Title:	**Pediatric Acute Respiratory Distress Syndrome (ARDS) Management (PARMA) Trial**
Short Title	PARMA
Drug or Device Name(s):	n/a
FDA IND	n/a
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ABBREVIATIONS AND DEFINITIONS OF TERMS

AECC	American-European Consensus Conference
AE	Adverse event
ARDS	Acute Respiratory Distress Syndrome
CHOP	Children's Hospital of Philadelphia
DCC	Data Coordinating Center
DSMB	Data Safety and Monitoring Board
EIT	Electrical Impedance Tomography
HR	Hazard Ratio
NICHD	National Institutes of Child Health and Development
ΔP	Peak inspiratory pressure minus PEEP
PARMA	Pediatric ARDS MAnagement
PCV	Pressure control ventilation
PEEP	Positive End-Expiratory Pressure
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
SAE	Serious Adverse Event
VFD	Ventilator-Free Days
VILI	Ventilator-Induced Lung Injury
V_T	Tidal Volume

ABSTRACT

Context: (Background)

Acute respiratory distress syndrome (ARDS) is characterized by acute onset of diffuse, bilateral pulmonary edema and severe hypoxemia not fully explained by cardiac failure, representing 10% of mechanically ventilated children in pediatric intensive care units (PICUs), with an associated mortality rate of up to 20%. Lung-protective ventilation with lower tidal volumes and driving pressures (defined as plateau pressure minus positive end-expiratory pressure, ΔP) is the backbone of ventilation strategies in adults, with variable adoption in pediatrics. However, pre-clinical and observational clinical data suggest that the tidal volume and ΔP limits extrapolated from adults are too restrictive for children. As lower tidal volumes and ΔP are associated with worse oxygenation and ventilation, overly restrictive lung-protective ventilation may contribute to prolonged ventilation via worse gas exchange in pediatrics with no improvement in outcomes, thus justifying an explicit trial of different ΔP strategies in pediatric ARDS.

Objectives: (primary and important secondary objectives)

We aim to test the efficacy of a high ΔP (25 cmH2O) versus low ΔP (15 cmH2O) ventilation on time to resolution of ARDS (alive and $PaO_2/FIO_2 > 300$), hypothesizing faster hypoxemia resolution (Aim 1), and improved lung aeration (Aim 2) with high ΔP.

Study Design:

Single-center, parallel-arm, unblinded phase 2A randomized trial.

Setting/Participants:

PARMA will be conducted primarily in the pediatric intensive care unit (PICU) at CHOP, with follow up until hospital discharge or 90 days (whichever comes first) in the CHOP PICU or inpatient floor setting. We will enroll children > 2 weeks and < 18 years receiving invasive mechanical ventilation meeting Berlin ARDS criteria, excluding severely moribund subjects or those with limitations of care.

Study Interventions and Measures:

We will compare a high ΔP (25 cmH_2O) versus low ΔP (15 cmH_2O) strategy on time to hypoxemia resolution (alive and $PaO_2/FIO_2 > 300$) while assessing effects on lung aeration as measured by non-invasive electrical impedance tomography (EIT).

PROTOCOL SYNOPSIS

Study Title	**Pediatric Acute Respiratory Distress Syndrome (ARDS) Management (PARMA) Trial**
Funder	NICHD
Clinical Phase	Phase 2A
Study Rationale	Acute respiratory distress syndrome (ARDS) is characterized by acute onset of diffuse, bilateral pulmonary edema and severe hypoxemia not fully explained by cardiac failure, representing 10% of mechanically ventilated children in pediatric intensive care units (PICUs), with an associated mortality rate of up to 20%. Lung-protective ventilation with lower tidal volumes and driving pressures (defined as plateau pressure minus positive end-expiratory pressure, ΔP) is the backbone of ventilation strategies in adults, with variable adoption in pediatrics. However, pre-clinical and observational clinical data suggest that the tidal volume and ΔP limits extrapolated from adults are too restrictive for children. As lower tidal volumes and ΔP are associated with worse oxygenation and ventilation, overly restrictive lung-protective ventilation may contribute to prolonged ventilation via worse gas exchange in pediatrics with no improvement in outcomes, thus justifying an explicit trial of different ΔP strategies in pediatric ARDS.
Study Objective(s)	**Primary** • To test the efficacy of a high ΔP (25 cmH2O) versus low ΔP (15 cmH2O) ventilation on time to resolution of ARDS (alive and PaO2/FIO2 > 300), hypothesizing faster hypoxemia resolution (Aim 1) with high ΔP **Secondary** • To test the efficacy of a high ΔP (25 cmH2O) versus low ΔP (15 cmH2O) ventilation on lung aeration , hypothesizing improved lung aeration (Aim 2) with high ΔP
Test Article(s) *(If Applicable)*	High ΔP (25 cmH2O) versus low ΔP (15 cmH2O) mechanical ventilation strategy
Study Design	Parallel group, unblinded, randomized controlled trial
Subject Population **key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1) age > 2 weeks (> 38 weeks corrected gestational age) and < 18 years (not yet had 18th birthday) 2) acute (≤ 7 days of inciting etiology) respiratory failure requiring invasive mechanical ventilation

	3) ventilated with endotracheal tube or tracheostomy for ≤ 7 days from inciting etiology onset 4) hypoxemia defined as $PaO_2/FIO_2 \leq 300$ (or $SpO_2/FIO_2 \leq 315$) on PEEP ≥ 5 cmH_2O on two consecutive measurements 4 hours apart and sustained at the time of consent and randomization 5) bilateral opacities on chest radiograph as determined by radiologist, clinical attending, or PI. **Exclusion Criteria** 1) hypoxemia caused primarily by hydrostatic pulmonary edema from heart failure or fluid overload 2) non-palliated or unrepaired cyanotic congenital heart disease 3) ventilated via tracheostomy at baseline prior to acute illness 4) obstructive airway disease determined to be the primary cause of respiratory failure 5) severe moribund state not expected to survive > 72 hours 6) any limitations of care at time of screening 7) escalation to high frequency oscillatory ventilation or extracorporeal support (i.e., meeting PARMA protocol failure criteria) at time of screening 8) previous enrollment in this study
Number Of Subjects	160 subjects, all at CHOP
Study Duration	Each subject's participation will last until hospital discharge or 90 days post-randomization, whichever comes first.
Study Phases	1) Screening and approach 2) Intervention 3) Follow-up
Efficacy Evaluations	The primary outcome (Aim 1A) of PARMA is time to sustained resolution of hypoxemia, defined as being alive with $PaO_2/FIO_2 > 300$ (or $SpO_2/FIO_2 > 315$) on two consecutive measurements 4 hours apart.
Pharmacokinetic Evaluations	*n/a*
Safety Evaluations	pneumothorax requiring chest tube; other air leak not requiring chest tubes; ventilator-associated pneumonia; acidosis requiring additional vasopressor support; protocol

	termination for failure criteria; new or progressive multiple organ dysfunction syndrome
Statistical And Analytic Plan	PARMA will be analyzed using Bayesian survival analyses, with effect size presented as a hazard ratio (HR). The main analysis will use a minimally informative prior centered at HR = 1 (log[HR] = 0) and precision = 10 (log scale). The primary outcome of hypoxemia resolution (Aim 1) will be assessed as a time to event (in hours) from randomization until the primary event of hypoxemia resolution. Subjects who die before hypoxemia resolution will remain in the risk set and be considered as being "never able to achieve hypoxemia resolution" (effectively being treated as a competing risk). Subjects who achieve hypoxemia resolution and die subsequent to that will be considered as having achieved the primary outcome. The high ΔP (comparator) arm will be compared to the low ΔP (reference) arm, and efficacy reported as HR with 95% credible intervals. Posterior probabilities under minimally informative priors will be computed for any benefit (HR > 1, meaning faster time to hypoxemia resolution with high ΔP), HR > 1.25, and HR > 1.5 (projected "true" effect size).
DATA AND SAFETY MONITORING PLAN	An independent Data and Safety Monitoring Board is required to oversee participant safety in the clinical trial and provide overall monitoring of interim data and safety issues. Our proposal for DSMB function reflects our prior experience, but we understand that DSMB function will be determined by NICHD. The purpose of the DSMB is to advise the NICHD and Dr. Yehya regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the protocol, assessments of data quality, performance of the clinical site, review of serious adverse events (SAEs) and other subject safety issues. The PI will send reports relating to these topics to DSMB members prior to each DSMB meeting. It is anticipated that the DSMB will meet every 6 months, but the DSMB will have the final say in determining meeting intervals. The DSMB will meet once prior to the start of the PARMA trial to approve the final protocol prior to implementation. We will draft a DSMB charter to guide its function for the trial and the charter will be approved by the DSMB. The charter will include rules of procedure, definitions of a meeting quorum, and information about meeting logistics and frequency. After the DSMB has approved its charter and the final protocol, this information will be sent to CHOP IRB.

