PROSpect
PRone and **OS**cillation **PE**diatric **C**linical **T**rial

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ABSTRACT

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.

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/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 in the care of pediatric patients with severe PARDS, that can provide back-up extracorporeal membrane oxygenation (ECMO) support are participating. Eligible patients with severe PARDS are 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. Our primary outcome is ventilator-free days (VFD) through day 28, 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. Our secondary outcome is nonpulmonary organ failure-free days. We will also 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 health-related quality of life (HRQL). Up to 1,000 patients with severe PARDS will be randomized by age group 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. Data will be analyzed per intention-to-treat for the primary analyses and per-protocol received for primary, secondary and exploratory analyses.

This clinical trial will provide the definitive evidence necessary for the field to consider a major change in clinical practice in the care of critically ill children with severe PARDS.

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, 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:

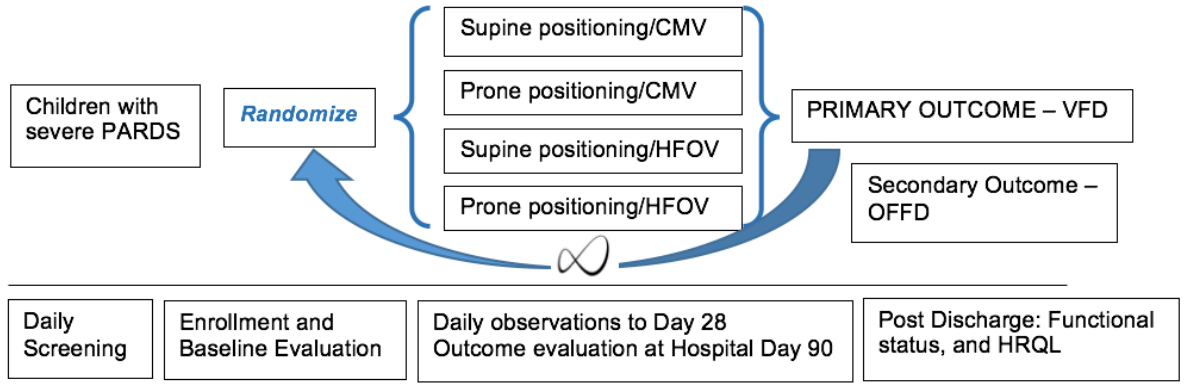
1. To compare the effects of prone positioning with supine positioning on ventilator-free days (VFD).
2. To compare the effects of HFOV with CMV on VFD.

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 8-15 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 blood gases meeting severe PARDS criteria (separated by at least 4 ± 2 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 any high-frequency mode of MV 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 interventional clinical trial not approved for co-enrollment
- 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 the full design including response-adaptive randomization and early stopping for a maximum total sample size of 1,000 patients, simulation results (based on 4,000 simulations) estimate that we would have 88.0% power for Scenario 1 and 91.3% 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 a stratified Wilcoxon rank-sum test, adjusting for ventilation strategy. Similarly, for ventilation strategy, analysis of the primary outcome will be performed on an intention-to-treat basis using a stratified Wilcoxon rank-sum test, adjusting for positioning strategy. Differences between positioning or ventilation strategies will be considered statistically significant if a one-sided p-value is <0.018. This threshold was obtained by simulation to control Type I error at the 0.025 level, given the response-adaptive randomization design. 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) using proportional hazards regression models.

Analysis of the secondary outcome, nonpulmonary organ failure-free days, will be performed on a per-protocol basis using stratified Wilcoxon rank-sum tests, and we will explore adjustment for age group and lung injury type using proportional hazards regression models. For analyses of 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. For secondary and exploratory outcomes, differences between positioning or ventilation strategies will be considered statistically significant if the two-sided p-value is <0.025.

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.

ABBREVIATIONS

AACN	American Association of Critical Care Nurses
AC	Assist Control
ANZICS	Australian and New Zealand Intensive Care Society
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic Society
BCH	Boston Children's Hospital
BMI	Body Mass Index
CAPD	Cornell Assessment of Pediatric Delirium
CCC	Clinical Coordinating Center
CCM	Critical Care Medicine
cm	Centimeter
cm H_2O	Centimeter of water pressure
CMV	Conventional Mechanical Ventilation
CXR	Chest X-ray
DCC	Data Coordinating Center
delta-P	HFOV amplitude
DSMB	Data and Safety Monitoring Board
DTPI	Deep Tissue Pressure Injury
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
eMOO	Electronic Manual of Operations
ENE	Eligible Not Enrolled
ERT	Extubation Readiness Test
ESPNIC	European Society of Pediatric and Neonatal Intensive Care
$ETCO_2$	End-tidal carbon dioxide
ETT	Endotracheal Tube
FiO_2	Fraction of inspired oxygen
FLACC	Facial expression, Leg movement, Activity, Cry and Consolability
FSS	Functional Status Scale
HALF-PINT	Heart And Lung Failure - Pediatric INsulin Titration Trial
HFOV	High-Frequency Oscillatory Ventilation
HIPAA	Health Insurance Portability and Accountability Act
HRQL	Health-Related Quality of Life
HSCT	Post Hematopoietic Stem Cell Transplant
IBW	Ideal Body Weight
IC	Integration Committee
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
I:E	Inspiratory-to-expiratory time
IMV	Intermittent Mandatory Ventilation
iNO	Inhaled Nitric Oxide
INRS	Individualized Numeric Rating Scale
IRB	Institutional Review Board
ISD	Information Services Department
IWS	Iatrogenic Withdrawal syndrome
kg	Kilograms
LPV	Lung Protective Ventilation
MODS	Multiple Organ Dysfunction Syndrome
mPaw	Mean airway pressure
MPI	Multiple Principal Investigator

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

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

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 <u>*severe*</u> 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 hypoxemia 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 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. 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 for primary, secondary and exploratory analyses.

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 air leak 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 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 cm H_2O above plateau pressure	30 cm H_2O 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.

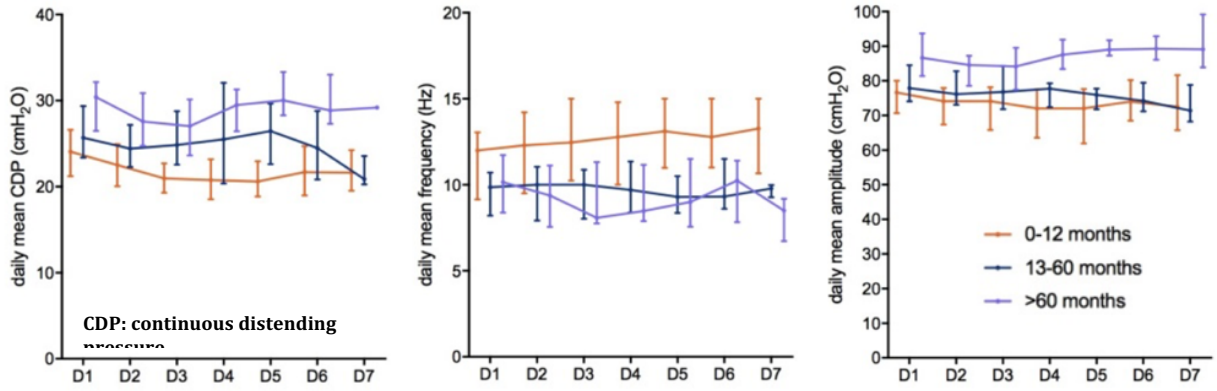
C.3 *RESTORE* HFOV Propensity Score Analysis

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 hypoxemia (OI ≥8.0). The degree of hypoxemia 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

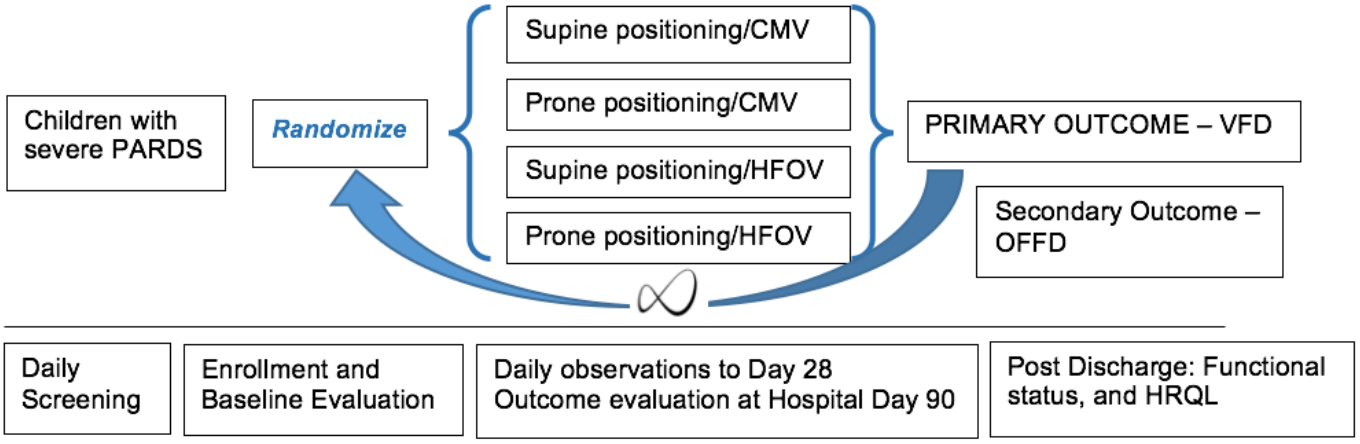
This is a two-by-two factorial, response-adaptive multi-center randomized controlled clinical trial that tests whether pediatric patients with severe PARDS randomized to supine versus prone positioning and to conventional mechanical ventilation versus high-frequency oscillatory ventilation exhibit more 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 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 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 blood gases meeting severe PARDS criteria separated by at least 4 ± 2 hours. Requiring two 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 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 any high-frequency mode of MV 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 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, acute abdomen or 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 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 4-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 4-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]
- **Extubation Readiness Test (ERT):** This standardized test will be implemented once daily at 07:00 ± 2H in subjects who are spontaneously breathing with an OI/OSI <6 and in whom there has there been a decrease and/or plateau in ventilator support over the previous 12 hours. The ERT is repeated at 16:00 ± 2H in subjects who fail the morning test for oversedation.[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 noninvasive ventilation (BiPAP, CPAP ≥5 cm H_2O, or HFNC ≥5 L/min). 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 positive pressure is <5 cm H_2O (continuous or bi-level) for at least 24 hours.

