

# Reevaluation Of Systemic Early neuromuscular blockade

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**ACRONYM:**

**ROSE**

**VERSION**

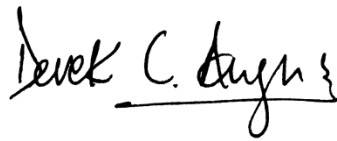
**VERSION VII**

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# 1 ABBREVIATIONS & DEFINITIONS

## 1.1 ABBREVIATIONS

**ACURASYS** = The ARDS and Curarisation Systematic study investigators

**ARDS** = Acute Respiratory Distress Syndrome

**BiPAP** = Bilevel Positive Airway Pressure

**BMI** = Body Mass Index

**BUN** = Blood Urea Nitrogen

**CCC** = Clinical Coordinating Center

**CPAP** = Continuous Positive Airway Pressure

**DSMB** = Data Safety Monitoring Board

**ECMO** = Extracorporeal Membrane Oxygenation

**EDEN** = Early versus Delayed Enteral Nutrition trial

**FACTT** = Fluid and Catheter Treatment Trial

**FiO<sub>2</sub>** = Fraction of Inspired Oxygen

**GCS** = Glasgow Coma Scale

**GRADE** = Grading of Recommendations Assessment, Development and Evaluation

**IBW** = Ideal Body Weight

**ICU** = Intensive Care Unit

**IL-1 $\beta$**  = Interleukin 1 $\beta$

**IL-6** = Interleukin 6

**IL-8** = Interleukin 8

**IMV** = Intermittent Mechanical Ventilation

**INR** = International Normalized Ratio

**ITT** = Intent to Treat

**IVRS** = Interactive Voice Response System

**LAR**=Legally Authorized Representative

**LTAC** = Long Term Acute Care Facility

**mBW** = Measured Body Weight

**MRC** = Medical Research Council

**NHLBI** = National Heart Lung and Blood Institute

**NMBA** = Neuromuscular blocking agent

**OSCILLATE** = Oscillation for Acute Respiratory Distress Syndrome Treatment Early

**PETAL** = Prevention and Early Treatment of Acute Lung Injury

**P/F** = PaO<sub>2</sub>/FiO<sub>2</sub> ratio

**PaCO<sub>2</sub>** = Partial pressure of arterial carbon dioxide

**PaO<sub>2</sub>** = Partial pressure of arterial oxygen

**PAP** = Pulmonary Artery Pressure

**PB** = Barometric Pressure

**PBW** = Predicted Body Weight

**PEEP** = Positive End-Expiratory Pressure

**PIN** = Personal Identification Number

**Pplat** = Plateau pressure

**PROSEVA** = Proning Severe ARDS Patients study investigators

**PTSD** = Post Traumatic Stress Disorder

**PS** = Pressure Support Ventilation

**RASS** = Richmond Agitation Sedation Scale

**S/F** = SpO<sub>2</sub>/FiO<sub>2</sub> ratio

**SOFA** = sequential organ failure assessment

**SBP** = Systolic Blood Pressure

**SBT** = Spontaneous Breathing Trial

**SpO<sub>2</sub>** = Oxygen Saturation via pulse oximetry

**SUSAR** = Serious and Unexpected Suspected Adverse Reactions

**SAEs**= Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure

**VFD** = Ventilator-free Days

**WBC** = White Blood Cell

## 1.2 DEFINITIONS

**Adverse Event:** Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

**Adverse reaction:** An adverse reaction means any adverse event caused by a drug. An adverse reaction are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

**Assisted breathing:** Any level of ventilatory support at pressures higher than the unassisted breathing thresholds. Completing 48 hours of UAB is defined as the date (calendar day) that the subject reaches exactly 48 hours of UAB. Example: if subject meets UAB at 1900 on 6/1/15 and does not return to assisted breathing, then the date of completing 48 hours of UAB would be 6/3/15.

**Controlled Ventilation:** Any mode with a backup rate that allows clinicians to either set tidal volume to a target or adjust pressures to target a tidal volume. Examples include volume assist control, pressure assist control, pressure regulated volume control.

