with parental/legal guardian consent and, if applicable, subject assent and consent from subjects turning 18 after PICU hospitalization. All subject data will be maintained with strict privacy measures. Online surveys and surveys completed over the telephone will be entered directly into a REDCap database. Paper surveys will be returned via a dedicated secure fax machine or by certified U.S. Mail. All data will be secured for the purpose of confidentiality, and these data will only be used for research purposes.

**c. *Potential Risks***

Potential risks associated with prone positioning include unplanned extubation or vascular line/invasive tube removal, plugging/obstruction of the endotracheal tube with secretions and/or

blood, main-stem bronchus intubation, transient hemodynamic instability or cardiac dysrhythmias related to patient turning, hypercarbia (unresponsive to ventilation protocols), clinically significant agitation (SBS +1/+2 for 2 consecutive hours), facial and eyelid edema, pressure injury (any dependent surface) or corneal abrasions.

Potential risks associated with the ventilation protocols include hemodynamic instability related to increased mean airway pressure, airleak (e.g., pneumothorax, pneumomediastinum), cardiac dysrhythmias related to increased mean airway pressure, mucous plugging / airway obstruction, clinically significant agitation (SBS +1/+2 for 2 consecutive hours), pressure injury (occipital or auricular).

In all groups, potential subject risk also includes blood loss associated with the blood draws. There are no expected risks associated with the follow-up study aside from the time burden and potential psychological stress imposed on the subjects and their families by the questionnaires and the structured telephone interviews. We anticipate that each interview will be completed in approximately 20 minutes. The other important risks associated are related to potential loss or release of confidential information. Each consenting parent will provide identifying and contact information, allow review of his/her child's hospital records and provide information about his/her child's health status, functional status and health-related quality of life. These risks, and the steps enacted to protect against these risks, will be specified in the parental/legal guardian consent forms, all of which will be HIPAA-compliant.

**2. Adequacy of Protection Against Risks**

**a. *Recruitment and Informed Consent***

Site co-investigators or their designee will screen their PICUs for potential subjects each day using the patient screening logs without identifying data. After verification that a patient meets eligibility criteria, the child's gender and ethnic background recorded in the medical record will be entered into the electronic screening form. This Health Insurance Portability and Accountability Act (HIPAA)-compliant database will also provide the registry of potentially eligible patients to determine whether a representative number of minorities and females have been enrolled in the study. Patients who meet study criteria but who do not consent to participate will be noted. Patient eligibility for enrollment will be determined after a complete review of the patient's demographic and clinical information. We will maintain a log of all non-enrolled patients (without identifying information) with rationale for non-enrollment (exclusion criteria, physician denial, etc.).

After verifying the patient's eligibility status with the patient's attending physician, the parent or legal guardian will be introduced to the site co-investigator or their designee by a member of the clinical team. The site co-investigator will provide information about the study and alternatives to participating in the study. Parents and legal guardians will be given ample opportunity to carefully consider study participation and read the informed consent document.

Given the criticality of the potential subject's condition, the investigator will work closely with the clinical care team to approach the parents or legal guardian(s) at a time that would not significantly overburden them. All consents will be obtained in writing. If a parent/legal guardian refuses consent, their management will be provided at the discretion of the bedside team. All subjects will be intubated, mechanically ventilated and sedated so will be unable to provide assent while acutely ill. Prior to hospital discharge, children ≥8 years of age who are cognitive capable will be asked to provide assent for follow-up using age-appropriate assent/consent forms (8-12 years; 13-17 years; 18+ after hospital discharge). If children do not assent to the study, they will not participate in follow-up. Subjects and their parents have a right to discontinue their participation in the study at any time and for any reason.

The decision to withdraw a subject from the study may be made for a variety of reasons including the request of the care team, patient or family, events related to or not related to the study or continued deterioration of the subject's clinical condition. The site co-investigator will record the primary reason for withdrawal. Every attempt will be made to continue data collection through Day 90 providing that the family/patient concurs with continued data collection.