Subjects will be assigned zero VFD if they remained intubated or died prior to day 28 without remaining extubated for more than 24 hours. For intubated subjects who are transferred to another hospital, we will attempt to obtain date/time of extubation from the outside hospital so that VFD can be calculated. In the event that this data cannot be obtained, these subjects will be assigned the worst possible outcome of zero VFD.

To accommodate the use of noninvasive ventilation (BiPAP, CPAP ≥5 cm H_2O, or HFNC ≥5 L/min), as a separate outcome, we will also compute the total duration of assisted breathing to include the use of noninvasive ventilation pre-intubation and post-extubation.

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 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 2-19 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. Teen (13-17 y) self-report, parent-report 2. Child (8-12 y) self-report, parent-report 3. Young child (5-7 y) parent-report 4. Toddler (2-4 y) parent-report 5. Infant (13-24 m) parent-report 6. Infant (1-12 m) parent-report	Physical, Cognitive, Emotional, Social	1 m-17 y	23 items / <5 min 23 items 23 items 21 items 45 items / <10 min 36 items / <7min
PedsQL™ Multi-dimensional Fatigue Scale V3 (Acute version – per age) 1. Teen (13-17 y) self-report, parent-report 2. Child (8-12 y) self-report, parent-report 3. Young child (5-7 y) parent-report 4. Toddler (2-4 y) parent-report	Physical, Cognitive	2-17 y	18 items / <4 min
PedsQL™ Cognitive Functioning Scale 1. Teen (13-17 y) self-report, parent-report 2. Child (8-12 y) self-report, parent-report 3. Young child (5-7 y) parent-report 4. Toddler (2-4 y) parent-report	Cognitive	2-17 y	6 items / <2 minutes
PedsQL Pediatric Pain Questionnaire, self-report	Physical	8-17 y	1 item / <1 min
Functional Status Scale (FSS), parent-report	Physical	1 m-17 y	6 items / 2-5 min
Pediatric Overall Performance Category (POPC), parent-report	Physical	1 m-17 y	1 item / 1 min
Pediatric Cerebral Performance Category (PCPC), parent-report	Cognitive	1 m-17 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] and FSS,[76,79] and the PRISM IV 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 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 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 goverance 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 severe PARDS, ensuring that blood removal is maintained under the cap of 3 mL/kg. At maximum, samples will be obtained on 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.

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. 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 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) 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, 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 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 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 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 a stratified Wilcoxon rank-sum test, adjusting for ventilation strategy. Similarly, for ventilation strategy, analysis of the primary outcome will be performed on an intention-to-treat basis using a stratified Wilcoxon rank-sum test, adjusting for positioning strategy. Differences between positioning or ventilation strategies will be considered statistically significant if a one-sided p-value is <0.018. This threshold was obtained by simulation to control Type I error at the 0.025 level, given the response-adaptive randomization design.

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 the statistical

model in section E.3. 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) using proportional hazards regression models. We will also make graphical comparisons using boxplots and Kaplan-Meier survival curves.

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 stratified Wilcoxon rank-sum tests. Differences between positioning or ventilation strategies will be considered statistically significant if the two-sided p-value is <0.025. This analysis will be performed on a per-protocol basis. In addition, we will explore adjustment for age group and lung injury type using proportional hazards regression models.

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. Differences between positioning or ventilation strategies will be considered statistically significant if the two-sided p-value is <0.025. Careful assessment of the results from exploratory analyses will be made, though no formal multiple comparisons procedures are planned.

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.

Data analyses will be performed using SAS® (Version 9.4, SAS Institute, Inc., Cary, NC), R (Version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria) 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 and 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. As 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 performed simulations based on these data, assuming that, for the least effective arm(s) in each simulation scenario, 10% of patients die, a further 4.2% of patients survive but accumulate zero VFD, and mean VFDs are 16 days including patients with zero VFD. We considered two main scenarios for sample size justification: in Scenario 1, there is a 2-day improvement in VFD by one intervention alone (e.g., prone) while the other intervention has no effect (e.g., HFOV). In Scenario 2, there is a 2-day improvement in VFD by each intervention, so the most efficacious treatment is 4 VFDs better than the least efficacious treatment.

Based on the full design including response-adaptive randomization and early stopping for a maximum total sample size of 1,000 patients, simulation results (based on 4,000 simulations) estimate that we would have 88.0% power for Scenario 1 and 91.3% power for each intervention for Scenario 2. In addition, response-adaptive randomization allocates more study patients to the superior intervention (or interventions). For example, for Scenario 1, approximately 64% of patients would be assigned to the more efficacious treatment (approximately 446 out of 700 on average).

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* subject 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.

Within 8 hours of an event, site co-investigators will enter all serious, protocol-related (probably or highly probably related) adverse events and/or unanticipated problems that are fatal/life-threatening into the study database. The DCC will run a SAE/UP report twice daily and immediately notify the MPI on-call of all newly reported events. 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 represents a SAE/UP, and a description of any corrective actions that are proposed in response to the SAE/UP. Within 48 hours of the event, the DCC will send a full narrative report of the event to the DSMB Chair, NHLBI Executive Secretaries, and NHLBI Clinical Trials Specialist. The DSMB Chair will confirm receipt and e-mail the DCC and NHLBI with recommendations, if any. The CCC Administrative Project Manager will report the event to the University of Pennsylvania IRB within 3 days and to each international clinical center for submission to their local ethics committee. Recommended protocol modifications will be implemented immediately.

Within 12 hours of an event, site co-investigators will enter all serious, protocol-related (probably or highly probably related) adverse events and/or unanticipated problems that are non-fatal/life-threatening into the study database. The DCC will run a SAE/UP report twice daily and immediately notify the MPI on-call of all newly reported events. 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 represents a SAE/UP, and a description of any corrective actions that are proposed in response to the SAE/UP. Within 96 hours of the event, the DCC will send a full narrative report of the SAE/UP to the DSMB Chair, NHLBI Executive Secretaries, and NHLBI Clinical Trials Specialist. The DSMB Chair will confirm receipt and e-mail the DCC and NHLBI with recommendations, if any. The CCC Administrative Project Manager will report the SAE/UP to the University of Pennsylvania IRB within 10 days and to each international clinical center for submission to their local ethics committee. Recommended protocol modifications will be implemented as specified.

Non-protocol-related SAE/UP and all other safety events will be tabulated and reported at each DSMB meeting.

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/Go-live meetings: Prior to enrolling subjects, all sites will participate in a 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 treatment fidelity 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 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 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 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 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, 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 (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, air leak (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), and pressure injuries (occipital/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 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. 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.

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Clinical Protocols – V.12.14.18

I. Ventilator Management Guidelines

A. Monitoring

1. All subjects require an arterial line and SpO_2 monitoring. Subjects supported on CMV also require $ETCO_2$ monitoring. Noninvasive data are recorded at least Q6H.

2. PICUs may continue using near-infrared spectroscopy (NIRS), transcutaneous gas monitoring, and volumetric capnography (CMV groups) if considered usual care.

B. Oxygenation and Ventilation Goals (all groups)

1. During the acute phase, the goal is adequate oxygenation and ventilation:
    a. Oxygenation: Pulse Oximeter Oxygen Saturation (SpO_2) 88-92%[1]
    b. Ventilation: pH $\geq$ 7.15 and $\leq$ 7.30 (irrespective of $PaCO_2$)[2,3]
    c. As the patient's clinical condition improves and criteria for extubation readiness testing (ERT) are met, oxygenation and ventilation parameters are normalized, i.e., SpO_2 ≥ 98% and pH ≤ 7.45.

2. Arterial blood gases and chest radiographs (CXR) are obtained per the discretion of the clinical team. If lung overinflation is present on CXR (i.e., diaphragms flat and/or depressed below the 10th posterior rib) consider decreasing mean airway pressure by 2 cm H_2O.

3. Neuromuscular blockade (NMB) is administered continuously for the first 24H post enrollment.[4] After the first 24H, NMB is administered per the discretion of the clinical team.

4. Ventilator disconnects: lung volume is re-established after all ventilator disconnects based on the mode of mechanical ventilation as described below (i.e., PEEP or mPaw titration).

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[1] When SpO_2 is used to assess arterial oxygenation, the following measures will be taken to improve accuracy: SpO_2 sensor will be checked to ensure optimal position, cleanliness, and consistent readings with satisfactory waveforms; no position changes or endobronchial suctioning for ≥ 10 minutes; no invasive procedures or ventilator changes for ≥ 30 minutes. SpO_2 will be observed for a minimum of 1 minute, and a representative value will be recorded on the appropriate source-document flowsheet.

[2] Use of cuffed/uncuffed ETTs will be documented.

[3] Per PALICC guidelines, the routine use of NaHCO3 administration is not recommended.

[4] Medication and mode (continuous or intermittent) per care team's discretion.

C. Strategy: Conventional Mechanical Ventilation (CMV)

Goal: Lung protective ventilation using ventilatory parameters and approaches consistent with those recommended by the Pediatric Acute Lung Injury Consensus Conference (PALICC).