	DSMB meetings to evaluate study protocols, prior to study implementation, may be open or closed according to the decision of the DSMB members. We suggest that these meetings should be open to members of the PARMA investigative team when there are no confidential components to these proceedings in order to facilitate the review and appropriate alterations of the protocol in response to DSMB concerns. The DSMB will meet no less frequently than every 6 months, with a focus on safety. The DSMB can recommend whether or not to terminate enrollment in PARMA because of potential safety concerns or study feasibility issues. We have not planned interim efficacy analyses in this phase 2 trial. Early stopping will only be considered if SAEs or enrollment rates lead to concerns about continuation of the trial. As per NICHD practices, the DSMB recommendations will be signed and submitted to the NICHD officer (who is usually the Executive Secretary for the DSMB) within a reasonable time after the DSMB meeting. After approval or modification by the NICHD, the officer will forward the DSMB report to the PI, who will forward to the IRB. In the unlikely event that the DSMB recommends emergent cessation of enrollment in PARMA because of safety concerns, this communication will be made during the debriefing segment of the DSMB meeting. If the NICHD staff concur with this recommendation, the PI will notify all PARMA-related investigators and staff to cease enrollment immediately.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Enrollment Window**	**Randomization (≤ 4 hours of consent)**	**Treatment Protocol**		**Follow-up**		
Visit Number	**0**	**1**	**1**	**2**	**3**	**4**	**5**
Study Days	**1**	**1**	**1**	**2-3**	**1-28**	**1-90**	**1-90**
Informed Consent/Assent	X						
Review Inclusion/Exclusion Criteria	X						
Demographics/Medical History	X						
Vital Signs: BP, HR, RR (medical record)	X						
Height and Weight (medical record)	X						
Prior/Concomitant Medications	X						
Clinical Laboratory Evaluation	X						
Randomization		X					
Ventilator protocol			X	X	X	X	X
EIT protocol			X	X			
Protocol Compliance		X	X	X	X	X	X
Primary outcome to day 28					X		
Hospital discharge						X	
90 days after randomization (if not discharged)							X
Adverse Event Assessment			X	X	X	X	X
Discontinuation of Ventilation Protocol							
Withdrawal from Study							

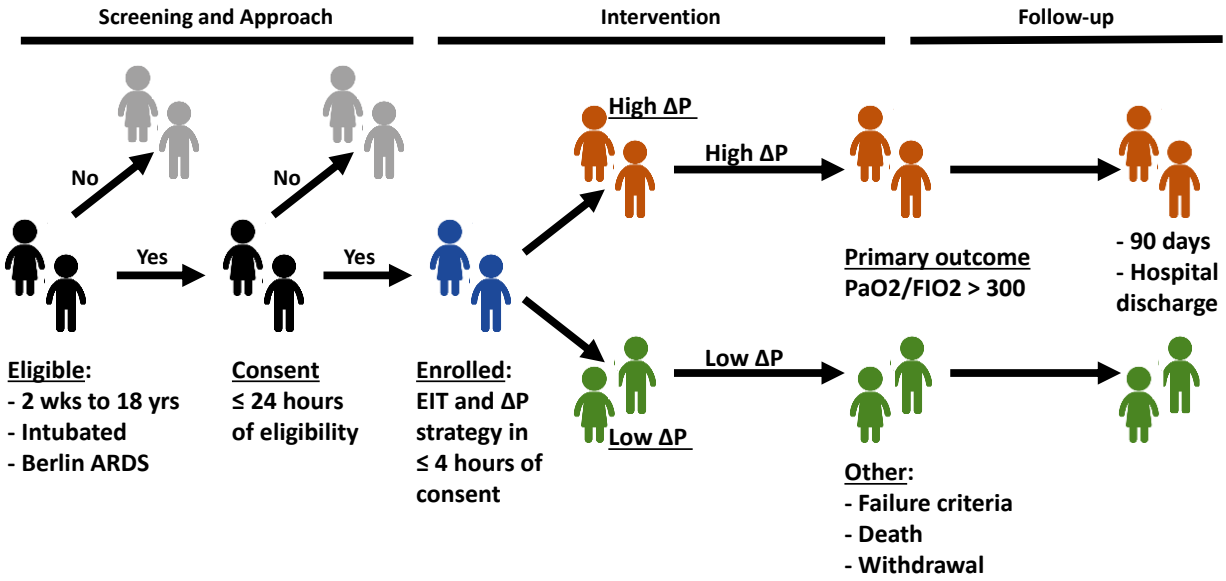

FIGURE 1: STUDY DIAGRAM

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1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

ARDS is characterized by acute onset of diffuse bilateral pulmonary edema and severe hypoxemia not fully explained by cardiac dysfunction.[1, 2] Primarily defined for adults, ARDS affects 45,000 children in the United States (US) annually,[3] representing 10% of mechanically ventilated children in pediatric intensive care units (PICUs)[4], with a mortality rate of 20% in the United States and 30% worldwide.[5-7] Despite several large multicenter trials, there are no specific therapies for adult[8-19] or pediatric[20-23] ARDS, and supportive care with lung-protective ventilation[24] and fluid restriction[25] remains the mainstay of treatment. In children, a lack of therapies is further compounded by uncertainty in management, as guidelines are typically extrapolated from adult ARDS, with uncertain applicability.[26] Pediatric ARDS possesses a distinct epidemiology,[27] outcomes,[28] and pathobiology,[29] necessitating studies specific to this population. We have published how the lower mortality rate in children necessitates alternative patient-centered outcomes for interventional trials.[30-32] Additionally, as risk factors and co-morbidities differ from adult ARDS,[27, 33, 34] the tradeoff between risks and benefits for any given intervention cannot be assumed to directly translate from adults to children. For example, in adult ARDS, prone positioning improved mortality,[35] and inhaled nitric oxide did not affect either mortality or the composite outcome of ventilator-free days (VFDs) at 28 days.[8] By contrast, prone positioning did not affect clinical outcomes in children,[36] whereas inhaled nitric oxide improved VFDs in children.[37]

Lung-protective ventilation, defined as limiting tidal volumes (V_T) and driving pressure (defined as plateau pressure [alveolar distending pressure] minus positive end-expiratory pressure [PEEP]), has been the focus of ARDS management since the publication of the landmark Respiratory Management in ARDS (ARMA) trial. ARMA compared high (V_T set to 12 mL/kg ideal body weight [IBW]) versus low (6 mL/kg) V_T, with respective plateau pressure limits of ≤ 50 cmH_2O and ≤ 30 cmH_2O,[24] and demonstrated improved survival and VFDs when ventilating with lower V_T and driving pressures. Subsequent re-analyses of multiple ARDS trials have implicated driving pressure as the causal variable for outcome, with lower mortality strongly associated with lower driving pressures.[38] More recent data suggests that the association between driving pressure and mortality is modified by baseline hypoxemia and lung elastance (“stiffness;” inverse of compliance).[39, 40] However, high versus low driving pressure strategies have rarely been tested in adults,[41] and never in pediatrics. The worse outcomes associated with high V_T and plateau pressures have been attributed to ventilator-induced lung injury (VILI), the inflammatory response caused by overdistension.[42-45] Thus, lung protective ventilation (V_T 4 to 8 mL/kg IBW and plateau pressure ≤ 30 cmH_2O) is currently the standard of care for adults. However, the association between lung-protective ventilation and improved outcomes is much more tenuous in pediatrics.

1.2 Name and Description of Investigational Product or Intervention

PARMA (Pediatric ARDS MAnagement) is a randomized, open-label, two-arm, phase 2A trial testing two different ΔP (peak pressure minus PEEP) strategies in pediatric ARDS. We will compare a high ΔP (25 cmH_2O) versus low ΔP (15 cmH_2O) strategy on time to hypoxemia resolution (alive and PaO_2/FIO_2 > 300) while assessing effects on lung aeration by electrical impedance tomography (EIT).

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

In pre-clinical models, juvenile rodents are less susceptible to experimental VILI both *in vivo*[46, 47] and *ex vivo*,[48] with less neutrophil influx to the lungs, lower levels of inflammatory cytokines, and preserved lung compliance and structure. Overall, pre-clinical animal data demonstrate that comparable ventilator settings are significantly more injurious in adult than in juvenile rodent lungs, reflecting differences in either intrinsic susceptibility or inflation patterns.

1.3.2 Clinical Studies

1.3.2.1 Clinical Studies in Adults

Lung-protective ventilation with low V_T and driving pressure has been the standard of care for ARDS management since the publication of the ARMA trial,[24] with improved survival and VFDs when ventilating with lower V_T and driving pressures. Subsequent re-analyses of multiple ARDS trials have implicated driving pressure as the causal variable for outcome, with lower mortality strongly associated with lower driving pressures.[38] The association between driving pressure and mortality is modified by baseline hypoxemia and lung elastance.[39, 40] However, high versus low driving pressure strategies have rarely been directly tested in adults.[41] The worse outcomes associated with high V_T and plateau pressures have been attributed to VILI, the inflammatory response caused by overdistension.[42-45]

1.3.2.2 Clinical Studies in Children

In pediatrics, there is no association between high V_T and mortality,[26] with high V_T associated with improved outcomes, such as lower mortality and more VFDs, in some studies.[49, 50] Comparable studies of driving pressure in pediatric ARDS also do not demonstrate a consistent association between higher driving pressures and worse mortality.[51] Unlike in adults, clinical trials of ventilator management have not been performed in children, and the existing clinical data is entirely composed of observational cohort studies, making causal inference problematic.

Our group has previously assessed the relative contributions of changes in driving pressure or oxygenation (as measured by PaO_2/FIO_2) after ventilator changes in adult ARDS.[39] We re-analyzed the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI)[52] and Expiratory Pressure (ExPress) trials,[53] and compared changes in driving pressure and PaO_2/FIO_2 after protocolized changes in PEEP. Adjusting for confounders, changes

in driving pressure were strongly associated with mortality, confirming the significance of driving pressure as causal for mortality in adult ARDS (Figure 2). In a comparable analysis in a pediatric ARDS cohort,[51] however, improvements in driving pressure were not associated with mortality. By contrast, improvements in PaO_2/FIO_2 were strongly associated with lower mortality, calling into question the clinical significance of modifying driving pressure in children. Overall, pre-clinical and clinical data support that children may be less susceptible to VILI, and that lung-protective V_T and pressure limits extrapolated from adults may be too restrictive in pediatrics.