All sites will undergo rigorous training in the administration of informed consent prior to enrollment. Site co-investigators and their designees will complete competency assessments in study procedures, randomization and human subject protections. International sites will demonstrate competence in ICH-GCP standards by remote site monitoring.

**b. *Protections Against Risk***

Risks associated with prone positioning will be minimized by strict adherence to the research protocol that is based on our previous prone positioning study. Risks associated with ventilation management will be minimized by strict adherence to the research protocol which is based on the PALICC guidelines.

We require that each enrolling site have at least 5 years of experience with both prone positioning and HFOV and have back-up extracorporeal membrane oxygenation (ECMO) support. Including only experienced centers augments patient safety. Requiring PICUs to have ECMO backup optimizes patient safety since all enrolled subjects will have severe PARDS and would not easily tolerate an inter-hospital transport for ECMO if study interventions failed.

Adaptive randomization will begin after 400 patients are randomized. After the 400$^{th}$ patient has been randomized and every 100 patients thereafter, new allocation probabilities will be computed based on ongoing intention-to-treat trial results, increasing allocation to well performing arms and decreasing allocation to poorly performing arms. With response adaptive randomization we expect to allocate more study patients to the superior intervention or interventions.

The total blood loss from all clinical and research-related activities will be monitored and kept below age/size dependent thresholds. All blood specimens will be obtained through existing vascular catheters or from wasted blood specimens.

Coding all subject data with a unique identification number will minimize risk to loss of subject confidentiality. Each site's enrollment log, linking Study ID Number to patient identity, will remain with the site co-investigators in a locked file in a locked office, accessible to study staff only. The eCRFs will not contain any personal identifying information, and all information received by the DCC will have no identifiable patient data. Web-based data collection will be protected by stringent authentication and authorization procedures. Users must have valid login credentials (authentication), database access privileges and specific permissions within the database (authorization). Authentication and authorization can only be granted and revoked by authorized system administrators within the DCC. All components within the system are tested on a regular basis by Boston Children's Hospital Information Services Department. Transaction logs are backed up daily and full back ups are performed weekly on all databases.

The CCC employs procedures to protect against the risk of unwanted loss or release of confidential follow-up information. Subject-specific data and completed mailed and telephone questionnaire data will be made available only to Dr. Curley and the CCC research staff. The only dataset with subject identifier information will be the subject tracking system used to follow-up and contact families. All other datasets will label subject records with a unique study number; specifically, clinical data will not reside with identifying data. Questionnaire data will be kept in locked files and/or password-protected data files.

We will prospectively monitor all specified events and the Principal Investigators will review their occurrence rates to determine whether there are any trends. Clinical aspects of care related to the prevention of iatrogenic injury, when identified, will immediately inform the care provided to patients enrolled into the study.

At the end of the telephone interview, parents and legal guardians will be specifically asked if they would like to have further conversations with their child's primary intensive care physician. If they would, then they will be provided with the phone number of the ICU physician's office, and CCC staff will also notify the site co-investigator directly that a subject or subject's family member desires additional contact. Risks associated with the study will be monitored by the Executive Committee, Steering Committee and Data and Safety Monitoring Board. Any publication arising from this study will maintain the anonymity of study participants.

**3. Potential Benefits of the Proposed Research to Human Subjects and Others**

Potential benefits to the critically ill subjects with severe PARDS include an improvement in ventilator-free days and/or nonpulmonary organ failure-free days. We anticipate no direct benefits to most subjects and their families who participate in the follow-up study, although some may benefit from the contact provided during telephone interviews.

Society in general and future critically ill children and their families will benefit, however, from the study's results, which will provide a better understanding of how positional and ventilation strategies can best be administered to critically ill children with severe PARDS. Potential benefits may outweigh potential risks.

**4. Importance of the Knowledge to be Gained**

Critical illness among children is a significant health problem because of a generally long life expectancy, any impairment in a child can have consequences that last for decades. These consequences are extremely important for the individual. However, the consequences may also impact society at large in terms of cost to provide prolonged medical services and lost work productivity.