1. **Initiating CMV**
   a. Ventilator modes include synchronized intermittent mandatory ventilation [SIMV] or assist control [AC]); Pressure Control Ventilation (PCV) or Pressure Regulated Volume Control (PRVC or equivalent)
   b. Monitor exhaled Vt (Vt_e) and percent ETT leak at the airway.[5]
   c. Suction the patient.
   d. Administer neuromuscular blockade (required for the first 24 hours).

2. **Initial settings CMV**
   a. **Tidal volume (Vt) or Peak Inspiratory Pressure (PIP):**
      1) Set to obtain Vt_e[6] 5-7 ml/kg (ideal body weight [IBW][7])
      2) Goal PIP ≤ 28 cm H_2O (may allow up to 32 cm H_2O for patients with poor chest wall compliance)
   b. **Inspiratory Time:** Set based on patient age[8] and disease condition.
      1) Rate adjusted to maintain pH with the target range. Assess flow-time scalar to assess for appropriate inspiratory time.
      2) I:E ratio: maximum 1:1[9]
   c. **Rate:** Titrate based on age and respiratory condition to maintain pH within prescribed goals.
   d. **Pressure Support (PS):**
      1) Pressure support set to maintain spontaneous Vt_e 5-7 mL/kg IBW
      2) Minimal PS (calculated to overcome endotracheal tube [ETT] resistance): 10 cm H_2O for ETT 3-3.5 mm, 8 cm H_2O for ETT 4-4.5 mm, and 6 cm H_2O for ETT ≥ 5 mm
   e. **Fraction of inspired oxygen (FiO_2):** As necessary to achieve SpO_2 88-92%

[5] Use a proximal airway sensor or Philips NM3™ monitor (or equivalent) at the ETT.
[6] Exhaled Vt is continuously monitored and documented every 6 hours.
[7] IBW (as predicted from height): See chart for <178 cm males and <164 females; If male height is >178 cm than IBW (kg) = 50 + 2.3(height in inches - 60); If females height is >164 cm than IBW (kg) = 45.5 + 2.3(height in inches - 60). [To convert inches to centimeters multiply inches times 2.54; to convert centimeters to inches multiply centimeters times 0.4.]
[8] 0-1 year: 0.4-0.65 sec; 1-2 years: 0.5-0.7 sec; 2-8 years: 0.6-0.9 sec; >8 years: 0.7-1.2 sec
[9] Inverse ratio ventilation not accepted.

f. **Positive End-expiratory Pressure (PEEP):**
1) PEEP titration maneuver (to determine optimal PEEP):

Step 1: Record start PEEP ($PEEP_{start}$), then increase PEEP by 2 cm H_2O every 5 minutes while observing SpO_2 and dynamic compliance (C_{dyn})
Step 2: Record PEEP at which SpO_2 starts to increase ($PEEP_{recruitment}$)
Step 3: PEEP should be increased until no further improvement in SpO_2 or Cdyn is noted or systolic blood pressure decreases ($PEEP_{hyperinflation}$). If during recruitment, SpO_2 > 97%, then reduce FiO_2 and continue recruitment.
Step 4: Once $PEEP_{hyperinflation}$ is noted, decrease PEEP by 2 cm H_2O every 5 minutes until SpO_2 decreases by more than 2 percentage points ($PEEP_{derecruitment}$). At this point, stop decreasing PEEP.
Step 5: Re-recruit: Increase PEEP to $PEEP_{hyperinflation}$ for 1-2 minutes (as clinically tolerated).
Step 6: Set PEEP at 2 cm H_2O above $PEEP_{derecruitment}$.

3. Ongoing CMV support

a. **Reassess the patient and fine-tune ventilator settings <u>at least</u> every 6 hours:** If measured Vt, SpO_2, and/or pH are not within the target range, then ventilator adjustments are made and the patient is reassessed within 30 minutes. Changes in more than one ventilator setting may be performed simultaneously.

b. **Titrate Vt_e and PIP:** Maintain Vt_e 5-7 ml/kg IBW. Exhaled Vt as low as 3 ml/kg for severe PARDS (OI ≥ 16 or OSI ≥ 13) is allowed to maintain PIP ≤ 28 cm H_2O (may allow up to 32 cm H_2O for patients with poor chest wall compliance).

c. **Titrate Respiratory Rate:** Goal is to achieve alveolar ventilation (based on pH goal) using Vt within goal range at the lowest respiratory rate.

d. **PEEP/FiO_2** table
If a patient's PEEP/FiO_2 is not compatible with the PEEP/FiO_2 table (e.g., immediately after enrollment or after urgent changes in FiO_2 or PEEP in response to desaturation, hypotension, etc.), either PEEP or FiO_2 (or both) are adjusted at 5-15 minute intervals until the PEEP/FiO_2 is compatible with the grid.

Titrate per PEEP-FiO_2 grid – Performed every 12 hours after ETT suctioning

FiO_2	.30	.40	.40	.40	.50	.50	.60
PEEP	5	5	8	10	10	12	12
FiO_2	.60	.70	.70	.80	.80		
PEEP	14	14	16	16	16*-18		

*PEEP of 16 cm H_2O in subjects <1 year of age

Decrease the FiO_2 level to maintain SpO2 88-92% then assess if patient is on PEEP level that corresponds with that FiO2. If not, increase/decrease PEEP to keep patient on the grid (vertical pair).

4. Escalation of Support

a. Brief periods (≤10 min) of SpO_2 < 85% or > 92% may be tolerated without making changes in PEEP or FiO_2. FiO_2 = 1.0 may be used for brief intervals (≤ 10 min) of transient desaturation or to prevent desaturation during treatments, such as suctioning or position changes.

b. **OXYGENATION:** If SpO_2 < 85% for more than 10 minutes

1. In the event of any abrupt clinical changes, assess for pneumothorax and obstructed/dislodged ETT.

2. Perform PEEP titration maneuver
   Step 1: Record start PEEP ($PEEP_{start}$), then increase PEEP by 2 cm H_2O every 5 minutes while observing SpO_2 and dynamic compliance (C_{dyn})
   Step 2: Record PEEP at which SpO_2 starts to increase ($PEEP_{recruitment}$)
   Step 3: PEEP should be increased until no further improvement in SpO_2 or Cdyn is noted or systolic blood pressure decreases ($PEEP_{hyperinflation}$). If during recruitment, SpO_2 > 97%, then reduce FiO_2 and continue recruitment.
   Step 4: Once $PEEP_{hyperinflation}$ is noted, decrease PEEP by 2 cm H_2O every 5 minutes until SpO_2 decreases by more than 2 percentage points ($PEEP_{derecruitment}$). At this point, stop decreasing PEEP.
   Step 5: Re-recruit: Increase PEEP to $PEEP_{hyperinflation}$ for 1-2 minutes (as clinically tolerated).
   Step 6: Set PEEP at 2 cm H_2O above $PEEP_{derecruitment}$.

3. If Vt_e < 5-7 mL/kg and PIP ≤ 28 cm H_2O, increase Vt_e to 5-7 mL/kg.

4. If Vt_e within range and/or PIP > 28 cm H_2O, assess for overdistension (e.g., increase in $PaCO_2$ with a patent airway). If present, perform PEEP titration as described above starting at Step 5 (use current PEEP as $PEEP_{hyperinflation}$).

c. **VENTILATION**: If primary respiratory acidemia (pH < 7.15) is present:
   Step 1: Increase ventilator rate in increments of 2-4 bpm until pH > 7.15 unless evidence exists for air trapping based on airway graphics. Do not exceed I:E 1:1. Ensure inspiratory time within range indicated in Table.
   Step 2: If Vt < 8 mL/kg, then increase Vt incrementally to 8 mL/kg (while maintaining pressure limitation).

5. Failed CMV

Four-hour pattern of either:

a. Persistent hypoxemia (SpO_2<85%) with FiO_2 1.0 and max PEEP per grid (16 cm H_2O for < 1 year of age; 18 cm H_2O for ≥ 1 year of age).
b. Persistent hypoventilation (pH < 7.15) with PIP > 32 cm H_2O and a respiratory rate that does not cause intrinsic PEEP (i.e., air trapping)[10]

[10] Document total PEEP by performing an expiratory hold maneuver so that auto-PEEP can be calculated.

6. **Weaning CMV –** As the patient's clinical condition improves and criteria for extubation readiness testing (ERT) are met, oxygenation and ventilation parameters are normalized, i.e., $SpO_2 \leq 98\%$ and pH ≤ 7.45
   a. Decrease ventilator settings as clinically indicated
   b. If $SpO_2 > 92\%$ and Vt_e 4-7 mL/kg: Decrease set PEEP and/or FiO_2 in tandem using the PEEP/FiO_2 grid, while maintaining Vt_e = 4-7 mL/Kg and ≤ 28 cm H_2O.
   c. If over ventilating such that pH ≥ 7.30[11]
      Step 1: <u>If Vte = 4-7 mL/kg</u>: Incrementally decrease ventilator rate by 2-4 bpm while maintaining spontaneous respiratory rate within physiologic range.[12,13]
      Step 2: <u>If Vte = 4-7 mL/kg and good spontaneous effort</u>: may consider Pressure Support Ventilation to maintain spontaneous Vte at 4-7 mL/kg. (Minimal PS per ETT size[14]).
   d. If at any time PIP above range, attempt to wean while maintaining Vte 4-7 mL/kg and pH > 7.30.

[11] Note that oxygenation and ventilation are not independent. If at any time decreasing ventilator pressure results in decreased oxygenation, maintain the same PIP or Vt and decrease the rate incrementally to achieve increase in $PaCO_2$.

[12] Spontaneous RR goal: <6 months 20-60; 6 mo-2 yrs 15-45; 2-5 yrs 15-40; >5 yrs 10-35.