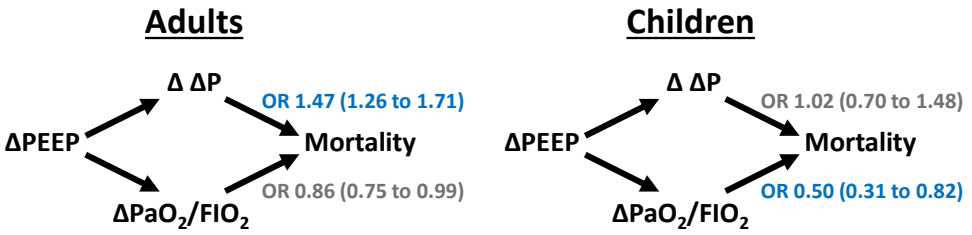


Figure 2: Relative importance of changes in driving pressure (ΔΔP) and changes in oxygenation (ΔPaO2/FIO2) on mortality in adult and pediatric ARDS. In re-analysis of ALVEOLI and ExPres (adult ARDS, ref. 39), ΔΔP after ventilator changes was more strongly associated with mortality than ΔPaO2/FIO2, adjusting for overall illness and baseline ARDS severity. In pediatric ARDS (ref. 32), however, ΔPaO2/FIO2 was more significant. Odds ratios (ORs) are per 1 SD increase in ΔΔP and ΔPaO2/FIO2.

1.4 Selection of Drugs and Dosages

The pediatric community has equipoise regarding the ideal driving pressure strategy. While pediatric ARDS guidelines are extrapolated from adults, including recommendations favoring lung-protective ventilation with lower V_T and ΔP, adherence is inconsistent.[54, 55] In the PALIVE point prevalence study, 41% of children received V_T > 8 mL/kg, and 6% received V_T > 12 mL/kg.[55] Peak pressures exceeded 30 cmH_2O in 50% of cases, and ΔP exceeded 25 cmH_2O (the high ΔP arm in PARMA) in 32% (Table 2). The multinational PARDIE study had detailed ventilator data in 422 children from 71 PICUs worldwide.[54] Similar to PALIVE, 45% of subjects in PARDIE received V_T > 8 mL/kg, 31% had peak pressures > 30 cmH_2O, and 20% had ΔP > 25 cmH_2O. Finally, our group at CHOP has prospectively enrolled children with ARDS since 2011 into a local ARDS registry.[56] In 1029 children with ARDS, 25% of subjects had ΔP > 25 cmH_2O. ΔP increased with increasing ARDS severity, highlighting the difficulty of using observational data to attribute causality for poor outcomes to higher ventilator pressures (Figure 3).

	Mean ± SD			% exceeding recommendations		
	V_T	PIP	ΔP	V_T > 8 mL/kg	PIP > 30 cmH2O	ΔP > 25 cmH2O
PALIVE (n = 124)	8.3 ± 3.3	26 ± 8	19 ± 9	41%	50%	32%
PARDIE (n = 422)	7.6 ± 2.1	29 ± 9	19 ± 5	45%	31%	20%
CHOP (n = 1029)	7.3 ± 1.6	31 ± 7	21 ± 6	27%	55%	25%

Table 2: Non-compliance with lung-protective recommendations in large pediatric ARDS cohorts.

Our group has extensive expertise with ARDS in both clinical and research domains. Our CHOP registry is the largest cohort of pediatric ARDS reported to date, and mechanical ventilation of all children is a specific focus of quality improvement and research efforts in the CHOP PICU. Furthermore, both low and high ΔP arms proposed for the PARMA trial are within the standard of care for children with ARDS at CHOP (Figure 5), suggesting clinician equipoise and a high probability of protocol fidelity in this phase 2A trial.

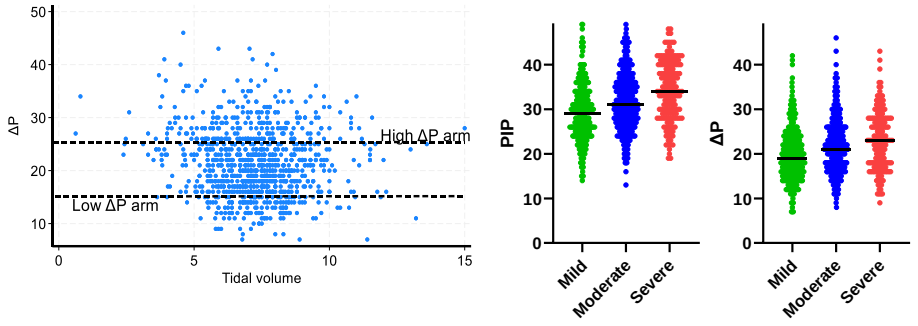


Figure 3: (Left) Scatter plot of ΔP and V_T of 1029 children at CHOP, with dashed lines at 15 (low arm of PARMA) and 25 cmH_2O (high arm). (Right) Peak pressure (PIP) and ΔP increase with increasing ARDS (Berlin) severity.

1.5 Relevant Literature and Data

Lung-protective ventilation with lower V_T and driving pressures is the backbone of ventilation strategies in adults, with variable adoption in pediatrics. However, pre-clinical and observational clinical data suggest that the V_T and driving pressure limits extrapolated from adults are too restrictive for children.[46-51] As lower V_T and driving pressures are associated with worse oxygenation and ventilation, overly restrictive lung-protective ventilation may contribute to prolonged ventilation via worse gas exchange in pediatrics with no improvement in mortality.

Given differences in physiology, the association between driving pressure and mortality may also be modified by age. Pediatrics, unlike adults, rarely uses volume control ventilation with measured plateau pressures (< 5% across North America); rather, the predominant strategy (> 70%) uses preset peak pressures.[54, 55] Our group has previously shown that peak pressures in pressure control approximate plateau pressures in volume control (upwardly biased 1 ± 0.6 cmH_2O),[57] suggesting that a trial comparing different levels of ΔP (defined as peak pressure minus PEEP) would be feasible, congruent with existing ventilation strategies, and clinically meaningful in pediatric ARDS.

1.6 Compliance Statement

This study will be conducted in full accordance all applicable CHOP Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented. The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects in accordance with CHOP IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

PARMA is a randomized, open-label, two-arm, phase 2A clinical trial testing two different ΔP (defined as peak pressure minus PEEP) strategies in pediatric ARDS. We will compare a high ΔP (25 cmH_2O) versus low ΔP (15 cmH_2O) strategy on time to hypoxemia resolution (alive and PaO_2/FIO_2 > 300) while assessing effects on lung aeration by EIT.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine the whether the high ΔP (25 cmH_2O) strategy (intervention) reduces time to hypoxemia resolution in children > 2 weeks to 18 years, relative to a low ΔP (15 cmH_2O) strategy.

2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Determine if there is a relationship between ΔP strategy (25 or 15 cmH_2O) with lung aeration determined by post-randomization EIT.
- Determine the relationship between ΔP strategy (25 or 15 cmH_2O) with VFDs at 28 days.
- Determine the relationship between ΔP strategy (25 or 15 cmH_2O) with mortality at 28 days, PICU discharge, and hospital discharge.
- Determine the relationship between ΔP strategy (25 or 15 cmH_2O) with new oxygen- or ventilator-dependency at discharge.
- Determine the relationship between ΔP strategy (25 or 15 cmH_2O) with new ventilator-associated pneumonia.
- Determine the relationship between ΔP strategy (25 or 15 cmH_2O) with new multiple organ dysfunction syndrome.
- Evaluate the tolerability and safety of the high ΔP (25 cmH_2O) strategy in pediatric ARDS.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design (Figure 1)

Screening and Approach: All PICU patients will be screened twice daily during weekdays, and once daily on weekends, for presence of study eligibility criteria. Patients are initially screened using an existing EPIC functionality to identify new instances of mechanical ventilations, and additional screening of potentially eligible subjects will be performed by trained research assistants and coordinators. Eligible subjects will be approached within 24 hours of meeting eligibility criteria for trial participation and informed consent.

Intervention: Intervention will start immediately after randomization, with initiation of EIT and of randomized ΔP strategy within 4 hours of consent. The Intervention Phase will continue until either the primary outcome or failure criteria are reached, withdrawal from the study, death, or 90 days from randomization.

Follow-Up: Follow-up will start once the Intervention Phase is finished and will continue until hospital discharge or 90 days post-randomization, whichever comes first.

3.1.1 Screening Phase

All PICU patients will be screened twice daily (once on weekends) by trained study staff. Eligible patients will be approached ≤ 24 hours of meeting criteria, defined as time of second confirmatory hypoxemia measurement. The parents or legal guardians will be approached, and the trained staff members will engage them in a discussion regarding reasons for the study, study procedures, the risks and benefits, and answer all questions. Following the above conversation, written informed consent from each patient's parent/legal guardian agreeing to participate in this study will be obtained.

3.1.2 Study Treatment Phase (start of the study intervention)

Ventilator Protocol: Subjects will have EIT (Timpel) bands placed and measurements taken at pre-randomization ventilator settings within 4 hours of consent. Randomized ΔP treatment arm will be delivered by PCV, with peak pressures set according to ΔP arm and PEEP assigned according to a PEEP/FIO_2 grid. Specific ventilator management details are provided below.