**Extubation:** Removal of an orotracheal, nasotracheal tube, or unassisted breathing with a tracheostomy

**Home:** Level of residence or health care facility where the patient was residing prior to hospital admission.

**Intention to Treat (ITT):** All eligible and consented patients who undergo randomization will be included in the ITT cohort for the purposes of analyzing the primary and secondary study outcomes.

**Invasive Mechanical Ventilation:** Assisted ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

**Legal Representative:** An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

**Mortality prior to discharge home before day 90:** This primary outcome includes deaths from all causes following randomization in any health care facility prior to discharge home until study day 90. Study subjects still in a health care facility at study day 91 are considered alive for this endpoint.

**Funding:** National Institutes of Health (National Heart Lung and Blood Institute)

**Sponsor:** The Clinical Coordinating Center at Massachusetts General Hospital

**Study Day:** The day of randomization is study day zero. The next day is study day one etc.

**Study Drug:** Randomly assigned cisatracurium

**Study hospital:** Defined as the hospital where the patient was randomized and enrolled.

**Study withdrawal:** Defined as permanent withdrawal from study before completion of study activities. This does not include those subjects who have completed the protocol procedures or stopped procedures because they have reached unassisted breathing. If a patient or surrogate requests withdrawal from the study the clinician should seek explicit permission to continue data collection.

**Suspected adverse reaction:** any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction (21 CFR 312.32(a))

**UAB (Unassisted Breathing):** Spontaneously breathing with face mask, nasal prong oxygen, room air, T-tube breathing, tracheostomy mask breathing, CPAP  $\leq$  5 without PS or IMV assistance, the use of noninvasive ventilation solely for sleep-disordered breathing, or use of a nasal high flow system.

## 2 TRIAL SUMMARY

**Title:** Reevaluation Of Systemic Early neuromuscular blockade (ROSE)

**Objective:** To assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison to a control group with no routine early neuromuscular blockade.

**Hypothesis:** Early neuromuscular blockade will improve mortality prior to discharge home before day 90, in patients with moderate-severe ARDS.

**Study Design:** Multi-center, prospective, 2-arm, unblinded, randomized clinical trial of two management strategies of neuromuscular blockade (also called skeletal muscle relaxant and muscle relaxant).

1. We will emphasize early screening and protocol initiation, and enroll a maximum of 1408 patients with a confirmed and established PaO<sub>2</sub>/FiO<sub>2</sub> < 150.
  - ✓ We will allow determination of PaO<sub>2</sub>/FiO<sub>2</sub> inclusion criteria from SpO<sub>2</sub> pulse oximetry measurement.
2. Early neuromuscular blockade group
  - ✓ Patients will receive a cisatracurium besylate bolus of 15 mg, followed by a continuous infusion of 37.5 mg/hour for 48 hours.
  - ✓ We will protocolize deep sedation to Ramsay of 5-6 (RASS of -4 to -5, or Riker of 1-2) before starting, and during, the 48 hour infusion. We do not mandate sedative type or dose.
  - ✓ We will protocolize high PEEP/FiO<sub>2</sub> titration (based on published, safe, feasible high PEEP protocols).
3. No routine early neuromuscular blockade group (control group)
  - ✓ We will recommend non-neuromuscular blockade interventions for refractory hypoxia and that neuromuscular blockade only be used for refractory elevated plateau pressure; treating clinicians can use neuromuscular blockade if thought necessary
  - ✓ We will recommend clinicians target light sedation titrated to a Ramsay 2-3 (RASS of 0 to -1, or Riker 3-4) and/or perform daily sedation interruption. Higher doses of sedation will be allowed for respiratory distress, ventilator dyssynchrony, or hypoxia. We do not mandate sedative type or dose.
  - ✓ We will protocolize high PEEP/FiO<sub>2</sub> titration (based on published, safe, feasible high PEEP protocols).
4. Prone positioning
  - ✓ We will recommend sites wait at least 12 hours (as per PROSEVA[1]) before proning, and to avoid automatic use of neuromuscular blockade with proning.
5. Other care



- ✓ We will protocolize low tidal volume ventilation and spontaneous breathing trials in both arms.
- ✓ We will provide recommendations for conservative fluid management in both arms.