[13] Increased RR can be from anxiety. May need to increase sedation or if anxiety appears to be from excessive work of breathing, then increase PS 2 cm H_2O (if Vt <6 mL/kg) or increase the ventilator rate until RR is within range. If RR is below range and if the patient is over sedated, then decrease sedation/analgesia.

[14] Minimal PS (calculated to overcome the resistance of the ETT): 10 cm H_2O if 3-3.5 mm ETT; 8 cm H_2O if 4-4.5 mm ETT; and 6 cm H_2O if ≥ 5 mm ETT.

D. Strategy: High Frequency Oscillatory Ventilation (HFOV)

Goal: The HFOV strategy 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.

1. **Initiating HFOV**
   a. Ventilator: 3100A if subject weight < 35 kg, 3100B if subject weight ≥ 35 kg. Alternate devices with similar gas exchange mechanisms (e.g., active exhalation) may be used once approved by the CCC.
   b. If part of usual care, correlate transcutaneous CO_2 monitoring with an arterial blood gas.
   c. Suction the patient.
   d. Administer neuromuscular blockade (required for the first 24 hours).
   e. Consider a fluid bolus (5 mL/kg) if concerned about hemodynamic instability.

2. **Initial Settings HFOV**
   a. **FiO_2**: As necessary to achieve SpO_2 88-92%
   b. **Frequency** at 8-12 Hz.
   c. **Amplitude** (delta-P) 60-90[15]
   d. **Mean Airway Pressure** (mPaw)
      1) Set the initial mPaw 5-6 cm H_2O above the current CMV monitored value. May use a smaller mPaw increase if air leak is present.
      2) Perform a **mPaw recruitment maneuver**:
         Step 1: Record start mPaw ($mPaw_{start}$)
         Step 2: Increase mPaw by 2 cm H_2O every 5 minutes and observe SpO_2
         Step 3: Record mPaw at which SpO_2 starts to increase ($mPaw_{recruitment}$)
         Step 4: Continue to increase mPaw as until SpO_2 no longer increases or systolic blood pressure starts to decrease (record as $mPaw_{hyperinflation}$).[16] If during recruitment SpO_2 > 97%, then first reduce the FiO_2 and continue recruitment.
         Step 5: Once $mPaw_{hyperinflation}$ is determined, decrease mPaw by 2 cm H_2O every 5 minutes and observe SpO_2
         Step 6: Record the mPaw at which the SpO_2 starts to decrease by more than 2 percentage points ($mPaw_{derecruitment}$). At this point, stop decreasing mPaw.
         Step 7: Increase mPaw to $mPaw_{hyperinflation}$ for 1-2 minutes, then decrease mPaw to 2 cm H_2O above $mPaw_{derecruitment}$
      3) Maintain mPaw at this setting until FiO_2 is weaned to ≤ 0.60 – wean FiO_2 when at goal SpO_2 for > 2 hours
   e. **Inspiratory Time**
      1) Initially set at 33%
      2) When amplitude is maximized and frequency is minimized (8 Hz), increase inspiratory time to 40% (and then 50%, if needed)
   f. **Bias Flow**

[15] Increased amplitude is required to provide adequate tidal volume for ventilation given the high starting frequencies.
[16] Consider 5 mL/kg fluid bolus if transient and gentle pressure on the liver bed improves saturation.

1) Initial settings per patient age:
   < 1 year of age: 15-25 L/min
   1 -8 years of age: 15-30 L/min [17]
   8 years of age: 25-40 L/min
2) Consider increasing bias flow if frequency is minimized at 8 Hz, mPaw is set at maximum, and/or patient has significant spontaneous respiratory effort.

3. Ongoing HFOV support

a. Reassess patient and fine-tune ventilator settings at least every 6 hours. If measured SpO_2 and/or pH are not within the target range, then ventilator adjustments are made and the patient is reassessed within 30 minutes. Changes in more than one ventilator setting may be performed simultaneously.

b. **Titrating mPaw**
mPaw titration maneuver – Performed every 12 hours after ETT suctioning
Step 1: Record the start mPaw ($mPaw_{start}$)
Step 2: Decrease mPaw by 2 cm H_2O every 5 minutes and observe SpO_2
Step 3: Record the mPaw at which the SpO_2 starts to decrease by more than 2 percentage points (this point is called $mPaw_{derecruitment}$). At this point, stop decreasing mPaw.
Step 4: Increase mPaw to either $mPaw_{start}$ or by 5-8 cm H_2O (whichever is greater) for 2 minutes
Step 5: Decrease mPaw to 2 cm H_2O above $mPaw_{derecruitment}$
Step 6: 1 hour after titration, obtain ABG and titrate Frequency/Power (see below)

Between mPaw maneuvers, FiO_2 may be gradually weaned to a minimum of 0.40 and/or mPaw may be decreased by 2 cm H_2O to maintain SpO_2 at goal.

c. Titrating FiO_2
If $SpO_2 \geq 92\%$ and $FiO_2 > 0.60$, reduce FiO_2 by 0.10 until FiO_2 0.40

d. Titrating Frequency and Power
Goal is highest frequency that achieves adequate alveolar ventilation.
a) Titration is performed, at least, every 6 hours
b) If the pH is too high (> 7.30)
   Step 1: Increase the frequency by 0.5-1 Hz (max 15 Hz)
   Step 2: If the frequency is 12-15 Hz, decrease the power by 10%

e. **If difficulty ventilating,** consider deflating ETT cuff (while maintaining current mPaw) to augment expiratory gas flow.

4. Escalation of Support

a. Brief periods (≤10 min) of $SpO_2 < 85\%$ or $> 92\%$ may be tolerated without making changes in mPaw or FiO_2. $FiO_2 = 1.0$ may be used for brief intervals (≤ 10 min) of transient desaturation or to prevent desaturation during treatments, such as tracheobronchial suctioning or position changes.

[17] Positioning – ventilation sequence: Position the patient before the mPaw procedure

b. **OXYGENATION**: If SpO_2 < 85% for more than 10 minutes
   1. Assess for occluded or dislodged ETT.
   2. Assess for overdistension (e.g., increase in $PaCO_2$ with a patent airway). If present, perform **mPaw titration maneuver** as described above; e.g., start with a decrease in mPaw.
   3. Increase FiO_2 in increments of 0.2 until SpO_2 > 85% and < 92%.
   4. Once SpO_2 stabilizes >85% and <92% for 5 minutes irrespective of FiO_2 or when FiO_2 reaches 1.0 perform a **mPaw recruitment maneuver**; e.g., start with an increase in mPaw.

c. **VENTILATION**: If primary respiratory acidemia (pH < 7.15) is present:
   Step 1: decrease the frequency by 0.5-1 Hz (minimum frequency of 8 Hz).
   Step 2: if the frequency is 8 Hz, increase the bias flow then inspiratory time to 40-50%.
   Step 3: if the power is not at 10, increase the power by 10%.

5. Failed HFOV

Four-hour pattern of either:
   a. Persistent hypoxemia (SpO_2<85%) at FiO_2 1.0 and mPaw > 35 cm H_2O
   b. Persistent hypoventilation (pH <7.15) with max power/amplitude at a frequency < 8 Hz

6. Conversion to conventional ventilation

Conversion to conventional ventilation is mandated when mPaw 15-20 cm H_2O and FiO_2 < 0.50. Extubation from HFOV will be considered a protocol deviation. When converting to CMV manage the patient per CMV protocol matching the initial PEEP to the FiO_2 per PEEP-FiO_2 grid. Typically there is a downward adjustment made to the mPaw of 2-4 cm H_20.

II. Suctioning and Re-recruitment (all groups)

A. For safety, the patency of the ETT is assessed Q12H by ETT suctioning.[18]

B. Routine suctioning is not recommended.

C. Consider suctioning with unexplained, rapid increases in $PaCO_2$[19] and/or decrease in chest movement or, for example, when there is an apparent "saw" pattern visible on the flow – time scalar when on CMV.[20] Care must be taken to maintain lung volumes during suctioning. Significant reductions in SpO_2 <85% after suctioning are managed with re-establishing lung volume per mode of mechanical ventilation utilized. Ventilation should be suspended during maneuver (as clinically tolerated) to avoid excessive peak airway pressure.

[18] Perform prior to recruitment maneuver.
[19] Increase in $ETCO_2$ (CMV) or TCO_2M (HFOV).
[20] There are no data to support specific recommendations on tracheobronchial suctioning technique. No attempt will be made to standardize suctioning practices across study sites, although closed suctioning is recommended per PALICC guidelines. Saline or no saline instillation can be used per study unit routine.

III. Daily Test for Patient Readiness for Extubation (all groups after 1st 24H)

A. Every day at 07:00 ± 2H[21-22] the patient is assessed for the following while in the supine position:

- Spontaneous breathing
- Oxygenation Index/Oxygen Saturation Index < 6
- Decrease and/or plateau in ventilator support over the previous 12 hours

If these criteria are present, then the patient is tested for readiness for extubation.