Mode of mechanical ventilation	Pressure control ventilation (PCV) delivered using synchronized intermittent mandatory ventilation with pressure support (common and preferred mode in CHOP PICU) or assist control
ΔP (peak pressure minus PEEP)	**1) high ΔP = 25 cmH_20: initial ΔP is set to 25 cmH_20, and adjusted between 20 and 30 cmH_20 (in increments of 2 cmH_20) to keep V_T ≤ 10 mL/kg IBW** **2) low ΔP = 15 cmH_20: initial ΔP is set to 15 cmH_20, and adjusted between 10 and 20 cmH_20 (in increments of 2**

	cmH$_2$0) to keep V_T > 5 mL/kg IBW
Tidal volume (V_T)	Kept between 5 and 10 mL/kg IBW (per ΔP parameters above)
Positive end-expiratory pressure (PEEP) and FIO_2 (assessed every 6 hours) to keep SpO_2 between 92% and 97%	Allowable PEEP/FIO_2 combinations: FIO_2: 0.30 to 0.40 — 0.41 to 0.55 — 0.56 to 0.80 — 0.81 to 1.0 PEEP: 5 to 8 — 10 to 12 — 12 to 14 — 14 to 18
Respiratory rate	Adjust per pH goal; keep ≤ 50 breaths per minute
Pressure support	**Match ΔP setting during Intervention Phase, even if able to wean respiratory rate, PEEP, or FIO_2; adjust per ventilator weaning pathway if in Follow-Up Phase**
Inspiratory time	Adjust to ensure inspiratory flow reaches zero
Plateau pressure monitoring	Inspiratory hold of 2 seconds every 12 hours
pH	Arterial pH ≥ 7.30; venous pH ≥ 7.25; respiratory rate and bicarbonate, but not ΔP, can be adjusted to achieve pH goals

Adjustments to Ventilator Protocol: Clinical teams will be given a protocol to assist with ventilator adjustments. At randomization, ventilator pressures will be set initially at either ΔP = 15 or 25 cmH20, and V_T assessed. The assigned ΔP treatment arm will be adjusted in increments of 2 to keep V_T in the assigned range, if necessary. The clinical team will assess that the pressures (PIP and PEEP), V_T. pH, and FIO_2 limits are compliant with the assigned arm no less frequently than every 4 hours. Ventilator settings will be monitored continuously (as per usual care) by the clinical team, with instructions to contact the research team for any realtime concerns. The research team will monitor ventilator settings, compliance, and be available for discussion at least twice per day. The research team will assist the clinical team in the determination that the V_T, pH, and FIO_2 limits cannot be maintained with the assigned ΔP arm, triggering failure criteria (section 4.3 below).

Other Procedures: The PICU has existing protocols for sedation, fluid management, ventilator weaning, and extubation readiness. Specific strategies are detailed below.

Sedation	CHOP Sedation Pathway	Fentanyl and dexmedetomidine infusions to keep State Behavioral Scale (SBS) between -1 and 0 (moderate sedation)
Fluid management	CHOP Maintenance Fluid Pathway	Total fluid limit instituted to keep all non-resuscitation fluids (medications, feeds, blood products) to no exceed 1x maintenance; this will apply until a subject achieves full enteral nutrition

Ventilator escalation	Suggested	Escalation for refractory hypoxemia will be suggested in this order: 1) neuromuscular blockade infusion (required if PEEP ≥ 12 cmH_20), 2) inhaled nitric oxide, 3) prone positioning for 16 hours/day, 4) high frequency oscillatory ventilation, 5) extracorporeal support
Corticosteroids	Not protocolized	Corticosteroid use for ARDS is left to clinician discretion
Vasopressors	Not protocolized	Hemodynamic support strategies are left to clinician discretion
Nutrition and insulin	Not protocolized	Enteral or parenteral nutrition, and hyperglycemia management, will be left to clinician discretion
Renal replacement therapy and diuretics	Not protocolized	Use and mode of renal replacement therapy or diuretic use are left to clinician discretion
Ancillary therapy documentation	Required	While the order of use, or the decision to use, the above therapies are not mandated, all ancillary therapy use will be recorded daily
Ventilator weaning (may occur after Intervention Phase)	CHOP Ventilator Weaning Pathway	The CHOP PICU ventilator weaning pathway is initiated when there is spontaneous breathing, PEEP < 12 cmH_20 and FIO_2 < 0.50; the pathway reduces respiratory rate, PEEP, and pressure support every 4 hours as tolerated until extubation readiness test
Extubation readiness (may occur after Intervention Phase)	CHOP ERT pathway (embedded in Ventilator-Weaning Pathway)	A spontaneous breathing trial (PEEP ≤ 8 cmH_20 and pressure support ≤ 8 cmH_20 for 1 to 2 hours) is initiated when PEEP ≤ 8 cmH_20 and FIO_2 ≤ 0.40; an endotracheal tube leak is assessed and dexamethasone recommended for leak > 20 cmH_20; subjects who pass this trial are extubated within 6 hours

Electrical Impedance Tomography (EIT): EIT is an FDA-approved non-radiating method of imaging lung aeration currently used at CHOP for clinical care, with an associated existing EPIC order. For PARMA, EIT will be performed post-randomization after stabilization of settings on the assigned ΔP study arm and no later than 8 hours after initiation of assigned protocol. EIT measurements will be repeated 24 to 72 hours after initial post-randomization EIT measurements while on the assigned ventilator protocol. If the subject is off of the assigned protocol (i.e., failure criteria or early termination), the repeat EIT will be deferred. EIT images will not routinely be made available to the clinical team, as they require some significant offline processing.

3.1.3 Follow-up Phase

Follow-up will start once the Intervention Phase is finished and will continue until hospital discharge or 90 days post-randomization, whichever comes first.

3.2 Allocation to Treatment Groups and Blinding

Randomization and Monitoring: Randomization will be performed in 1:1 permuted blocks using a randomization module available in Research Electronic Data Capture (REDCap). Treatment allocation will be concealed to the clinical team until after enrollment has been confirmed. Compliance with assigned treatment group, adherence to ventilator protocol, and adherence to protocolized co-interventions will be monitored.

Blinding: The intervention will not be blinded to clinicians or investigators. Blinding is not feasible for an intervention as fundamental and as clinically labile as ventilator management. To minimize selection bias that could occur due to pre-enrollment awareness of ΔP assignment, randomization will occur only after informed consent has been obtained.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Subject Study Participation

The study duration per subject will begin at screening, and for enrolled subjects, will last up to hospital discharge or 90 days after randomization, whichever comes first.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted entirely at CHOP, with screening in the PICU and follow-up until hospital discharge or within 90 days of randomization.

We will enroll (consent) 180 subjects to produce an anticipated 160 evaluable subjects.

3.4 Study Population

Eligibility criteria were designed to enroll children with Berlin-defined ARDS[2] without limitations of care and expected to survive > 72 hours in the CHOP PICU. We specifically chose Berlin criteria rather than the 2015[58] or 2022[59] PALICC pediatric ARDS criteria for two reasons. First, the PALICC defines ARDS severity using oxygenation index, rather than PaO_2/FIO_2, which incorporates mean airway pressures (mPaw). However, the high ΔP arm in PARMA will have higher mPaw (by definition), and the Berlin definition (using PaO_2/FIO_2) may be a more reliable metric of hypoxemia severity and resolution. Second, PALICC has less restrictive radiographic criteria (unilateral opacities allowed), and so we anticipate all subjects with Berlin ARDS in PARMA would also meet criteria for the PALICC definition of pediatric ARDS.

3.4.1 Inclusion Criteria (examples)

1) age > 2 weeks (> 38 weeks corrected gestational age) and < 18 years (not yet had 18th birthday)

2) acute (≤ 7 days of inciting etiology) respiratory failure requiring invasive mechanical ventilation

3) ventilated with endotracheal tube or tracheostomy for ≤ 7 days from inciting etiology (e.g., pneumonia, sepsis, trauma, aspiration, cardiac arrest, pancreatitis, engineered T cell therapy, among others) onset

4) hypoxemia defined as $PaO_2/FIO_2 \leq 300$ (or $SpO_2/FIO_2 \leq 315$) on PEEP ≥ 5 cmH_2O on two consecutive measurements 4 hours apart and sustained at the time of consent and randomization

5) bilateral opacities on chest radiograph as determined by radiologist, clinical attending, or PI

3.4.2 Exclusion Criteria

1) hypoxemia caused primarily by hydrostatic pulmonary edema from heart failure or fluid overload

2) non-palliated or unrepaired cyanotic congenital heart disease

3) ventilated via tracheostomy at baseline prior to acute illness

4) obstructive airway disease determined to be the primary cause of respiratory failure

5) severe moribund state not expected to survive > 72 hours

6) any limitations of care at time of screening

7) escalation to high frequency oscillatory ventilation or extracorporeal support (i.e., meeting PARMA protocol failure criteria) at time of screening

8) previous enrollment in this study

4 STUDY PROCEDURES

4.1 Screening Visit

All PICU patients will be screened twice daily (once on weekends) by trained study staff. Eligible patients will be approached ≤ 24 hours of meeting criteria, defined as time of second confirmatory hypoxemia measurement.

4.2 Study Treatment Phase

4.2.1 Visit 1

Subjects will have EIT (Timpel) bands placed and measurements taken at pre-randomization ventilator settings within 4 hours of consent. Randomized ΔP treatment arm will be delivered by PCV, with peak pressures set according to ΔP arm and PEEP assigned according to a PEEP/FIO_2 grid. Specific ventilator management details are provided below.

- Ventilator protocol
- Imaging protocol
- Co-intervention protocol
- Medical Record Review for data collection

4.2.2 Visit 2

EIT measurements will be repeated 24 to 72 hours after initial post-randomization EIT measurements while on the assigned ventilator protocol. If the subject is off of the assigned protocol (i.e., failure criteria or early termination), the repeat EIT will be deferred.