This study will help provide a definite answer to the role of prone positioning and HFOV for children with severe PARDS. First, this would be the first large-scale, multi-center, multi-national randomized controlled trial of interventions designed to improve clinical outcomes for severe PARDS. The global nature of this investigation will improve international implementation of the outcomes. Second, the protocol is physiology-based in terms of the use of prone positioning as well as the management of HFOV. Testing these interventions will establish a standard of care that will influence the care of the vast majority of pediatric patients supported on mechanical ventilation, future studies evaluating new or different combinations of sedative agents and clinican education.

**5. Data and Safety Monitoring Plan**

The CCC and DCC will work with the NHLBI to appoint an independent data and safety monitoring board (DSMB). The DSMB will be responsible for monitoring subject safety, implementation of the study protocol and reviewing the quality of study data. The DSMB will review, make recommendations and approve the final protocol and informed consent documents prior to implementation. The DSMB will review the progress of the trial, including assessments of participant risk versus benefit, data quality and timeliness, participant recruitment, accrual and retention, site performance and other factors that can affect study outcome. The DSMB chair will receive reports of all serious adverse events throughout the conduct of the study. If the DSMB recommends a study change for patient safety or ethical

reasons, the Principal Investigators will be responsible for implementing the recommendations as expeditiously as possible, according to standard NIH policies.

The DSMB may recommend that the trial be stopped if:

- The intervention is associated with an increased dependency on mechanical ventilation, increased mortality or increased adverse events.
- Compliance to the study protocol and/or recruitment is well below acceptable goals and the ability of the study to achieve its goals is seriously compromised.
- Evidence external to the study renders it unethical to continue the study.

All specified adverse events will be prospectively monitored and recorded on study eCRFs. All specified events will be reviewed monthly for trends by the Operations Committee then the Executive Committee. Clinical aspects of care related to the prevention of iatrogenic injury, when identified, will inform the care provided all patients via the Steering Committee. The reporting of each event will include a description of the event, required interventions, patient's condition after the event, an estimate of the extent of injury and prevention strategies. The relationship of the study protocol to the event will be classified by the bedside clinicians as follows:

- Not related: The event is clearly related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
- Remote: The event was most likely related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
- Possible: The event follows a reasonable temporal sequence from the implementation of study treatments and/or is consistent with known events related to the study treatments but is possibly related to factors such as the subject's clinical state.
- Probable: The event follows a reasonable temporal sequence from the implementation of study treatments and/or is consistent with known events related to the study treatments and cannot be reasonably explained by factors such as the subject's clinical state.
- Highly Probable: The event follows a reasonable temporal sequence from the implementation of study treatments and/or is consistent with known events related to the study treatments and cannot be reasonably explained by factors such as the subject's clinical state. In addition, the event occurs immediately following the titration of study treatments, or improves on changing study treatments, or reappears on repeat initiation of study treatments.

The severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the bedside clinicians as follows:

- Mild: Does not impact (in any way) the patient's course of illness.
- Moderate: Impacts the subject's course of illness but is not life-threatening or incapacitating.
- Severe: Fatal, life threatening, permanently disabling; severely incapacitating; requires/prolongs inpatient hospitalization.

Within 24 hours, site co-investigators must report all study-related serious adverse events (SAE) and unanticipated problems (UP) to Dr. Curley (or the MPI on call), the CCC and to the DCC. The CCC and DCC will work with the site co-investigator to prepare a detailed description of the

SAE/UP, an explanation of the basis for determining that the event presents a SAE/UP and a description of any corrective actions that are proposed in response to the SAE/UP. Within 72 hours of the SAE or UP, the DCC will send the full narrative report to the DSMB Chair and NHLBI Executive Secretary. The CCC will report the SAE/UP to the University of Pennsylvania IRB and to each international clinical center for submission to their IRB. Recommended protocol modifications will be implemented immediately.

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