B. Daily Test

1. Hold enteral feedings
2. If FiO_2 is not set at 0.5, set FiO_2 at 0.5[23]
3. If PEEP is not set at 5 cm H_2O, set PEEP at 5 cm H_2O
4. Evaluate SpO_2 after the above changes
    a. If $SpO_2 \geq 95\%$, change mode to PSV with set PS min based on size of ETT
        1. 10 cm H_2O if ETT 3-3.5 mm
        2. 8 cm H_2O if ETT 4-4.5 mm
        3. 6 cm H_2O if ETT ≥ 5 mm
    b. Monitor SpO_2, exhaled Vt, and RR

C. Ready for extubation

1. The patient is potentially ready for extubation (from a pulmonary perspective) if all 3 of the following are present for ≥ 2 hours:
    a. $SpO_2 \geq 95\%$ with $FiO_2 \leq 0.5$ and PEEP ≤ 5 cm H_2O
    b. Exhaled Vt ≥ 5 mL/kg
    c. Respiratory rate within respiratory rate goal of age:
        i. <6 months 20-60; 6 mo to 2 yrs 15-45; 2 to 5 yrs 15-40; >5 yrs 10-35
2. If the patient does not meet the above criteria because of excessive sedation, the care team may elect to wean the patient's sedation (per the sedation protocol) and retest the patient after the wean. If the patient does not meet the criteria at 16:00 ± 2H, they are returned to their pre-test ventilator settings and re-tested the following morning.
3. If they meet the above criteria, then the medical team is notified that the patient is ready (from a pulmonary perspective) for unassisted breathing.
4. Extubation may be delayed for the following non-pulmonary reasons:[24]
    - Neurological unresponsiveness and inability to protect one's airway
    - Inaudible leak around an uncuffed/deflated cuff ETT[25]
    - Scheduled test/procedure that requires deep sedation/anesthesia

D. Extubation Guidelines

1. May extubate to FiO_2 higher than on ventilator, then wean FiO_2 every two hours to room air to maintain SpO_2 >92%.

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[21] If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 07:00 ± 2H then the test can be delayed up to 4 hours.
[22] For prone positioned patients, the one hour post-supine ABG is used for OI calculation.
[23] Stop feeding per institutional standard
[24] Should extubation be delayed, the reason for the delay will be recorded on data sheet.
[25] In this case, the care team by elect to prescribe dexamethasone for 24-48 hours.

2. If patient develops respiratory distress after extubation and if stridor is present may consider dexamethasone IV. ± racemic epinephrine treatment Q15 minutes x 2 (1-2 years 0.25 mL or >2 years 0.5 mL).
3. If stridor is not present, may consider noninvasive ventilation or high-flow nasal cannula if patient is alert, cooperative and able to protect their airway.
4. Should reintubation be required within 24H, cause and date/time is recorded on data sheet.

E. Patient management if reintubation is required:

- For patients extubated to, but not liberated from, noninvasive ventilation (BiPAP, CPAP ≥5 cm H_2O, or HFNC ≥5 L/min), patients should be managed per their allocated intervention.
- For patients extubated to pressure support <5 cm H_2O and reintubated within 24 hours of extubation, patients should be managed per their allocated intervention.
- For patients extubated to pressure support <5 cm H_2O and reintubated more than 24 hours after extubation, patients are preferably but not required to be managed per their allocated intervention.

IV. Positional Therapy Protocol

A. Both Groups

1. Positioning – ventilation sequence: Enrolled subjects will be placed in their randomized position first then transitioned to their randomized mode of mechanical ventilation.
2. Standard beds, per PICU's routine, will be used.
3. The head of the bed will be elevated at least 30 degrees.
4. When supine, positioning includes a cyclic rotation from full supine to right lateral/supine to full supine to left lateral/supine to full supine. If the care team believes that a subject cannot tolerate full turns than half turns (listing)[26] will be made every 2 hours to prevent the development of pressure injuries.
5. When supine, a draw sheet will be placed under the patient to facilitate patient turns every two hours. The patient's occiput will be cushioned using pressure-relieving materials (pillow, jell pillow, or similar). The patient's heels are elevated off the bed using an appropriate size pillow placed under the patient's lower legs. Side positioning will be maintained using a soft wedge. Only pressure relieving material will be placed under the patient (no rolled blankets, densely filled stuffed animals, etc.). The integrity of the patient's ear is verified whenever they are positioned on their side.

B. Supine Group

1. Patients assigned to the supine group will remain in supine.
2. If hypoxemia (SpO_2<85%) is persistent, may want to consider performing a maneuver to re-establishing lung volume (per ventilation mode) to increase the amount of aerated lung.
3. **Failed Supine:** Four-hour pattern of persistent hypoxemia (SpO_2<85%)
    a. CMV: with FiO_2 1.0 and max PEEP per grid (16 cm H_2O for < 1 year of age; 18 cm H_2O for ≥ 1 year of age).
    b. HFOV: with FiO_2 1.0 and mPaw > 35 cm H_2O

C. Prone Group

1. Patients assigned to prone positioning will be positioned prone within 4 hours of randomization and will remain prone for at least 16 consecutive hours/day.[27] When supine, patients may be returned prone position ≤ 8H if the SpO_2 decreases to <85% for more than 5 minutes.
2. To assure that each group is assessed at the same time each day (10:00 ± 2 hours), the prone positioned group will be returned supine after the morning assessment.[28] The subject's SpO_2 will be assessed immediately before and two hours after each supine-to-prone turn each prone-to-supine turn.
3. When subjects less that 8 years of age are prone positioned, the patient's head, upper chest, and pelvis are elevated to allow the abdomen to be unrestrained from the bed.
4. Prone positioning will be accomplished per associated procedure.[29]

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[26] Listing is defined as half turns in a patient's position for the purpose of shifting pressure points.
[27] We selected a continuous 16-hour period of prone positioning to remain consistent with the PROSEVA trial.
[28] Thus patients may not be positioned prone for 16 consecutive hours on their first day.
[29] Units using the Rotoprone bed as a standard of care in adolescents may continue to use the bed.

a. Depending on the size of the patient, each turn procedure (supine to prone; prone to supine) will involve 2-4 individuals including the patient's nurse and respiratory therapist.[30] During the turn procedure, one person (usually the respiratory therapist) will be delegated the primary responsibility of ETT protection.
b. When prone, the subject's head is turned to the side; arms are flexed up; and the lower limbs are cushioned so that the patient's toes are off the bed. The subject's abdomen will not be supported; specifically, rolls will not be used to the elevate the subject's upper chest, and pelvis to allow the abdomen to be unrestrained from the bed.
c. Prone repositioning includes a cyclic rotation from full prone to right lateral/prone to full prone to left lateral/prone to full prone. When tilted into a lateral prone position, the patient's dependent arm is repositioned against their torso and the non-dependent arm is flexed at the elbow and positioned up towards the patient's head. If the care team believes that the patient cannot tolerate full turns than half turns (listing) will be made every 2 hours to prevent the development of pressure injuries.

5. Unless a change in management is anticipated, procedures that require anterior access to the patient will be accomplished during the 8-hour supine time period.[31] If the care team decides to reposition a patient supine for a procedure during the subject's 16-hour prone period, the site co-investigator must be consulted. The care team and site co-investigator may elect to return the patient prone to complete their daily protocol after an evaluation of the clinical situation.
6. Failed Prone: Four-hour pattern of persistent hypoxemia (SpO_2<85%)
    a. CMV: with FiO_2 1.0 and max PEEP per grid (16 cm H_2O for < 1 year of age; 18 cm H_2O for ≥ 1 year of age).
    b. HFOV: with FiO_2 1.0 and mPaw > 35 cm H_2O
7. **Criteria for stopping prone positioning**
    a. Improving lung function consistent with resolving PARDS and the subject is close to meeting criteria to be tested for extubation readiness; Specifically, spontaneous breathing and OI < 8 (OSI < 7.5) in the supine position for at least 4 hours after the end of the last prone session. After 28 days of prone positioning, all patients who are still intubated can be positioned per the discretion of their care team.
    b. 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. If available, documentation of an increase in dead space reflecting a decrease volume of perfused lung after a supine-to-prone turn will be obtained.
8. **Prone positioning will be immediately discontinued in** an emergency: for example, 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.
9. Evolving clinical situations that may also preclude daily PP, that is, acute abdomen or Stage III pressure injury that cannot be managed in the PP.

[30] Two individuals can safely turn an infant, three individuals can safely turn a toddler and young school-aged child, four individuals can safely turn an older school-aged child and adolescent.
[31] Chest films may be obtained in the prone position.

V. Prone Position Procedure

A. Preparation for Prone Positioning

1. If < 8 years of age: (Note: No cushioning is required if ≥ 8 years of age.)
   - Create individually sized head, chest, pelvic, distal femoral, and lower limb cushions[32] using egg crate material (Eggcrate; Span American Medical Systems, Greenville, SC) or its equivalent to allow the patient's abdomen to be unrestrained from the patient's bed and to provide skin protection.
     1. The chest cushion should measure: slightly less than the right-to-left greater tubercle of the upper arm; equal the subject's anterior-posterior width; and wide enough to cover the subject's sternum when compressed.[33]
     2. The pelvic cushion should measure slightly smaller than the right-to-left iliac crest and be slightly smaller than the subject's anterior-posterior width.
     3. The head pillow should allow the subject's head to be slightly higher than their chest.
     4. A small cushion should be placed under the distal femur to elevate the subject's knees off the bed.
     5. The lower limb cushion should elevate the subject's toes off the bed.
2. On supine AP CXR, assure that the tip of the ETT is deeper than 1/3 of the thoracic trachea.[34]
3. Assess the security of the endotracheal tube (ETT), vascular lines, and SpO_2 probe (by applying gentle traction) and reinforce as necessary. If necessary, re-tape the ETT to the upper lip.[35] Place a protective layer of plastic tape over the white adhesive tape holding the ETT.[36]
4. If the patient is receiving neuromuscular blockade, provide eye protection. Specifically, cleanse, lubricate, then covered both eyes with plastic wrap.
5. If the patient is supported on high frequency oscillatory ventilation, apply a transparent film dressing over the anterior surface bony prominences to protect the skin against a friction injury.
6. Move EKG electrodes to the lateral aspects of the upper arms and hips.
7. Remove clothing surrounding thorax and abdomen.
8. Coil then secure bladder catheter to inner thigh.
9. Suction the patient's oropharynx.
10. Temporarily cap nonessential vascular lines and the patient's nasogastric tube. Review the start and end point of all that is left attached to the patient. Arrange the remaining vascular lines and bladder catheter tubing to prevent excessive tension.
11. May provide pre-procedural sedation at the discretion of the nurse caring for the patient.

