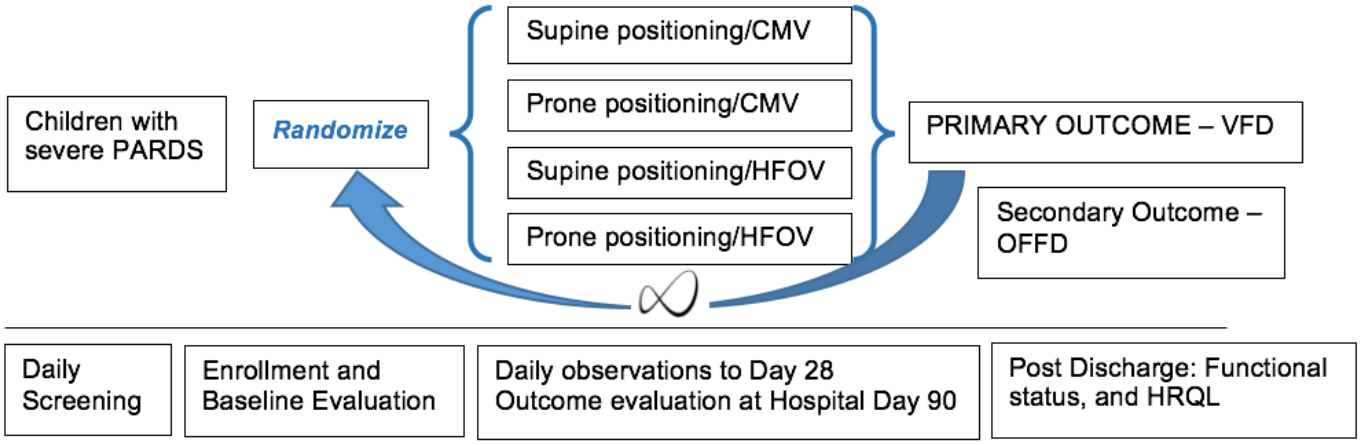
MV	Mechanical Ventilation
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NIRS	Near-infrared spectroscopy
NM_3	Philips NM3 monitor
NPUAP	National Pressure Injury Advisory Panel
NRS	Numeric Rating Scale
OFFD	Organ Failure-Free Days
OI	Oxygenation Index
OSCAR	OSCillation for ARDS
OSCILLATE	OSCILLation for ARDS Treated Early
OSI	Oxygen Saturation Index
PACCMAN	Pediatric Acute and Critical Care Medicine Asian Network
$PaCO_2$	Partial pressure of carbon dioxide
PALICC	Pediatric Acute Lung Injury Consensus Conference Group
PALISI	Pediatric Acute Lung Injury and Sepsis Investigator Network
PaO_2	Partial pressure of oxygen
PARDIE	Pediatric ARDS Incidence and Epidemiology
PARDS	Pediatric Acute Respiratory Distress Syndrome
pCAM-ICU	Pediatric Confusion Assessment Method for the Intensive Care Unit
PCPC	Pediatric Cerebral Performance Category
PCV	Pressure Control Ventilation
PedsQL	Pediatric Quality of Life Inventory
PEEP	Positive End-Expiratory Pressure
PELOD-2	PEdiatric Logistic Organ Dysfunction-2
PF ratio	PaO_2/FiO_2 ratio
pH	Potential of hydrogen
PICU	Pediatric Intensive Care Unit
PIP	Peak Inspiratory Pressure
POPC	Pediatric Overall Performance Category
Pplat	Pressure Plateau
PRISM IV	Pediatric Risk of Mortality IV
PROSEVA	Proning Severe ARDS Patients
PROSpect	PRone and OScillation PEdiatric Clinical Trial
PRVC	Pressure Regulated Volume Control
PS	Pressure Support
QC	Quality Control
RCT	Randomized Controlled Trial
RESTORE	Randomized Evaluation of Sedation Titration for Respiratory Failure
SAE	Serious Adverse Event
SBS	State Behavioral Scale
SC	Steering Committee
SIMV	Synchronized Intermittent Mandatory Ventilation
SOP	Standard Operating Procedures
SpO_2	Pulse oximeter oxygen saturation
UOP	Urine Output
UP	Unanticipated Problem
VFD	Ventilator-Free Days
VILI	Ventilator-Induced Lung Injury
V/Q	Ventilation Perfusion matching

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; 18-20 years) and direct/indirect lung injury. Adaptive randomization will first occur after 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. At these randomization update analyses, 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 for primary, secondary and exploratory analyses.