### **Inclusion Criteria**

1. Age  $\geq$  18 years
2. Presence of all of the following conditions for  $\leq$  48 hours

- i. (I) PaO<sub>2</sub>/FiO<sub>2</sub> < 150 with PEEP  $\geq$  8 cm H<sub>2</sub>O.<sup>a,b,c</sup>

#### **OR, IF ABG NOT AVAILABLE**

SpO<sub>2</sub>/FiO<sub>2</sub> ratio that is equivalent to a PaO<sub>2</sub>/FiO<sub>2</sub> < 150 with PEEP  $\geq$  8 cm H<sub>2</sub>O (Appendix A1), and a confirmatory SpO<sub>2</sub>/FiO<sub>2</sub> ratio between 1-6 hours after the initial SpO<sub>2</sub>/FiO<sub>2</sub> ratio determination.<sup>c,d</sup>

- ii. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
- iii. Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present (Appendix L)

<sup>a.</sup> If altitude >1000m, then PaO<sub>2</sub>/FiO<sub>2</sub> < 150 x (PB/760).

<sup>b</sup> These inclusion criteria ensure a non-transient, established hypoxia that persists despite elevated PEEP and time. Initial, post-intubation, PEEP is typically < 8 cm H<sub>2</sub>O.

<sup>c</sup> The qualifying PaO<sub>2</sub>/FiO<sub>2</sub> or the SpO<sub>2</sub>/FiO<sub>2</sub> must be from intubated patients receiving at least 8 cm H<sub>2</sub>O PEEP.

<sup>d.</sup> When hypoxia is documented using pulse oximetry, a confirmatory SpO<sub>2</sub>/FiO<sub>2</sub> ratio is required to further establish persistent hypoxia. Qualifying SpO<sub>2</sub>/FiO<sub>2</sub> must use SpO<sub>2</sub> values less than or equal to 96% Qualifying SpO<sub>2</sub> must be measured at least 10 minutes after any change to FiO<sub>2</sub>.

The 48-hour enrollment time window begins when criteria i-iii are met. Criteria may be met at either the Network or referring hospital. The first qualifying SpO<sub>2</sub>/FiO<sub>2</sub> (not the confirmatory SpO<sub>2</sub>/FiO<sub>2</sub>) is used determine this time window.

### **Exclusion Criteria**

1. Lack of informed consent
2. Continuous neuromuscular blockade at enrollment
3. Known pregnancy
4. Currently receiving ECMO therapy
5. Chronic respiratory failure defined as PaCO<sub>2</sub> > 60 mm Hg in the outpatient setting
6. Home mechanical ventilation (non-invasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing
7. Actual body weight exceeding 1 kg per centimeter of height
8. Severe chronic liver disease defined as a Child-Pugh score of 12-15 (Appendix A2)
9. Bone marrow transplantation within the last 1 year

10. Expected duration of mechanical ventilation < 48 hours
11. Decision to withhold life-sustaining treatment; except in those patients committed to full support except cardiopulmonary resuscitation
12. Moribund patient not expected to survive 24 hours; if CPR provided, assess for moribund status  $\geq 6$  from CPR conclusion
13. Diffuse alveolar hemorrhage from vasculitis
14. Burns > 70% total body surface
15. Unwillingness to utilize the ARDS Network 6 ml/kg IBW ventilation protocol
16. Previous hypersensitivity or anaphylactic reaction to cisatracurium
17. Neuromuscular conditions that may potentiate neuromuscular blockade and/or impair spontaneous ventilation (Appendix A2)
18. Neurologic conditions undergoing treatment for intracranial hypertension
19. Enrollment in an interventional ARDS trial with direct impact on neuromuscular blockade and PEEP
20. PaO<sub>2</sub>/FiO<sub>2</sub> (if available) >200 after meeting inclusion criteria and before randomization *Oxygenation may improve during the 48 hour enrollment window. This exclusion criterion ensures that patients with mild ARDS are not included in the study.*
21. Endotracheal ventilation for greater than 120 hours (5 days)
22. Patient has completed lung transplant evaluation and has been officially listed for lung transplant by UNOS

**Randomization and Study Initiation Time Window:** All patients must be enrolled and randomized within 48 hours of meeting inclusion criteria. After randomization, the low tidal volume protocol must be initiated within two hours (if not already being used). In the intervention arm, deep sedation followed by neuromuscular blockade must be initiated within four hours of randomization.