B. Prone Positioning

1. The bedside nurse(s)/respiratory therapist team will coordinate the turn.
2. Preplan who will be responsible for what patient aspect (e.g., head/ETT - respiratory therapist; chest/arms – Nurse 1; hips/legs – Nurse 2).

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[32] Roll loosely and/or cut to appropriate compressed size. Tape along edges to retain shape. Cover egg crate material with pillowcases so that they can easily slide under the patient.

[33] Avoid hyperextension of the patient's shoulder girdle - shoulders should fold into cushion.

[34] Marcano et al. Cephalad movement of tracheal tubes due to PP of pediatric patients with ARDS. CCM 2000; 28(12supp); A31.

[35] To prevent pressure necrosis, the ETT should not be positioned at the corner of the mouth.

[36] Draining oral secretions will loosen the white adhesive tape.

3. Review technique:
   a. Infants/toddlers: levitate up, turn 45 degrees, pause/reassess, turn prone, levitate up to place cushions under the subject.
   b. Children <8 years: using all the bed linens under the subject - slide patient to the edge of the bed away from the ventilator, place new draw sheet over patient; position chest and pelvic cushions over new draw sheet; place new full sheet over entire patient; create a mummy effect by tucking the edges of the full sheet under patient; turn patient 45 degrees toward ventilator, pause/reassess, position patient prone on new linen and cushions/remove old linen.
   c. Children >8 year: using all the bed linens under the subject - slide patient to the edge of the bed away from the ventilator, place new draw sheet over patient; place new full sheet over entire patient; create a mummy effect by tucking the edges of the full sheet under patient; turn patient 45 degrees toward ventilator, pause/reassess, position patient prone on new linen and remove old linen.
4. During the turn keep the patient's head in alignment with their body – avoid hyperextension; contain the patient's arms next to their torso; support the patient's legs so that the toes of the upper leg point in the direction of the turn.
5. Patients are turned toward the ventilator without disconnecting the patient from the ventilator.[37] If the patient must be disconnected from the ventilator consider clamping the ETT using a smooth clamp to avoid the loss of lung volume. If the patient requires ETT suctioning, turning is delayed until the patient is suctioned and has returned to pre-suctioning ventilator settings.[38]
6. Ventilator management: If deemed necessary by the care team, the FiO_2 may be manipulated to maintain the target SpO_2 during repositioning. After study blood gases are obtained ventilator settings can be adjusted to achieve target blood gases.[39]
7. Talk the patient through the turn.

C. Immediately after Prone Positioning

1. Reassess the security and patency of all tubes/lines.
2. Reassess SpO_2, blood pressure cardiac rhythm, breath sounds.
3. Reassess ETT/Tracheostomy air leak; may readjust cuff volume, head position, or delivered Vt to assure adequate ventilation.
4. Uncap/reattach capped off lines/nasogastric tube.
5. Position the patient:
   a. Turn head to side and cushion head and ear with pressure relieving material. Place an absorbent diaper under the patient's mouth to catch draining naso/oropharyngeal secretions.
   b. If < 8 years, avoiding excessive flexion/extension of the spine, cushion the upper chest, and pelvis using either a rolled eggcrate or foam pad - allowing the abdomen to protrude. In adolescent females, check that the breasts/nipples are not pinched. In males, check that the penis and scrotum are unrestrained.
   c. Flex arms up.
   d. Position knees and feet off bed using a roll under the distal femur and lower leg.

[37] Prevent a loss of lung volume. If patient is disconnected from ventilator than re-recruitment maneuvers may be used to reestablish lung volume.
[38] Extremely important in vulnerable patients who decompensate with multiple procedures.
[39] If the patient is supported on HFOV the care team should anticipate the need to increase the oscillator's power to maintain the same $PaCO_2$ while in the prone position.

e. Check that everything attached to the patient is not pressing against their skin (e.g., ETT balloon port) and that the patient's skin in not pinched in any way (e.g., peri-umbilical area).

D. Supine Repositioning

1. The bedside nurse/respiratory therapist team will coordinate the turn.
2. The precautions and techniques described above apply with the following changes.
3. Consider performing the patient's daily suctioning procedure at hour 14.[40]
4. Patients are turned away from the ventilator without disconnecting the patient from the ventilator.[41]
5. Position the patient:
   a. Cushion head using pressure-relieving materials (pillow, jell pillow).
   b. Elevate the patient's heels off the bed using an appropriate size pillow.

[40] Bronchial drainage may be enhanced while in the prone position.

[41] Prevent a loss of lung volume. If patient is disconnected from ventilator than re-recruitment maneuvers may be used to reestablish lung volume.

VI. Prone Positioning Check Sheet

Preparation (Prior to getting help into room)	
❑	If < 8 years of age: Create cushions using egg crate material (head, chest, pelvic, distal femoral, & lower limb). No cushions necessary if ≥ 8 years of age.
❑	Check ETT on CXR - tip should be in the lower 1/3 of the thoracic trachea.
❑	Assess the security of the ETT, vascular lines, SpO_2 probe and reinforce as necessary. ○ Retape the ETT to the upper lip on the side of the mouth that will end in the "up" position. ○ Place a protective layer of plastic tape over the white adhesive tape holding the ETT.
❑	Protect eyes if chemically paralyzed &/or open (cleanse, lubricate, cover with plastic wrap).
❑	If HFOV, apply plastic film dressing over anterior bony prominences to avoid friction injury.
❑	Move EKG electrodes to the lateral aspects of the upper arms and hips.
❑	Remove clothing surrounding thorax and abdomen.
❑	Coil then secure bladder catheter to inner thigh.
❑	Suction the patient's oropharynx. (If ETT suctioned, postpone turn until unit patient returned to pre-suctioning ventilator settings).
❑	Temporarily cap nonessential vascular lines and the patient's NGT/JT.
❑	Final Check - Review the start and end point of all that is left attached to the patient. Arrange the remaining vascular lines and Foley catheter tubing to prevent excessive tension.
❑	Premed with comfort medications at the discretion of the bedside nurse.
Turing (Bedside nurse/RT team.)	
❑	Call for RT and at least one other nurse.
❑	Preplan responsibility: RT - Head/ETT; Nurse 1 - chest/arms; Nurse 2 - hips/legs.
❑	Review technique: ○ Infants/toddlers: Levitate = levitate up, turn 45 degrees, pause/reassess, turn prone, to place cushions under the subject. ○ Children: Mummy = using all bed linens - slide patient to the edge of the bed away from the ventilator, place new draw sheet over patient; (If < 8 years: position chest and pelvic cushions over draw sheet); place full sheet over entire patient; create a mummy effect by tucking the edges of the full sheet under patient; turn patient 45 degrees toward ventilator, pause/reassess, position patient prone on new linen and cushions/remove old linen.
❑	Keep head in alignment with body, avoid hyperextension, keep arms next to torso, point toes of the upper leg in the direction of turn.
❑	Turn toward the ventilator without disconnecting. (FiO_2 may be manipulated to maintain target SpO_2. All other ventilator settings remain constant until 1-hour post turn ABG obtained.)
❑	Talk the patient through the turn.

Immediately after the Turn	
❑	Reassess the security and patency of all tubes/lines.
❑	Reassess SpO_2, blood pressure, cardiac rhythm, & breath sounds.
❑	Reassess ETT/Trach leak (May adjust cuff volume, head position, delivered Vt to assure adequate ventilation.)
❑	Uncap/reattach capped off lines/NGT/NJT.
❑	Position the patient: o Turn head to side & cushion head and ear with pressure relieving material. o Place an absorbent diaper under the patient's mouth. o If < 8 years: Avoid excessive flexion/extension of the spine. In adolescent females, check that the breasts/nipples are not pinched. In males, check that the penis and scrotum are unrestrained. o Flex arms up. o Position knees and feet off bed using a roll under the distal femur and lower leg. o Check that everything attached to the patient is not pressing against their skin (ETT balloon port) and that the patient's skin in not pinched in any way (peri-umbilical area).
Return to Supine	
❑	Precautions & techniques described above apply.
❑	Consider performing the patient's daily suctioning procedure at hour 14 (2 hours before turn)
❑	Patients are turned away from the ventilator without disconnecting.
❑	Position the patient: o Cushion head using pressure-relieving materials (pillow, jell pillow). o Elevate the patient's heels off the bed using an appropriate size pillow.

VII. 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 followed so that ventilator management can be described and for study outcomes.