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; 18-20 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

- Open Abdomen
- Currently receiving either prone positioning or any high-frequency mode of MV with current illness (Up to 4 hours of prone positioning and/or any mode of high-frequency mode of MV is allowed as long as the therapies are off for least 4 hours prior to the subject meeting oxygenation criteria.)
- 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 interventional clinical trial not approved for co-enrollment
- 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:

- During the acute phase (OI ≥8), 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.
- Continuous 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 (OSI 7.5) in the supine position for at least 4 hours after the end of a prone session or (2) pattern of no effect 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, Stage 3 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 (Vt_e) 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

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 pressure supported breathing (BiPAP, CPAP ≥5 cm H_2O, or HHFNC ≥5 L/min) to the first time positive pressure 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 2-21 years; Infant Scales for subjects <2 years; http://www.pedsql.org) with associated modules (see table).[77,78] See section D.8 for information on the timing of assessments.

Measure	Domain*	Age Group	Number of Items / Time Required
Child			
PedsQL™ 4.0 Generic Core or Infant Scales (Acute version – per age) 1. Young adult (18-25 y) self-report, parent-report 2. Teen (13-18 y) self-report, parent-report 3. Child (8-12 y) self-report, parent-report 4. Young child (5-7 y) parent-report 5. Toddler (2-4 y) parent-report 6. Infant (13-24 m) parent-report 7. Infant (1-12 m) parent-report	Physical, Cognitive, Emotional, Social	1 m-21 y	23 items / <5 min 23 items 23 items 23 items 21 items 45 items / <10 min 36 items / <7min
PedsQL™ Multi-dimensional Fatigue Scale V3 (Acute version – per age) 1. Young adult (18-25 y) self-report, parent-report	Physical, Cognitive	2-21 y	18 items / <4 min

2. Teen (13-18 y) self-report, parent-report 3. Child (8-12 y) self-report, parent-report 4. Young child (5-7 y) parent-report 5. Toddler (2-4 y) parent-report			
PedsQL™ Cognitive Functioning Scale 1. Young adult (18-25 y) self-report, parent-report 2. Teen (13-18 y) self-report, parent-report 3. Child (8-12 y) self-report, parent-report 4. Young child (5-7 y) parent-report 5. Toddler (2-4 y) parent-report	Cognitive	2-21 y	6 items / <2 minutes
PedsQL Pediatric Pain Questionnaire, self-report	Physical	8-21 y	1 item / <1 min
Functional Status Scale (FSS), parent-report	Physical	1 m-21 y	6 items / 2-5 min
Pediatric Overall Performance Category (POPC), parent-report	Physical	1 m-21 y	1 item / 1 min
Pediatric Cerebral Performance Category (PCPC), parent-report	Cognitive	1 m-21 y	1 item / 1 min
Parent			
PedsQL™ Family Impact Module 2.0 (acute version)	Physical, Cognitive, Emotional, Social	-	36 items / 5 min

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] FSS,[76,79] PedsQL,[77,78] (clinician and parent-report) and the PRISM IV score.[80,81]

Schedule of clinical and laboratory evaluations:

Data Collection Schedule	Screening	Baseline	Daily PICU to Day 28*	PICU Discharge
Demographic data	X	X		
Past and present medical history, pre-enrollment CXR	X	X		
PCPC, POPC, FSS score		X		X
Preadmission PedsQL – parent report		X		
Admission PRISM IV 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 and unanticipated adverse events		X	X	