**Efficacy:** The primary outcome is all-cause mortality prior to discharge home before day 90.

1. **Secondary outcomes:**
  1. ICU acquired weakness
  2. IL-6 levels (plasma)
  3. Hospital mortality to day 28
  4. Ventilator free days to day 28
  5. Organ failure free days to day 28
  6. ICU-free days at day 28
  7. Hospital-free days at day 28
  8. Physiologic measures
  9. Long term outcome assessments
  10. Use of rescue procedures

11. Paralysis recall, in-hospital
12. Supraventricular tachycardia and new onset atrial fibrillation

**Sample Size/Interim Monitoring:**

1. With a 35% mortality rate in the control arm and 27% mortality rate in the intervention arm, the maximum required total sample size is 1408 subjects.
2. The principal analysis will be intent-to-treat, based upon randomization assignment.
3. Trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB) to determine if the study should stop for superiority of either Active or Control therapy. There will be two interim analyses and a final analyses conducted when approximately each successive 1/3 of the patients have been enrolled.

### **3 TRIAL DESCRIPTION**

#### **3.1 BACKGROUND**

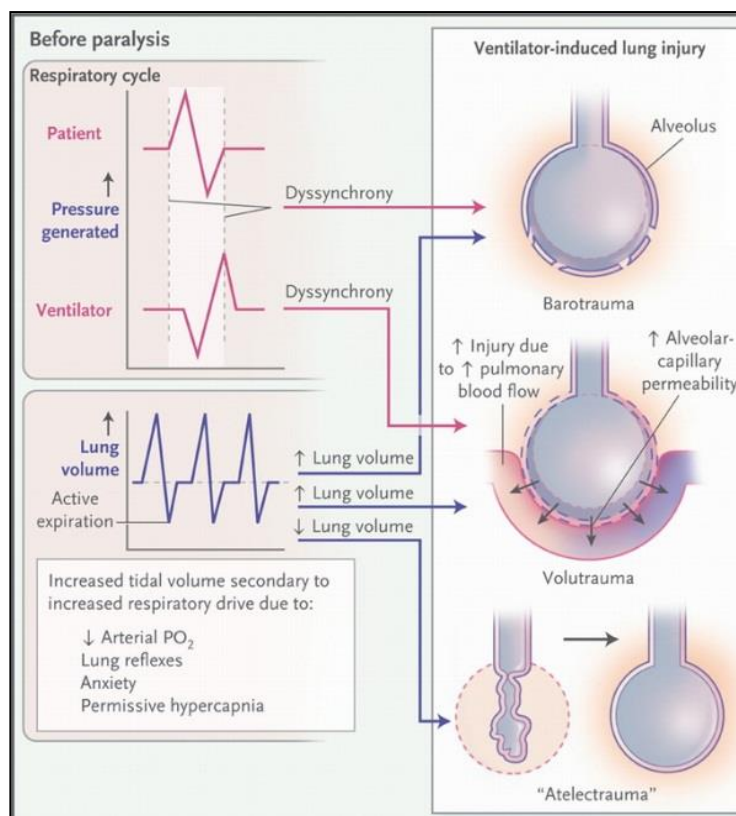
In 2010, the ACURASYS trial reported early neuromuscular blockade (also called skeletal muscle relaxant or muscle relaxant) administration improved adjusted survival for moderate to severe ARDS in a 340 patient trial conducted in 20 French ICUs.[2] While intriguing, this approach has not been widely adopted in the U.S., and key limitations exist. First, the trial was underpowered. Mortality benefit was noted only after statistical adjustment; crude 90d mortality did not differ. Control mortality was also lower than predicted (though higher than many recent ARDS trials)[3, 4] and the authors concluded “given the observed mortality in our placebo group, the current study was underpowered”. Second, the mechanism responsible for the improvement in outcome with neuromuscular blockade is unclear. One possible explanation is that neuromuscular blockade results in improvement in patient-ventilator asynchrony with subsequent reduction in ventilator-induced lung injury and inflammation. Third, assessment of a known side effect of the intervention, muscle paresis, has been criticized as inadequate. As a result of these concerns, the critical care community has collectively recommended another phase III clinical trial to definitively test the safety and efficacy of neuromuscular blockade in patients with ARDS.[5, 6]