VIII. Hemodynamic Management Guidelines (all groups)

A. Patients will be managed using a fluid conservative strategy, as outlined below.[42]
B. The goal is adequate cardiac output to meet the metabolic needs of the patient, specifically, an acceptable blood pressure for age,[43] brisk capillary refill, and adequate peripheral perfusion to achieve adequate end organ perfusion.
C. The care team will delineate daily mean arterial BP goals.[44]
D. Hypotension, as defined by American Heart Association PALS guidelines,[45] is managed per the shock protocol for resuscitation.
E. If hypotension is not present (may be on dopamine ≤ 5 mcg/kg/min, or epinephrine ≤ 0.03 mcg/kg/min, or any dose of milrinone), determine the appropriate column by evaluating the effectiveness of the circulation. Locate the appropriate instruction box by determining fluid balance (hourly input and urine output).
F. Fluid management in subjects with concurrent acute renal failure are managed at the discretion of the care team.
G. Hemodynamic assessments will be documented at least every four hours. These measurements include systolic blood pressure, urine output/kg/hr, clinical assessment of the effectiveness of the arterial circulation, and central venous pressure (if available). Standard methods for assessing the effectiveness of arterial circulation, that is, capillary refill time, cutaneous "mottling" of the extremities, and core-extremity temperature differences will be used.
H. Fluid Management
    1. Maintenance fluids are calculated per standard pediatric practice.[46]
    2. The care team will determine the type of fluid (colloids, crystalloids) administered.
    3. All fluids, including IV continuous infusions, IV intermittent medications, blood products, IV and enteral nutrition, will contribute to the patient's hourly total. Medications should be administered using the least amount of fluid possible.
    4. Of note, routine pRBC transfusion for a hemoglobin >7 g/dl, without evidence of severe hypoxemia, poor tissue perfusion, active bleeding, or hemodynamic instability, is not recommended.
    5. In choosing fluids, ensure normoglycemia.
I. Furosemide is used to achieve desired fluid balance.
    1. Consider withholding if:
        a. vasopressor or a fluid bolus given in the last 24 hours OR
        b. renal failure present (dialysis dependence) OR oliguria with creatinine 2x upper limit of normal for age OR oliguria with creatinine <2x upper limit of normal for age and urinary studies indicative of acute renal failure.
    2. Begin continuous IV infusion of 0.05 mg/kg/hr (consider 0.5 mg/kg initial bolus) **OR** bolus 0.5-2 mg/kg/dose IV (single suggested max bolus: 20 mg) every 6-12 hours **OR** last known effective dose.
    3. Double continuous infusion hourly, after the first 6 hours, until urine output >0.5

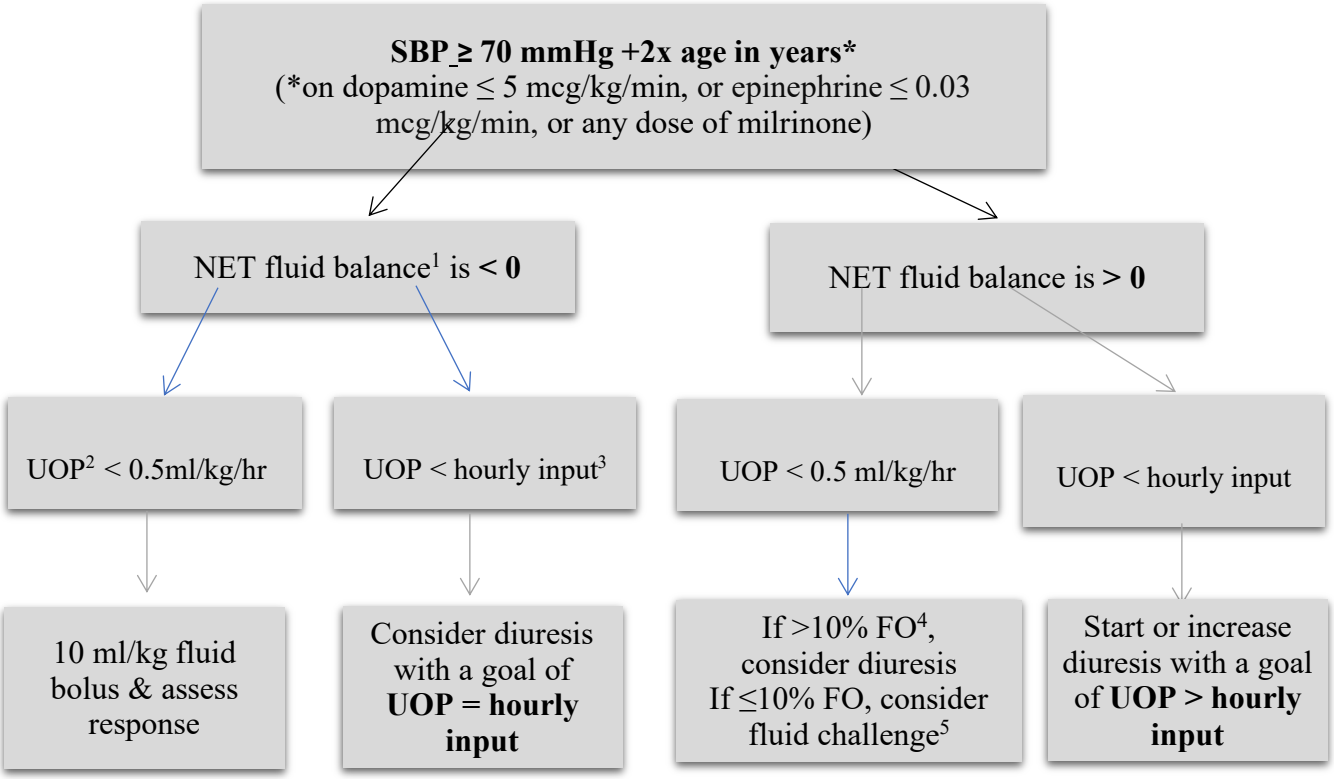
[42] Sections of this protocol were modified from that provided by Stacey Valentine, MD; University of Massachusetts
[43] Blood pressure that is associated with normal lactate, urine output, delta skin-core < 2 degrees C and normal capillary refill.
[44] The use of a central venous catheter is not mandated. CVP includes internal jugular, subclavian or long femoral line in the absence of abdominal pathology. Consider with reproducible waveforms.
[45] Hypotension is defined as a systolic blood pressure <70 mmHg + 2x age in years.
[46] Maintenance fluids universal standard: 100 ml/kg first 10 kg + 50 ml/kg second 10 kg + 25 ml/kg third plus kg.

ml/kg/hour **OR** maximum infusion of 0.5 mg/kg/hr or maximum total daily dose of 8 mg/kg (not to exceed -600 mg/day).

a. Discontinue if:
   1) no response to maximum dose after 1 hour **OR**
   2) intravascular pressure declines to a cell not requiring furosemide therapy.

4. May repeat diuretic trial q 24 hours.
5. The care team may elect to add a second diuretic to achieve the above stated clinical outcomes.

Fluid balance algorithm



[1] **NET fluid balance** = total measured fluids administered to the patient from admission to study randomization (including all nutrition, medications, blood products and intravenous fluids) – total of fluids removed or excreted from the patient (in milliliters) divided by body weight (in kilograms).
[2] **UOP** = urine output as measured in ml/kg/hour. If a Foley catheter is not in place, average each void over the period that elapsed since the previous void.
[3] **Hourly input** = total fluids being given including all continuous infusions, nutrition, intermittent medications and/or blood products.
[4] **Fluid overload** percentage = [(Total intake (L) – Total output (L)) /weight (kg)] x 100%
[5] **Fluid challenge** = 5-10 ml/kg given via push/pull technique with bedside monitoring of HR and BP. If no improvement in HR, consider start of diuresis to augment urine output.

J. Fluid Bolus may be required to reestablish adequate tissue perfusion.
   1. Use 10-15 ml/kg (ideal body weight) normal saline, Ringer's lactate, pRBCs, or albumin. Administer as rapidly as possible then reassess patient. Repeat up to 3 times daily if indicated by protocol.
   2. Fluid bolus may be withheld if bolus was given within 24 hours and such bolus did

not result in a sustained increase in filling pressure.

K. Inotropes may be necessary to maintain adequate tissue perfusion. Choice at the discretion of the clinical care team.
   1. Dopamine
      a. Start at 5 mcg/kg/min and increase by 5 mcg/kg/min in increments at ~15-minute intervals until ineffective circulation reversed or maximum dose of 20 mcg/kg/min is reached.
      b. Wean by 1-2 mcg/kg/min every 1-2 hours as tolerated, beginning 4 hours after signs of ineffective circulation are reversed.
   2. Epinephrine:
      a. Start at 0.03 mcg/kg/min and increase by 0.02 mcg/kg/min in increments at ~15-minute intervals until ineffective circulation reversed or maximum dose of 0.1 mcg/kg/min is reached.
      b. Wean by 0.01-0.02 mcg/kg/min every 1-2 hours as tolerated, beginning 4 hours after signs of ineffective circulation are reversed.
   3. Milrinone:
      a. Milrinone is administered with a loading dose (optional) followed by a continuous infusion. Volume expanders should be made available to counteract both vasodilator and decreases in filling pressures.
      b. Loading Dose (optional): 50 mcg/kg IV x 1 administered slowly over 20 minutes.
      c. Maintenance Dose: Continuous infusion 0.25-0.75 mcg/kg/min.
   4. Dobutamine
      c. Start at 5 mcg/kg/min and increase by 5 mcg/kg/min in increments at ~15-minute intervals until ineffective circulation reversed or maximum dose of 20 mcg/kg/min is reached.
      d. Wean by 1-2 mcg/kg/min every 1-2 hours as tolerated, beginning 4 hours after signs of ineffective circulation are reversed.