Daily data, extracted from existing documentation at 10:00±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 the positioning protocols 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, cardiac dysrhythmias, 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, air leak (e.g., pneumothorax, pneumomediastinum), cardiac dysrhythmias related to increased mPaw, mucous plugging/airway obstruction, 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 ETT extubation, and catheter-associated bloodstream infection (if the line was inserted in the PICU) through 24 hours after PICU discharge. 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

With parental/legal guardian permission, we will collect blood and endotracheal aspirate samples for future studies of genomics, proteomics and metabolomics of PARDS. The sample collection will allow the investigative team to probe the biological basis for potentially disparate outcomes between *PROSpect* treatment groups and allow the study of the trajectory of PARDS illness and recovery. Fiduciary oversight of the biorepository rests with the Biorepository Governance Committee as outlined in *PROSpect* Policy for the Use of *PROSpect* Biospecimens. The governance committee will consider and approve the use of biorepository samples and subsequent data sharing for studies of high scientific merit that support the study of children with severe respiratory failure. Such studies will provide objective measures of PARDS, intermediate outcomes for clinical trials and allow for early interventions and prevention of PARDS. *PROSpect* provides a unique opportunity to collect biomarker samples in conjunction with a wealth of clinical data for further study. Blood sampling will be based on the child's weight and when enrollment occurs with relationship to the day of moderate-severe PARDS, ensuring that blood removal is maintained under the cap of 3 mL/kg. At maximum, blood samples will be obtained on moderate-severe PARDS Day 0, 1, 2, 3, 5, 7, 10, 14, 21 and 28, processed locally, then shipped to Children's Hospital of Philadelphia (CHOP) for bio-banking. The collection of blood samples will be an optional component of this study as parents/legal guardians can choose to participate during informed consent. ETA samples will be obtained using discarded entotracheal secreations on severe PARDS Day 0, 3, and 28 or End of Study (whichever occurs first), again processed locally, then shipped to Children's Hospital of Philadelphia for bio-banking. For purposes of Biorepository sampling, EOS is defined as extubation.

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.

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; 18-20 years) and by direct/indirect lung injury (8 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 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. At these randomization update analyses, 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.

Each of the four strategies has a probability of death π_j. The four π_j's are assigned independent Beta(0.5, 0.5) priors, which is the standard Jeffreys prior. Using Supine/CMV as the base strategy, we define θ_{Prone}, θ_{HFOV} and $\theta_{Interaction}$ as the effects of the positioning and ventilation strategies on duration of mechanical ventilation among those who do not experience death within 28 days, comparing these three strategies to Supine/CMV. For these Supine/CMV patients, we model the duration of mechanical ventilation as follows as Gamma(α, β) with any values larger than 28 truncated to 28. The distribution of duration of mechanical ventilation for these patients for the other three strategies is defined similarly; we assume they all use the same shape parameter α but different rate parameters as follows:

- Supine/CMV: rate parameter β
- Prone/CMV: rate parameter $\beta \times \theta_{Prone}$
- Supine/HFOV: rate parameter $\beta \times \theta_{HFOV}$
- Prone/HFOV: rate parameter $\beta \times \theta_{Prone} \times \theta_{HFOV} \times \theta_{Interaction}$.

We place gamma priors on θ_{Prone}, θ_{HFOV} and $\theta_{Interaction}$, each with prior mean 1. The gamma shape parameters are 3 for θ_{Prone} and θ_{HFOV} and 10 for $\theta_{Interaction}$. Since the prior distribution for $\theta_{Interaction}$ is more tightly concentrated around 1, the model encourages additivity unless it is

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 *moderate-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 moderate-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 60 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 moderate-severe PARDS, that can provide back-up extracorporeal membrane oxygenation (ECMO) support will participate.[5] Approximately 60 PICUs will enroll up to 1,000 pediatric patients (≥2 weeks of age and ≥42 weeks post gestational age and <21 years of age) intubated and mechanically ventilated with moderate-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) ≥12 or oxygenation saturation index (OSI) ≥10. We will require two blood gases meeting moderate-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

vascular catheters or from wasted blood specimens. Endotracheal tube aspirates will be obtained from discarded samples.