4.3 Subject Completion/Withdrawal

Successful Completion: Achievement of the primary outcome terminates the assigned ventilator protocol. After 28 days (timing of primary outcome), providers are encouraged but not mandated to continue with the assigned protocol. We will continue to gather data until hospital discharge up to 90 days after randomization.

Failure Criteria: Refractory hypoxemia or respiratory acidosis will typically prompt escalation to high frequency oscillatory ventilation or extracorporeal support, and will trigger a suspension of the assigned ΔP protocol. In some cases, the clinical team may wish to cross over into pressures used in the alternative ΔP protocol, which will still count as failure criteria. Subsequent ventilator management, including when weaning off of conventional or high frequency oscillatory ventilation or extracorporeal support, will be left to a physician's discretion. The CHOP PI (Dr. Yehya) will record the primary reason for withdrawal. Every attempt will be made to continue data collection, providing that the family/patient concurs with continued data collection.

Early Termination: The assigned ventilator protocol can be suspended or permanently discontinued if, in the treating physician's judgment, it is no longer safe to continue. A protocol deviation will be documented only if the subject is withdrawn from the study due to a lack of protocol adherence absent clinical indication. Parents and legal guardians can also request withdrawal from the study and discontinue study procedures. Every attempt will be made to continue data collection, providing that the family/patient concurs with continued data collection.

4.4 Stopping Rules

The DSMB will review all trial data, with a focus on safety data, at a frequency of no less than every 6 months (approximately every 20 enrolled subjects). While we do not provide explicit stopping rules for PARMA, the DSMB can make recommendations to change/alter the trial procedures or to stop the trial for safety based on their review of adverse events.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Detailed clinical data will be recorded, including demographics (age and sex), severity of illness (Pediatric Risk of Mortality [PRISM] IV; Pediatric Logistic Organ Dysfunction [PELOD] 2), co-morbidities (prematurity, immunocompromised status, stem cell transplant), and ARDS etiology (e.g., pneumonia, sepsis, trauma, aspiration). Pre- and post-randomization ventilator settings, oxygenation, ancillary therapy use, and adverse events will be documented daily until discontinuation of invasive ventilator support. Organ failures (PELOD 2 score derived from labs), vasopressor support, and clinical outcomes will be monitored until hospital discharge. REDCap will serve as the data collection interface.

5.1.2 Laboratory Evaluations

5.1.2.1 Table: Clinical Laboratory Tests (validated tests performed in a CLIA/CAP lab)

Category	Tests
Hematology	Hemoglobin, hematocrit, platelet count, WBC with differential
Liver function tests	SGOT/AST, SGPT/ALT, total Bilirubin
Renal function tests	BUN, creatinine
Blood gas	PaO2, PaCO2

5.2 Efficacy Evaluations

The primary outcome (Aim 1A) of PARMA is time to sustained resolution of hypoxemia, defined as being alive with $PaO_2/FIO_2 > 300$ (or $SpO_2/FIO_2 > 315$) on two consecutive measurements 4 hours apart. This is because improved oxygenation is strongly associated with outcome in pediatric ARDS,[4, 37, 51, 60] and is the most plausible mechanism for the efficacy of a high ΔP strategy, both for composite outcomes such as VFDs (by shortening invasive ventilator duration and avoidance of rescue therapies), as well as mortality (improved organ function via improved gas exchange and reduced morbidity associated with prolonged ventilation). This outcome is censored at 28 days (672 hours).

5.3 Safety Evaluation

Adverse events (AEs), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration. Notably, ARDS is a life-threatening condition for which we expect a wide range of events as part of the routine clinical course. Secondary Safety Endpoints include: pneumothorax requiring chest tube; acidosis requiring additional vasopressor support; protocol termination for failure criteria; other air leak not requiring chest tubes. Ventilator-

associated pneumonia; new or progressive multiple organ dysfunction syndrome[61] are being recorded as secondary aims, and also serve as potential safety outcomes.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary outcome (Aim 1A) of PARMA is time to sustained resolution of hypoxemia, defined as being alive with $PaO_2/FIO_2 > 300$ (or $SpO_2/FIO_2 > 315$) on two consecutive measurements 4 hours apart. This is because improved oxygenation is strongly associated with outcome in pediatric ARDS,[4, 37, 51, 60] and is the most plausible mechanism for the efficacy of a high ΔP strategy, both for composite outcomes such as VFDs (by shortening invasive ventilator duration and avoidance of rescue therapies), as well as mortality (improved organ function via improved gas exchange and reduced morbidity associated with prolonged ventilation). This outcome is censored at 28 days (672 hours).

6.2 Secondary Endpoints

The secondary endpoints are:

- Lung aeration determined by pre- versus post-randomization EIT
- VFDs at 28 days
- New oxygen- or ventilator-dependency at discharge
- Mortality at 28 days, PICU discharge, and hospital discharge
- Safety Endpoints listed above in section 5

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Efficacy Analysis

PARMA will be analyzed using Bayesian survival analyses, with effect size presented as a hazard ratio (HR). All analyses will be “intention to treat.” The main analysis will use a minimally informative prior centered at HR = 1 (log[HR] = 0) and precision = 10 (log scale). The primary outcome of hypoxemia resolution (Aim 1A) will be assessed as a time to event (in hours) from randomization until the primary event of hypoxemia resolution. Subjects who die before hypoxemia resolution will remain in the risk set and be considered as being “never able to achieve hypoxemia resolution” (effectively being treated as a competing risk). Subjects who achieve hypoxemia resolution and die subsequent to that will be considered as having achieved the primary outcome. The high ΔP (comparator) arm will be compared to the low ΔP (reference) arm, and efficacy reported as HR with 95% credible intervals. Posterior probabilities under minimally informative priors will be computed for any benefit (HR > 1, meaning faster time to hypoxemia resolution with high ΔP),

HR > 1.25, and HR > 1.5 (projected "true" effect size). Additional analyses will be conducted with standardized priors reflecting pessimistic (priors centered at HR 0.8) and optimistic (priors centered at HR 1.2) scenarios, as we have done before.[62, 63] As this is the first trial of different ΔP ventilation strategies on hypoxemia resolution in pediatric ARDS, reasonable data-driven priors from previous publications, including adult trial data, were not available. The standardized prior framework (minimally informative, pessimistic, optimistic) reflects a range of plausible priors with the same precision under which the PARMA trial data can be adjusted to derive posterior probabilities.

For Aim 1B, we will assess whether the effect size of high versus low ΔP ventilation differs according to age (continuous in years and as strata of < 1 year, 1 to < 5 years, 5 to < 12 years, and 12 to 18 years), pre-randomization elastance ($\Delta P/V_T$ with V_T normalized to IBW), and pre-randomization PaO_2/FIO_2.

For Aim 2, pre- and post-randomization EIT images (in the immediate 8 hours after randomization) will be used to determine the change in aeration. Lung images will be divided into 4 ROIs along the axial and sagittal planes, and impedance (i.e., aeration) will be determined for each region. Post-randomization end-expiratory lung impedance (EELZ) values and elastance (measured at the ventilator) will be compared to pre-randomization to determine whether ventilator changes results in recruitment (increased EELZ; unchanged or improved elastance), overdistension (increased EELZ; worsened elastance), or atelectasis (decreased EELZ; worsened or unchanged elastance). This analysis will be repeated with the second set of post-randomization EIT measurements (performed 24 to 72 hours after randomization), again compared to pre-randomization EIT. We will compare the proportion of subjects with improved recruitment and with overdistension, relative to pre-randomization EIT, between high and low ΔP arms, with effect sizes presented as relative risk (RR). RR > 1 implies a greater proportion of subjects with the reported aeration (e.g., recruitment) with high ΔP.

We will compute the posterior probability under minimally informative priors for any benefit when comparing 28-day mortality, PICU mortality, and hospital mortality between high and low ΔP arms. Effect sizes will be presented as RR, with RR < 1 meaning lower mortality risk with high ΔP. Additional analyses will be conducted with standardized priors reflecting pessimistic (priors centered at RR 1.2) and optimistic (priors centered at RR 0.8) scenarios, and with data-driven priors using effect sizes from prior adult V_T trials, including ARMA.[24]

Analyses of VFDs and other free-day clinical endpoints will be conducted as described above for hypoxemia resolution, with death prior to the main event being treated as a competing risk and effect sizes presented on the HR scale with HR > 1 meaning superiority of high ΔP ventilation. The main analyses will be conducted using minimally informative priors (as per main analysis), with additional analyses conducted using standardized priors reflecting pessimistic (priors centered at HR 0.8) and optimistic (priors centered at HR 1.2) scenarios, and with data-driven priors using effect sizes from prior adult V_T trials.

6.3.3 Safety Analysis

The frequencies of AEs by type, body system, severity and relationship to study intervention will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.4 Sample Size and Power

Sample size was evaluated using trial simulations. We assumed that time to hypoxemia resolution and competing event followed Weibull distributions, using data from > 1000 pediatric ARDS cases at CHOP between 2011 and 2023 to estimate the shape and scale parameters. Using a projected “true” HR of 1.5 favoring high ΔP ventilation, 160 subjects would provide 80% power to detect a > 90% probability of any benefit (HR > 1) with high ΔP at a type I error rate = 0.07 (10,000 simulations) assuming a minimally informative prior (centered at HR = 1 and precision = 10 [log scale]). In this phase 2A trial, we accept 80% power to detect a 90% probability of any benefit at a type I error rate < 0.1 in anticipation of a larger trial.

