PROTOCOL SUMMARY

Title: *PROSpect*: PRone and OScillation PEdiatric Clinical Trial

Phase: This is an NIH-Defined Phase III Clinical Trial.

Funding: 1 UG3 HL141736-01 and 1 U24 HL141723-01

Committees: Executive Committee, Advisory Committee, Data and Safety Monitoring Board, CCC-DCC Operations Committee, Integration Committee, Steering Committee, Associated Study Committee, Publications and Presentations Committee

Background and significance:
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. 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) in the management of these young patients. 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 of pediatric critical care.

Study aims: In children with severe PARDS:

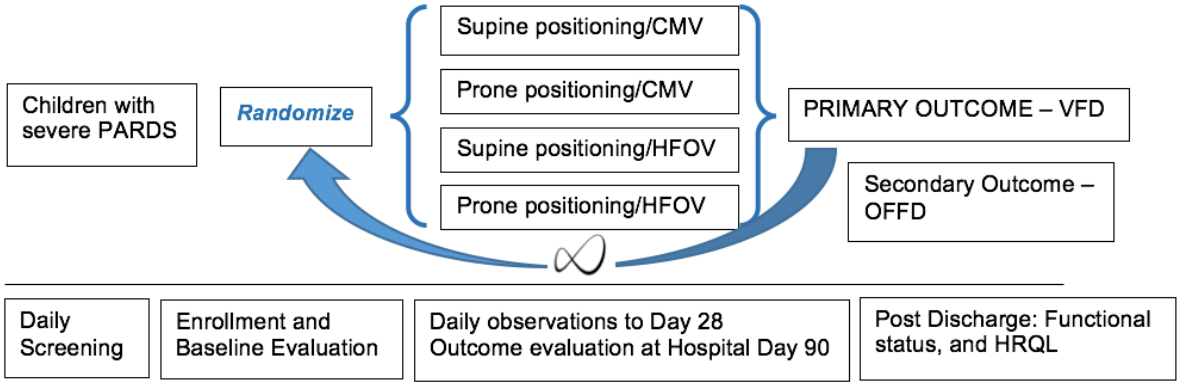
1. To compare the effects of prone positioning with supine positioning on ventilator-free days (VFD).
2. To compare the effects of HFOV with CMV on VFD.

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

Exploratory: To explore the interaction effects of prone positioning with HFOV on VFD and to investigate the impact of these interventions on 90-day in-hospital mortality and, among survivors, the duration of mechanical ventilation, pediatric intensive care unit (PICU) and hospital length of stay and trajectory of post-PICU functional status and health-related quality of life (HRQL).

Study design:
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 CMV versus HFOV exhibit more VFD over a 28-day period. Improvement in VFD will be considered within the context of patient safety; specifically, patients must also exhibit a similar safety profile.

Study scheme:



Study population: Critically ill pediatric patients with severe PARDS

Treatment groups: Patients 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. The Data Coordinating Center (DCC) will manage the randomization process centrally and will stratify enrollment by age group (<1; 1-7; 8-17 years) and direct/indirect lung injury.

- *Supine positioning*: Patients randomized to supine positioning will remain supine.
- *Prone positioning*: Patients randomized to receive prone positioning will be positioned prone ≥16 hours per day for a maximum duration of 28 days.
- *Conventional Mechanical Ventilation* (CMV): The CMV arm will use a ventilation strategy consistent with Pediatric Acute Lung Injury Consensus Conference Group (PALICC) recommendations. The strategy includes: (1) low tidal volume to obtain expired tidal volume (Vte) of 5-7 ml/kg (ideal body weight [IBW]); (2) Peak Inspiratory Pressure (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).
- *High Frequency Oscillatory Ventilation* (HFOV): The HFOV arm will use a ventilation strategy consistent with PALICC recommendations. For reproducibility across centers we will restrict the HFOV ventilator to the SensorMedics 3100A if patient weight <35 kg or SensorMedics 3100B if patient weight ≥35 kg. 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) of 60-90, a mPaw recruitment maneuver and a weaning strategy.
- *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 extracorporeal membrane oxygenation (ECMO) cannulation. Reciprocal treatments, when used, will be managed per *PROSpect* protocol. Subjects cannulated for ECMO will be discontinued from further study treatments and followed so that ventilator management can be described and for study outcomes.

Inclusion criteria:
- Pediatric patients ≥2 weeks of age (≥42 weeks post gestational age) and <18 years of age
- Intubated and mechanically ventilated with severe PARDS for <48 hours per PALICC guidelines (chest imaging consistent with acute pulmonary parenchymal disease and OI ≥16 or OSI ≥12.3). We require two consecutive blood gases meeting severe PARDS criteria (separated by at least 4 hours during which time the clinical team is actively working to recruit lung volume and optimize the patient's hemodynamic status per PALICC guidelines; specifically, incremental decremental PEEP changes to optimize lung volume. 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:
- 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 with FiO_2 <0.30 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
- Morbid 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

Study sample size: Up to 1,000 patients with severe PARDS randomized by age group and direct/indirect lung injury from approximately 50 PICUs, about 2/3 U.S. and 1/3 international.

Subject participation duration: 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).

Outcome measures:
Primary: VFD through day 28
Secondary: Nonpulmonary OFFD through Day 28
Exploratory:

- Interaction effects of prone positioning with HFOV on VFD
- 90-day in-hospital mortality
- Among survivors:
    - Duration of mechanical ventilation
    - PICU and hospital length of stay
    - Post hospital discharge functional status and health-related quality of life

Statistical issues:

Primary hypothesis: Children with severe PARDS treated with prone positioning or HFOV will demonstrate more VFD. We hypothesize that a superior treatment would improve VFD by at least 2 days, a clinically meaningful difference.

Sample size: Power calculations are based on data from the *RESTORE* trial. Of 2,449 *RESTORE* patients, 712 patients met *PROSpect* eligibility criteria. 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 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). 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.

Statistical analysis plan: 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. Analysis of the primary outcome will also be performed on a per-protocol basis, and we will explore adjustment for age group (<1, 1-7, 8-17 years) and lung injury type (direct; indirect). For analyses of secondary and exploratory outcomes, we will use logistic regression for binary outcomes, proportional hazards regression for time to event outcomes and linear regression for continuous outcomes to compare supine vs prone positioning subjects and CMV vs HFOV subjects. These analyses will be performed on a per-protocol basis and will control for age group and lung injury type.

Adaptive randomization will begin after 400 patients are randomized. After the 400th 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.