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 contain limited personal identifying information (i.e. date and time of intubation). 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/legal guardians/adult participants will be specifically asked if they would like to have further conversations with their child's or their 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 moderate-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 moderate-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

Vt	Tidal volume
Vte	Expired tidal volume
WAT-1	Withdrawal Assessment Tool - Version 1
WBFPS	Wong-Baker Faces Pain Scale
WFPICCS	World Federation of Pediatric Intensive and Critical Care Societies

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 60 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.[3] 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 moderate-severe PARDS and would not easily tolerate an inter-hospital transport for ECMO if study interventions failed.[4]

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.

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 Vt_e and percent ETT air leak measured at the airway. Criteria for failed CMV include a 2-hour pattern of either persistent hypoxemia (SpO_2 <85%) with FiO_2 1.0 and max PEEP per grid or persistent hypoventilation (pH <7.15) with PIP >32 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 8-15 Hz, an amplitude (delta-P) 60-90, a mPaw recruitment maneuver and a weaning strategy. The protocols delineate ongoing HFOV support, escalation of support, weaning of support and conversion to CMV. Criteria for failed HFOV include a 2-hour pattern of either persistent hypoxemia (SpO_2 <85%) at FiO_2 1.0 and mPaw >35 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. Aside from Q12H ETT patency check, 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 recorded daily. Pressure injuries will be staged and managed according to National Pressure Injury Advisory Panel (NPUAP) guidelines.[68]

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 Qualtrics database that is separate from the *PROSpect* clinical database. Parents/legal guardians will provide contact information for young adults. Following the consent process for young adults the information will be updated or confirmed. Contact information for young adults who decline participation will be destroyed. All emails and telephone numbers will be verified by the CCC 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.

Before hospital discharge, the CCC will call or email parents/legal guardians/young adults 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 parent/guardian/young adult are unable to be reached 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/young adults based on their stated preference. If a participant is still hospitalized or re-hospitalized during the data collection period, all data collection may proceed or be held until the patient returns home per parent's/participant's discretion. If held, we will resume data collection per schedule based upon the PICU discharge date. If re-hospitalized, parents/legal guardian/young adult will be asked to obtain or give permission to allow the PENN team to obtain a copy of the child/young adult'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 2-21 years; Infant Scales for subjects <2 years; http://www.pedsql.org) with associated modules.[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/adult participant, children 8-20 years years who are cognitively capable (PICU discharge PCPC ≤3) will be asked to self-report their HRQL. We will also ask parents and young adults who live outside their parent's home to complete a brief survey about their ongoing resource use and healthcare needs. Parent/legal guardian of young adults will provide a parent-report if the participant resides in the same household.

At the end of follow-up period, 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

clearly contradicted in the data. Here, α has a prior density proportional to $\alpha^{-1.5}$ on [1,100] and β has an exponential prior distribution with mean 1/15.

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

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

We construct new allocation probabilities beginning with defining:

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

These $r_{\mathrm{X/Y}}$ 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 $r_{\mathrm{X/Y}}$ 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 duration of mechanical ventilation. The square root results in moving the probability closer to equal randomization to limit the aggressiveness of the response-adaptive randomization, and the standard error component acts to avoid strong imbalances in the data. This response-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 and data quality. Early stopping rules for futility and efficacy are described below.

Stopping Early for Futility: Early stopping for *futility* will be considered at the time of randomization update analyses, after 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. 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 the time of randomization update analyses, after 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. 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

guidelines). A second blood gas is not required for OI ≥16. 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 children, 2 weeks to 21 years of age, who are typically cared for in Pediatric ICUs.

Eligible patients with moderate-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 hypoxemia 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; 18-20 years) and direct/indirect lung injury. Adaptive randomization will first occur after 400 patients are randomized and have been followed for 28 days, and every 100 patients thereafter. At these randomization update analyses, 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 for primary, secondary and exploratory analyses.

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/participant 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/participant 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/adult participants will be invited to participate as well as cognitively capable (Pediatric Cerebral Performance Category ≤3) subjects 8-20 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.

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 moderate-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 moderate-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.