L. Shock Guidelines

   1. Fluid Bolus: Use 20 ml/kg (ideal body weight) normal saline or Ringers Lactate. Administer as rapidly as possible then reassess patient. Repeat bolus at least up to 6 times daily if indicated by protocol.
   2. Vasopressor Therapy: Choice of any single agent or any combination of the following to re-establish and maintain normal blood pressure for age:
      a. Dopamine 5 mcg/kg/min, increase in 2 mcg/kg/min steps q 3-5 min to maximum of 20 mcg/kg/min. (Note: Dopamine <3 mcg/kg/min is not considered a vasopressor.)
      b. Norepinephrine at 0.05 mcg/kg/min, increase in 0.05 mcg/kg/min steps q 3-5 min to maximum of 1 mcg/kg/min.
      c. Epinephrine at 0.05 mcg/kg/min, increase in 0.05 mcg/kg/min steps q 3-5 min to maximum of 0.3 mcg/kg/min.
      d. Phenylephrine at 0.1 mcg/kg/min, increase in 0.1 mcg steps q 3-5 min to maximum of 1.5 mcg/kg/min

IX. Sedation Guidelines (all groups)

A. The goals of comfort therapy include analgesia, amnesia, anxiolysis, and compliance with routine care.

B. The patient's level of comfort is assessed per phase of illness and criticality:
   1. Sedation levels will be scored using a valid and reliable pediatric sedation assessment instrument; e.g., the State Behavioral Scale (SBS) or the COMFORT Behavioral Scale at least every 4 hours while intubated.
   2. Pain levels will be scored using an age-appropriate pain scale at least every 4 hours while in the PICU. The pain scale used depends on the patient's age and verbal/cognitive capacity: e.g., the Face, Legs, Activity, Cry, Consolability (FLACC) scale in nonverbal children 0 to 6 years of age, the individualized numeric rating scale (INRS) in nonverbal cognitively impaired children age 6 and older, and the Wong-Baker Faces Pain Scale (WBFPS) in verbal children age 3 and older. All pain scales range 0-10 with higher scores indicating more pain.
   3. In patients receiving neuromuscular blockade, pain/agitation is judged to be present by the bedside nurse when a patient demonstrates a ≥20% increase in heart rate or blood pressure when stimulated.
   4. Delirium screening using either the Cornell Assessment of Pediatric Delirium (CAPD) or the Pediatric or Preschool Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU/psCAM-ICU) will be accomplished at least daily while in the PICU.
   5. Patients weaning from ≥5 days of sedation are monitored for Iatrogenic withdrawal syndrome (IWS) using the Withdrawal Assessment Tool-1 (WAT-1). The WAT-1 scale ranges 0-12 with higher scores indicating more withdrawal symptoms at least Q12 hours.

C. The patient's care team will prescribe a level of sedation/analgesia on daily rounds. Oversedation will be avoided. Nurses will use a sedation protocol to maintain the patient's level of comfort in the prescribed range.[47] Developmentally appropriate adjunct measures should be utilized whenever possible to help minimize the risks of excessive pharmacological intervention.

D. Patients will receive pre-procedural comfort medications at the discretion of their care team.

[47] See Curley, M.A.Q., Wypij, D., Watson, R.S., Grant, MJ.C., Asaro, L.A., Cheifetz, I.M., Dodson, B.L., Franck, L.S., Gedeit, R.G., Angus, D.C., Matthay, M.A., for the RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. (2015). Protocolized Sedation versus Usual Care in Pediatric Patients Mechanically Ventilated for Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA, 313(4):379-389.* (PMID: 25602358; PMC4955566)

X. Skin Care and Pressure Injury Guidelines (all groups)

A. The goal of therapy is to maintain skin integrity.

B. A daily skin assessment will be performed and recorded on every patient during the acute treatment phase. A Braden QD will be obtained three times per week on Monday, Wednesday and Fridays. After the acute treatment phase, the Braden QD performed and recorded every Wednesday until PICU discharge. Pressure injuries will be staged and managed according to National Pressure Injury Advisory Panel (NPUAP) guidelines.[48]

C. Pressure injuries will be prevented by applying universally accepted prevention strategies. Specifically, patients will be turned (listed; offloaded) every two hours. Turn schedules will be documented. Specific patient padding will be delineated in the eMOO. All offloading and pressure injury prevention surfaces will consist of pressure redistribution material. Foam dressings may be placed on bony prominences and labeled with a "P" for prevention. Preventative foam dressings may be worn for 7 days and peeled back daily to examine the skin beneath.

D. Pressure injuries will require an evaluation by a Skin Care Specialist as soon as possible after identification. In addition to continuing aggressive prevention strategies:

- Stage 1 pressure injuries may be treated by the application of a transparent film dressing or a sting-free barrier film dressing. Sting-free barrier film dressings applied daily or twice daily to bony prominences are also ideal to protect from friction-shear injury during supine/prone positioning. Sting-free barrier film also protects skin from medical adhesive-related skin injury (also called epidermal stripping or skin tears).

- Stage 2 pressure injuries will be treated by the application of an absorbent foam dressing. Foam dressings that are applied over Stage 2 wounds should be labeled with a "2" to correspond with the Stage so providers know what is beneath. Foam dressings on Stage 2 pressure injuries should be worn for 5 days and peeled back daily to examine the skin beneath. Open blisters also benefit from an absorbent foam dressing.

- Stage 3 and 4 pressure injuries will be treated according to a dry or moist wound bed. A dry Stage 3 or 4 will be treated with NSS moistened gauze dressing. A moist Stage 3 or 4 will be treated with a calcium alginate dressing. Label a secondary dressing with a "3" or "4" to correspond with the Stage so providers know what is beneath.

[48] Classify as Stage 1 or 2 or 3 or 4, based on the deepest tissue type exposed. Stage 1 pressure injuries include reversible non-blanchable erythema of intact skin; Stage 2 pressure injuries include partial thickness skin loss involving epidermis and/or dermis; Stage 3 pressure injuries include full thickness skin loss involving damage and necrosis of subcutaneous tissue that may extend down to, but not though, underlying fascia; and Stage 4 include full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures. If the wound base cannot be evaluated, classify as: Deep Tissue Pressure Injury (DTPI) when the skin is intact with deep red, purple or maroon discoloration or blood blister(s) or as Unstageable when the base is obscured by slough or eschar. If on a mucosal membrane, document, but do not stage. National Pressure Ulcer Advisory Panel NPUAP Pressure Ulcer Stages http://www.npuap.org/resources/educational-and-clinical-resources/npuap-pressure-injury-stages/, Accessed October 12, 2018.

- Unstageable pressure injuries may be treated with an active Leptospermum honey/hydrocolloid product.

- Deep Tissue Pressure Injuries (DTPI) should be protected with offloading. No dressing is needed.

- Mucosal pressure injuries require removing the source of pressure (e.g., changing the side or location of a medical device).

Appendix 1: Ideal Body Weight (kg) by Length (cm), Gender and Age Weight-for-Recumbent-Length: 2 Weeks to 36 Months

Recumbent Length (cm)	Weight (kg)			Recumbent Length (cm)	Weight (kg)	
	Male	Female			Male	Female
45	2.29	2.31		74.5	9.51	9.34
45.5	2.39	2.40		75.5	9.74	9.57
46.5	2.59	2.61		76.5	9.97	9.79
47.5	2.80	2.82		77.5	10.21	10.02
48.5	3.02	3.04		78.5	10.43	10.24
49.5	3.25	3.26		79.5	10.66	10.47
50.5	3.48	3.49		80.5	10.89	10.69
51.5	3.72	3.72		81.5	11.12	10.91
52.5	3.96	3.96		82.5	11.34	11.13
53.5	4.21	4.20		83.5	11.57	11.35
54.5	4.47	4.45		84.5	11.79	11.57
55.5	4.72	4.69		85.5	12.02	11.80
56.5	4.98	4.94		86.5	12.24	12.02
57.5	5.24	5.19		87.5	12.47	12.24
58.5	5.50	5.44		88.5	12.70	12.46
59.5	5.76	5.70		89.5	12.92	12.69
60.5	6.02	5.95		90.5	13.16	12.91
61.5	6.28	6.20		91.5	13.39	13.14
62.5	6.54	6.45		92.5	13.62	13.37
63.5	6.79	6.70		93.5	13.86	13.61
64.5	7.05	6.95		94.5	14.10	13.84
65.5	7.30	7.20		95.5	14.34	14.08
66.5	7.56	7.44		96.5	14.59	14.33
67.5	7.81	7.69		97.5	14.84	14.58
68.5	8.06	7.93		98.5	15.10	14.83
69.5	8.30	8.17		99.5	15.35	15.09
70.5	8.55	8.41		100.5	15.62	15.36
71.5	8.79	8.64		101.5	15.89	15.63
72.5	9.03	8.88		102.5	16.16	15.91
73.5	9.27	9.11		103.5	16.43	16.19

This chart is an example from the National Center for Health Statistics. Charts used locally should match the norms of the enrolled subject.

Appendix 2: Ideal Body Weight (kg) by Length (cm), Gender and Age Weight-for-Recumbent-Length: 3-18 Years

Recumbent Length (cm)	Weight (kg)			Recumbent Length (cm)	Weight (kg)	
	Males	Females			Males	Females
77-80	10.53	10.34				
80-82	11.19	10.98				
82-84	12.09	11.86		130-132	27.4	26.8
86-88	12.54	12.31		132-134	28.4	28.0
88-90	13.2	12.9		134-136	29.8	29.4
90-92	13.6	13.3		136-138	31.2	31.0
92-94	14.0	13.8		138-140	32.7	32.4
94-96	14.4	13.8		140-142	34.3	34.1
96-98	14.9	14.20		142-144	35.7	35.6
98-100	15.5	14.90		144-146	37.5	37.0
100-102	16.0	15.40		146-148	39.1	38.1
102-104	16.7	16.0		148-150	40.7	39.2
104-106	17.2	16.6		150-152	42.3	40.7
106-108	17.9	17.3		152-154	43.6	41.8
108-110	18.7	17.8		154-156	45.4	43.3
110-112	19.2	18.6		156-158	46.7	44.7
112-114	20.0	19.2		158-160	48.1	46.0
114-116	20.8	19.7		160-162	49.4	48.1
116-118	21.4	20.5		162-164	50.8	51.4
118-120	22.2	21.2		164-166	63.8	59.3
120-122	23.0	22.0		166-168	65.64	61.14
122-124	23.8	22.9		168-170	67.48	62.98
124-126	24.6	23.6		170-172	69.32	64.82
126-128	25.5	24.5		172-174	71.6	66.66
128-130	26.4	25.5		174-176	73	68.5
				176-178	74.84	70.34
				178-180	76.68	72.18

This chart is an example from the National Center for Health Statistics. Charts used locally should match the norms of the enrolled subject.

- If male height is >178 cm, then IBW (kg) = 50 + 2.3[(height in cm * 0.3937) – 60]
- If female height is >164 cm, then IBW (kg) = 45.5 + 2.3[(height in cm * 0.3937) – 60]