6.5 Interim Analysis

We have not planned interim efficacy analyses in this phase 2 trial. However, the DSMB will review the data and AEs no less frequently than every 6 months with a focus on safety. Early stopping will only be considered if SAEs or enrollment rates lead to concerns about continuation of the trial.

7 STUDY INTERVENTION

7.1 Description

PARMA is a randomized, open-label, two-arm, phase 2A clinical trial testing two different ΔP (defined as peak pressure minus PEEP) strategies in pediatric ARDS. We will compare a high ΔP (25 cmH_2O) versus low ΔP (15 cmH_2O) strategy on time to hypoxemia resolution. The “device” being tested is ventilator settings on a CHOP standard Evita V500 (Dräger) ventilators.

We will also use Enlight 2100s (Timpel Medical) for this study. These are free-standing EITs with full graphical interface and ability to integrate with V500 ventilators, currently approved for both clinical and research use, with an existing EPIC order.

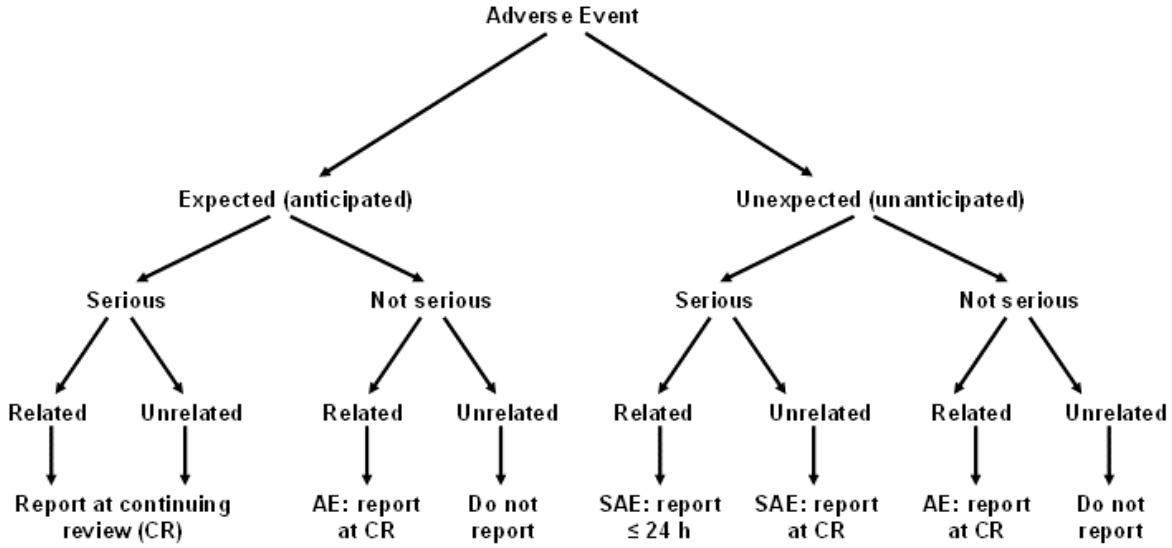
8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study, daily during the intervention phase.

8.2 Adverse Event Reporting

The overall approach to categorizing and reporting AEs is provided below:



Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse intervention experience occurring in relation to study procedures that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- prolongation of existing hospitalization, or
- a persistent or significant disability/incapacity

Important medical events that may not result in death, be life-threatening, or require escalation of care may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke resulting in only limited disability may be considered a mild stroke, but would be an SAE.

8.4.1 Relationship of SAE to study procedures or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, SAEs that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening or Unexpected	24 hours	Within 3 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	24 hours	Within 3 business days
All other AEs	N/A	Brief Summary may be at CR

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

An independent Medical Monitor will be appointed by the PI. The CHOP-based PI (Dr. Yehya) and/or research coordinators will report SAEs that are both unexpected and probably or possibly related within 24 hours of becoming aware of the event, with a detailed completed report sent to the IRB and Medical Monitor within three working days of the event. The Medical Monitor will assess all SAEs. For each SAE that is both unexpected and probably or possibly related to study, Dr. Yehya will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The Medical Monitor will sign each SAE report after review. All SAE reports will be retained, and all SAE reports will be available for review by DSMB members and NICHD staff.

Event	**Expected in pediatric ARDS**	**Serious adverse event**	**Pre-specified safety outcome**
Death	Yes	Yes	Yes
Pneumothorax requiring chest tube	Yes	Yes	Yes
Other air leak not requiring chest tubes	Yes	Yes	Yes
Ventilator-associated pneumonia	Yes	Yes	Yes
New or progressive multiple organ dysfunction syndrome (increase in organ failure score or death 7 days after randomization)	Yes	Yes	Yes
Cardiac arrest	No	Yes	No
Arrythmia	No	Yes	No
Hypotension	Yes	No	No
Need for extracorporeal membrane oxygenation	Yes	Yes	No

Need for renal replacement therapy	Yes	Yes	No
Brain herniation	No	Yes	No
New-onset seizures (without history of epilepsy)	No	No	No
Pulmonary embolus/deep vein thrombosis	No	Yes	No
Placement of new tracheostomy	Yes	Yes	No
Increase in vasopressor support due to acidosis	Yes	No	Yes
Protocol termination due to failure criteria	No	No	Yes

In the unlikely event that the Medical Monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NICHD staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the Medical Monitor, or if the NICHD staff and the DSMB chairperson cannot be reached expeditiously, the Medical Monitor will notify the PI to pause enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB. In accordance with IRB requirements, the investigator will be required to report such events to the CHOP IRB. After notification of the NICHD Program Official or Project Officer, and the DSMB chairperson, of unexpected, study-related SAEs, decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to PI, who will be instructed to report this to the IRB. The DSMB will review all AEs (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The PI will prepare a Summary Report of AEs for the DSMB meetings, classified with the MedDRA coding system.

8.7 Medical Emergencies

Unanticipated problems are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The CHOP-based PI (Dr. Yehya) will report unanticipated problems to the IRB within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the IRB within three working days of the event. The PI will also report these unanticipated problems to the NICHD Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with IRB requirements, Dr. Yehya is required to report such unanticipated problems to the IRB. In the event that the Medical Monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NICHD staff cannot be reached

expeditiously, the PI will pause enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Randomization will be performed in 1:1 permuted blocks using a randomization module available in Research Electronic Data Capture (REDCap). Treatment allocation will be concealed to the clinical team until after informed consent has been obtained and enrollment confirmed. Compliance with assigned treatment group, adherence to ventilator protocol, and adherence to protocolized co-interventions will be monitored.

9.1.2 Blinding

The intervention will not be blinded to clinicians or investigators. Blinding is not feasible for an intervention as fundamental and as clinically labile as ventilator management. To minimize selection bias that could occur due to pre-enrollment awareness of ΔP assignment, randomization will occur only after informed consent and enrollment.

9.2 Data Collection and Management

Detailed clinical data will be recorded, including demographics (age and sex), severity of illness (Pediatric Risk of Mortality [PRISM] IV; Pediatric Logistic Organ Dysfunction [PELOD] 2), co-morbidities (prematurity, immunocompromised status, stem cell transplant), and ARDS etiology (e.g., pneumonia, sepsis, trauma, aspiration). Pre- and post-randomization ventilator settings, oxygenation, ancillary therapy use, and adverse events will be documented daily until discontinuation of invasive ventilator support (i.e., extubation or removal of ventilator for subjects with tracheostomy). Organ failures (PELOD 2 score), vasopressor support, and clinical outcomes will be monitored until hospital discharge or 90 days, whichever is sooner. REDCap will serve as the data collection interface, and will require password-protected access.

Site investigators and research staff will be trained to collect data using electronic case report forms (CRFs). The CRF will be password-protected with safeguards to maintain confidentiality for all data entered into the CRF.

An electronic Manual of Operations (MOO) describing Standard Operating Procedures (SOP) for data collection will be prepared to ensure consistent documentation. The PICU research team will maintain an enrollment log that will link each potential subject to a unique study number. All data collection forms will contain this unique study number. Enrollment logs will be maintained by the PICU research team in a secure location accessible to study staff only. Identifiable information will be collected and stored locally, but no identifiable information will be transmitted to the Data Coordinating Center (DCC) at Penn. All data received at the DCC will be coded using a subject ID.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with HIPAA on subject privacy and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Coding all subject data with a unique identification number will minimize risk of loss of subject confidentiality. The enrollment log, linking subject ID Number to patient identity, will be secured in an encrypted, password-protected shared drive with regular back-ups managed by CHOP Information Services team. Only Dr. Yehya (CHOP-based PI) and the research team will have access to this 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 the CHOP Information Services Department. Transaction logs are backed up daily and full back ups are performed weekly on all databases.

The research personnel have all completed training and received certification in Human Subjects Research Protection and HIPAA. All project staff hired will also successfully complete this training prior to engaging in any research with study participants and renew this training as required by their institution. The investigators and staff are fully committed to the security and confidentiality of all data collected for this study. In addition, all personnel involved have received Human Subjects Protection and HIPAA education. Investigators and staff involved with this study will be required to sign agreements from the DCC that relate to maintenance of passwords, information system security, and data confidentiality. No identifiable data will be used for future study without first obtaining IRB approval.

No identifiable data will be used for future study without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

DMSB: An independent Data and Safety Monitoring Board is required to oversee participant safety in the clinical trial and provide overall monitoring of interim data and safety issues. Our proposal for DSMB function reflects our prior experience, but we understand that DSMB function will be determined by NICHD. The purpose of the DSMB is to advise the NICHD and Dr. Yehya regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the protocol, assessments of data quality, performance of the clinical site, review of serious adverse events (SAEs) and other subject safety issues. The CHOP PI will

send reports relating to these topics to DSMB members prior to each DSMB meeting. It is anticipated that the DSMB will meet annually, but the DSMB will have the final say in determining meeting intervals. The DSMB will meet once prior to the start of the PARMA trial to approve the final protocol prior to implementation. We will draft a DSMB charter to guide its function for the trial and the charter will be approved by the DSMB. The charter will include rules of procedure, definitions of a meeting quorum, and information about meeting logistics and frequency. After the DSMB has approved its charter and the final protocol, tis will be sent to the CHOP IRB.

DSMB meetings to evaluate study protocols, prior to study implementation, may be open or closed according to the decision of the DSMB members. We suggest that these meetings should be open to members of the PARMA investigative team when there are no confidential components to these proceedings in order to facilitate the review and appropriate alterations of the protocol in response to DSMB concerns. The DSMB will meet no less frequently than every 6 months (approximately every 20 projected enrollments), and can be contacted or fully activated ad hoc, if necessary. The DSMB can recommend whether or not to terminate enrollment in PARMA because of potential safety concerns or study feasibility issues. We have not planned interim efficacy analyses in this phase 2 trial. Early stopping will only be considered if SAEs or enrollment rates lead to concerns about continuation of the trial.

As per NICHD practices, the DSMB recommendations will be signed and submitted to the NICHD officer (who is usually the Executive Secretary for the DSMB) within a reasonable time after the DSMB meeting. After approval or modification by the NICHD, the officer will forward the DSMB report to the PI. The PI will forward the report to the IRB. In the unlikely event that the DSMB recommends emergent cessation of enrollment in PARMA because of safety concerns, this communication will be made during the debriefing segment of the DSMB meeting. If the NICHD staff concur with this recommendation, the PI will notify all PARMA-related investigators and staff to cease enrollment immediately.

Medical Monitor: An independent Medical Monitor will be appointed. The CHOP-based PI (Dr. Yehya) and/or study staff will report <u>SAEs that are both unexpected and probably or possibly related</u> to study procedures within 24 hours of becoming aware of the event, with a detailed completed report sent to the IRB within three working days of the event. The Medical Monitor will assess all SAEs. For each SAE that is both unexpected and probably or possibly related to study interventions, Dr. Yehya will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The Medical Monitor will sign each SAE report after review. All SAE reports will be retained, and all SAE reports will be available for review by DSMB members and NICHD staff.

In the unlikely event that the Medical Monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NICHD staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the Medical Monitor, or if the NICHD staff and the DSMB

chairperson cannot be reached expeditiously, the PI will pause enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB. In accordance with IRB requirements, the site investigator will be required to report such events to the CHOP IRB. After notification of the NICHD Program Official or Project Officer, and the DSMB chairperson, of unexpected, study-related SAEs, decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to PI, who will be instructed to report this to the IRB. The DSMB will review all AEs (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The PI will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

The CHOP PI will monitor and review the study progress, subject safety, and the accuracy and security of the emerging data.

9.4.2 Risk Assessment

The potential risks of this study are related to 1) potential exposure to less effective or less safe ΔP (above minimal risk with the potential for direct benefit), and 2) breach of confidentiality (not above minimal risk).

Potential risks associated with the ventilation protocol (e.g., hemodynamic instability, shock, cardiac dysrhythmias, pneumothorax, air leak, agitation, prolonged mechanical ventilation) are all part of the natural history of ARDS. Thus, all of these potential risks are associated with the ventilation protocols. These risks, and the steps enacted to protect against these risks, will be specified in the parent/legal guardian consent forms, all of which will be HIPAA-compliant.

Several people and organizations may have access to identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data. These groups include: members of the research team and other authorized staff at CHOP; people from agencies and organizations that perform independent accreditation and/or oversight of research such as the Department of Health and Human Services, Office for Human Research Protections, and the NIH who is sponsoring this research. The parent/legal guardian will be made aware of the requirement that the participant's deidentified data will be shared through NIH databases. These data will not include identifiers like their name, medical record number or date of birth. If the parent/legal guardian agrees, data including some identifiable information can be retained for the purposes of future research at CHOP. To gain access to this data, CHOP researchers must promise not to try to re-identify the participant. The parent/legal guardian can tell us during the consent conversation whether they will allow the participant's data to be shared in this way.

Protection against Risks: Study participation is voluntary. The parent/legal guardian(s) do not have to take part for their child to receive care at CHOP. If they decide not to take part or if they change their mind later, there will be no penalties or

loss of any benefits to which they were otherwise entitled. Additionally, the DSMB, Medical Monitor, and AE/SAE reporting plans will minimize risks of harm.

Ventilator Protocol: Both high and low ΔP arms are within the typical range of values used at CHOP,[51] in North America,[55] and worldwide[54] for pediatric ARDS. Moreover, patients will only be considered eligible if the treating attending physician deems it safe for the patient to receive either ΔP strategy. Thus, all patients will receive a ventilation strategy that a) uses pressures and V_T within the range of standard of care for pediatric ARDS (both at CHOP and worldwide), and b) judged to be safe by the treating physician. However, because there is a prospect of a relative benefit in relative effectiveness and/or safety for ΔP arm over the other, subjects may be randomized to an arm with relatively inferior efficacy or relatively worse safety. Several safeguards have been put in place to minimize risk of randomized (rather than clinician-prescribed) ventilation strategy, including:

- Approval of the trial protocol by experts of the CHOP Critical Care Scientific Review Committee
- Use of a prescribed range of ΔP and V_T within each arm of the trial, with room to adjust as clinically indicated and still maintain separation of ΔP between arms, thus ensuring that excessively high or low V_T will be avoided, thus protecting subjects from acidosis or very high V_T
- Continuous monitoring of ventilator parameters as part of standard of care, and frequent communication between clinical and research teams
- Any patients for whom clinician judgment deems it unsafe to use a specific ΔP strategy will be excluded from enrollment, with the reasons documented
- Pre-specified failure criteria when oxygenation or ventilation targets are not met with the protocol
- Parent or clinician ability to terminate the protocol after randomization
- Leveraging existing CHOP Pathways for sedation, fluid management, ventilator weaning, and extubation readiness to minimize variation of ancillary therapies
- Independent and regular monitoring by DSMB (approximately every 6 months = every 20 subjects), with a focus on safety and review of AEs; the DSMB is empowered to alter the protocol or stop the trial for safety considerations

The higher ΔP strategy specifically could plausibly be associated with a relatively higher risk of pneumothorax requiring chest tube, other air leak not requiring chest tubes, or new or progressive multiple organ dysfunction syndrome (which has been associated with adults, but not children, with higher V_T). To mitigate these risks, we reiterate the prescribed range of ΔP and V_T within each arm of the trial and the ability to adjust. The higher ΔP strategy could also shorten time on the ventilator, and plausibly decrease risk for ventilator-associated pneumonia; and have better gas exchange with less acidosis, thus improving hemodynamic stability and lowering risk for new or progressive multiple organ dysfunction syndrome.

The lower ΔP strategy specifically could plausibly be associated higher rates of acidosis requiring additional vasopressor support, ventilator-associated pneumonia (via longer ventilation), and overall prolonged ventilation. To mitigate these risks, we again highlight the prescribed range of ΔP and V_T within each arm of the trial to mitigate acidosis. The lower ΔP strategy could also have lower rates of pneumothorax or other air leak, and if those complications were to sufficiently prolong ventilation, then the lower ΔP strategy could actually shorten overall time on ventilation.

Finally, all risks that have been reported with (but not necessarily causally linked to) use of either high or low ΔP listed above are consistent with the risks subjects could experience simply having a diagnosis of ARDS. Neither strategy is a priori anticipated to increase mortality.

Breach of Confidentiality: All data and records generated during this study will be kept confidential in accordance with HIPAA on subject privacy and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Coding all subject data with a unique identification number will minimize risk to loss of subject confidentiality. The enrollment log, linking subject ID Number to patient identity, will be secured in an encrypted, password-protected shared drive with regular back-ups managed by CHOP Information Services team. Only Dr. Yehya (CHOP-based PI) and the IRB-approved research team will have access to this 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 the CHOP Information Services Department. Transaction logs are backed up daily and full back ups are performed weekly on all databases.

The research personnel have all completed training and received certification in Human Subjects Research Protection and HIPAA. All project staff hired will also successfully complete this training prior to engaging in any research with study participants and renew this training as required by their institution. The investigators and staff are fully committed to the security and confidentiality of all data collected for this study. In addition, all personnel involved have received Human Subjects Protection and HIPAA education. Investigators and staff involved with this study will be required to sign agreements from the DCC that relate to maintenance of passwords, information system security, and data confidentiality. No identifiable data will be used for future study without first obtaining IRB approval.

9.4.3 Potential Benefits of Trial Participation

Both high and low ΔP arms are within the typical range of values used at CHOP,[51] in North America,[55] and worldwide[54] for pediatric ARDS. Moreover, patients will only be considered eligible if the treating attending physician deems it safe for the patient to receive either ΔP strategy. Thus, all patients will receive a ventilation strategy

that is a) standard of care for pediatric ARDS, and b) judged to be safe by the treating physician. However, because there is a prospect of a relative benefit in effectiveness and/or safety for ΔP arm over the other, subjects may be randomized to an arm with relatively superior efficacy or relatively improved safety. This would result in a greater probability of faster hypoxemia resolution without increase in adverse side effects.

9.4.4 Risk-Benefit Assessment

Each subject has the potential to be randomized to either high or low ΔP strategy, with the possibility that one strategy is superior and will lead to faster resolution of hypoxemia, better aeration (on EIT), and shorter time receiving invasive ventilation without increasing the risk of adverse events or mortality. Thus, there is a clear possibility of direct benefit to subjects in this trial. Given that the high or low ΔP arms use pressures consistent with current pediatric ARDS management from review of multiple cohort studies, the risks of the trial are balanced by the potential for direct benefit. Furthermore, the benefits to the medical and scientific community, and to future children, would be substantial, as PARMA would provide the first high-quality evidence to guide ventilator management in pediatric ARDS. Given the prevalence of children who are mechanically ventilated in the US and worldwide, PARMA has the potential to inform the design of future studies that will test the efficacy of different ventilator strategies in mechanically ventilated children with or without ARDS, rather than continuing to rely on adult paradigms and data that may not apply to pediatric respiratory failure.

PARMA will be the first clinical trial to test ventilation strategies in pediatric ARDS, thereby providing the first high-quality data to inform these guidelines in critically ill children. Our trial directly addresses the concerns of applying adult data to pediatrics without re-assessment of the balance of risks and benefits, and overcomes the shortcomings of using observational data to infer causality for a therapy that is intrinsically linked to illness severity. Furthermore, we intend to identify a plausible mechanism for benefit from high ΔP and assess the stability of these benefits across a range of outcomes and subgroups. Overall, the results of PARMA will inform the anticipated larger, multicenter practice-changing trial of mechanical ventilation strategies in pediatric ARDS. Finally, given the lower prevalence and mortality of pediatric ARDS, relative to adults, our Bayesian trial designs and analyses will inform care without proposing unrealistic and implausible effect sizes or unreasonably large sample sizes. PARMA is the first necessary step towards assessing whether a small practice change can ultimately improve outcomes in mechanically ventilated children in the US and worldwide.

9.5 Recruitment Strategy

Recruitment: The Pediatric Acute Respiratory distress syndrome (ARDS) MAnagement (PARMA) trial will be conducted entirely in the pediatric intensive care unit (PICU) at the Children's Hospital of Philadelphia (CHOP), a tertiary/quaternary care free-standing children's hospital serving a catchment area encompassing four states in the Northeastern US. The PICU is one of the largest in the US, currently

has 75-beds, admits > 4500 patients annually, and mechanically ventilates > 1200 subjects annually, of whom ~90 meet criteria for ARDS.

All patients in the PICU will be screened twice daily (once per weekend, as per current routine) by trained study staff. Detailed eligibility criteria will be shared and available to PICU screeners, leveraging modifications to existing screening processes already in place for ARDS studies (e.g., automated identification of subjects on invasive mechanical ventilation and for new intubations). Eligible patients will be approached ≤ 24 hours of meeting eligibility criteria, defined as when the second confirmatory hypoxemia measurement is made. The parents or legal guardians of patients who meet eligibility criteria will be approached for study enrollment. The site PI or trained staff members will engage them in a discussion regarding reasons for the study, the study procedures, and the risks and benefits and answer all questions. Following the above conversation, written informed consent from a patient's parent/guardian agreeing to participate in this study will be obtained. Regardless of where this discussion takes place, all reasonable safeguards to ensure patient privacy will be taken. If it is necessary for a study team member to discuss the study with the parent/legal guardians via phone (e.g., parent/legal guardian cannot be physically present, but time permits for prospective informed consent), then written informed consent will still be obtained by other means, to include faxing or emailing, to make the informed consent form available for review and for a signature. Subjects will be approached without language limitation as CHOP has extensive interpreter resources for multiple non-English languages available to researchers. Treatment allocation will be concealed to the clinical team until after informed consent obtained and enrollment confirmed.

Retention: The research team will be extensively trained in the screening process, eligibility criteria, and in study procedures. PARMA will be advertised to the CHOP PICU faculty, nurses, and respiratory therapists via multiple existing venues, including research conferences and weekly operational meetings. Aspects of the PARMA protocol that are congruent with existing ventilation practices at CHOP will be emphasized in order to facilitate acceptance and adherence. Compliance with assigned treatment group, adherence to ventilator protocol, and adherence to protocolized co-interventions will be monitored. The intervention will not be blinded to clinicians or investigators as blinding ventilator management is neither feasible nor safe in critically ill children. We will provide targeted intervention to study staff if enrollment drops < 50% consent of eligible subjects and if protocol adherence falls < 70%. Subjects who meet failure criteria will continue to have data recorded, and subjects who are withdrawn due to family request will be asked whether data can still be collected. Primary, secondary, and safety endpoints will be monitored and determined through hospital discharge or 90 days post-randomization, which will minimize loss to follow-up.

9.6 Informed Consent/Assent and HIPAA Authorization

9.6.1 Screening

Potential subjects will be recruited as part of routine clinical research practice within the PICU. The documentation of a newly placed endotracheal tube (ETT) or a newly admitted patient with an ETT or tracheostomy will be the primary trigger to consider eligibility. Once a potential patient with ARDS is identified, a member of the PICU research team will ensure that all eligibility criteria are met, to include a confirmation from a study PI, prior to study enrollment. After verification that a patient meets eligibility criteria, the child's medical record number, sex, and racial/ethnic background recorded in the medical record will be entered into a screening log. The screening log will provide a 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 are not enrolled will be noted. A log will be maintained of all enrolled and non-enrolled patients (without identifying information) with rationale for non-enrollment (e.g., meets exclusion criteria, physician denial, parent/legal guardian denial).

9.6.2 Main Study

Enrollment via Prospective Informed Consent: Eligible patients may be enrolled into the study after prospective informed consent obtained by a PI or designee trained in the details of the study (who may also be a member of the PICU staff and approved PARMA research staff) under 45 CFR 46. Study investigators and PICU research study staff will undergo rigorous training in the administration of informed consent prior to enrolling any subjects. Investigators and their designees will complete competency assessments in study procedures, randomization, and human subject protections. For patients who meet inclusion criteria and do not meet any exclusion criteria and sufficient time is available to seek prospective informed consent properly and ethically, the parent/legal guardians will be approached for study enrollment. A trained member of the study team (including PICU attendings trained as study coinvestigators) will engage them in a discussion reviewing the elements of informed consent under 45 CFR 46, including but not limited to the reasons for the study, the study procedures, the risks and benefits, and provide time for questions to be asked and answered. A study team physician will also be available to explain the medical aspect of the study and answer questions during the consent process. Due to anticipated critical nature of the patients' condition, this discussion may take place at the patient's bedside or in an alternative location (e.g., family conference room) at the parent/guardian's option and the consenter's discretion. Regardless of where this discussion takes place, all reasonable safeguards to ensure patient privacy will be taken. If it is necessary for a study team member to discuss the study with the parent/legal guardians via phone (e.g., parent/legal guardian cannot be physically present, but time permits for prospective informed consent), then written informed consent will still be obtained by other means, to include: faxing, or emailing, to make the informed consent form available for review and for a signature. Additionally, we will utilize e-signatures and videoconferencing as previously permitted after review by the CHOP IRB. Subjects

will be approached without language limitation as CHOP has extensive interpreter resources for multiple non-English languages available to researchers.

For patients who meet inclusion criteria and do not meet any exclusion criteria and sufficient time is available to seek prospective informed consent properly and ethically, we will also obtain written permission for HIPAA Authorization on the combined consent-HIPAA authorization form. We will provide a copy of the combined consent-HIPAA authorization document to the parent/guardian and will write a note in the patient's medical record documenting the informed consent discussion.

9.6.3 Consent/HIPAA Authorization Plan for Subjects Who Reach Age of Majority

There is a small possibility of subjects being enrolled while > 17 years and 9 months of age but < 18 years, who will remain in the study period for the 90-day maximum follow-up period. These subjects run the risk of attaining majority age (> 18 years) during the study follow-up window. No subjects will themselves consent or assent at enrollment, as they will be sedated and intubated (by definition of eligibility) as all ARDS subjects are expected to be. For potential subjects who require re-consent, if they are no longer under sedation and do not have discernible neurocognitive deficits, we will re-approach for written consent.

9.6.4 Individuals with Limited English Proficiency

Individuals who have a non-English language preference (NELP) will be eligible for PARMA. These subjects will be consented using either in-person or remote (ORC-compliant telephone) interpreter services and documented using the CHOP Short Form process, including signatures from the interpreter.

9.6.5 Waiver of Assent

Waiver of Assent: We plan for a waiver of assent for all patients due to the critical nature of the patients' illness with ARDS, as they will be (by definition of eligibility) intubated, sedated, with high potential for altered mental status and neurologic dysfunction from hypoxemia, making them unable to participate in a meaningful way. However, any patients who are capable and willing to participate in the prospective informed consent discussion (in rare scenarios where it is appropriate) will be involved and engaged in this process.

9.7 Payment to Subjects/Families

There are no plans to reimburse, incentivize, or provide payments to subjects or families.

10 PUBLICATION

The proposed trial will be registered with clinicaltrials.gov by the study PI prior to subject enrollment. Results will be submitted to clinicaltrials.gov within 12 months of completing subject enrollment, immediately following peer review and journal publication of the main publication, in accordance with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. No individually identifiable PHI will be published.

The informed consent documents and the post-enrollment information sheet will include a specific statement that aggregate data from the clinical trial will be posted to clinicaltrials.gov in compliance with government policies and the internal policies of the Children's Hospital of Philadelphia (CHOP).

In addition to clinicaltrial.gov, upon submission of aggregate deidentified data for peer-reviewed publication we will ensure that the resulting main peer-reviewed publication occurs as "open-access."

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