#### **3.2 NEUROMUSCULAR BLOCKADE – POTENTIAL BENEFITS AND MECHANISMS**

One of the earliest ARDS Network trials demonstrated that low tidal volume ventilation led to an absolute reduction in mortality of 9%.[7] This ventilator strategy presumably reduced ventilator induced lung injury by avoiding alveolar over distension. Recent ARDS studies have examined whether ventilatory strategies such as high positive end expiratory pressure (PEEP) or high frequency oscillation may improve outcome. All of these trials have focused on adjusting the ventilator portion of the patient-ventilator interface. Therapies directed at reducing patient’s metabolic demands and improving the patient’s ability to interface with the ventilator, may also attenuate ventilator induced lung injury. Neuromuscular blockade may improve the patient

component of the patient-ventilator interface. Oxygen consumption of respiratory muscles normally represents only 1%-3% of cardiac output. Due to the decreased pulmonary compliance in ARDS, the work of breathing escalates and can constitute as much as 24% of the increased cardiac output[8]. These increases in cardiac output and blood flow across an injured pulmonary vasculature can generate higher filtration pressures and promote the formation of lung edema. By removing the ability of the respiratory muscles to contract, neuromuscular blockade reduces the oxygen consumption of these muscles, which in turn reduces cardiac output directed towards these muscles, increases the mixed venous partial pressure of oxygen, and can increase the partial pressure of oxygen in arterial blood. These same reductions in cardiac output diminish the volume of blood flow through the pulmonary capillaries, decrease the pulmonary vascular pressure gradient, and the accumulation of alveolar fluid. Vigorous expiratory effort can also result in alveolar collapse and reduced end-expiratory lung volumes. By preventing active expiration, neuromuscular blockade may create a more homogenous distribution of PEEP and tidal volumes, preventing barotrauma/volutrauma and “atelectrauma” resulting in less ventilator-induced lung injury[5] (See Figure 1).

**Figure 1**



### 3.3 NEUROMUSCULAR BLOCKADE – POTENTIAL HARMS

In the recent past, neuromuscular blockade was commonly used for ventilated patients with acute respiratory failure.[9] However, with its increased utilization, neuromuscular blockade was

implicated in the development of a severe and persistent neuromuscular weakness[10], though this association has been recently challenged[11]. Due to the concerns for these long term debilitating side effects combined with the availability of more efficacious sedative agents, the prolonged use of neuromuscular blocking agents for critically ill patients who require mechanical ventilation diminished over time.

### 3.4 RECENT FRENCH CLINICAL TRIALS

Based on the rationale outlined above, Papazian and colleagues examined the efficacy of neuromuscular blockade for ARDS. Their first study was a randomized controlled trial to determine the effects of 48 hours of neuromuscular blockade on gas exchange in patients with severe ARDS[12]. All patients were heavily sedated to a Ramsay score of six before randomization. Patients randomized to neuromuscular blockade demonstrated significant improvements in PaO<sub>2</sub>/FiO<sub>2</sub> ratio during the first five days of their ICU course when compared to placebo. A second study evaluated the effects of neuromuscular blockade on pulmonary and systemic markers of inflammation in patients with ARDS[13]. All patients underwent a bronchoalveolar lavage (BAL) before randomization and at 48 hours. Neuromuscular blockade resulted in a decrease in IL-1 $\beta$ , IL-6, and IL-8 levels in the BAL fluid at 48 hours. There was also a significant decrease in serum concentrations of IL-6 and IL-8 in the patients who received neuromuscular blockade. Similar to their first study, patients who received neuromuscular blockade had a significant improvement in their oxygenation. Their third and most prominent study (ACURASYS), as noted above, showed decreased mortality with early neuromuscular blockade [2].

### 3.5 CURRENT PRACTICE IN PETAL SITES AND CLINICAL EQUIPOISE

To determine the utilization of neuromuscular blockade for patients with moderate to severe ARDS, we surveyed the principal investigators of the current PETAL network hospitals. Overall, 35 investigators answered the survey; representing all 12 PETAL sites. Only 11% of investigators stated that continuous neuromuscular infusions were commonly used for ARDS patients with a PaO<sub>2</sub>/FiO<sub>2</sub> < 150 at their hospitals. In this survey, commonly was defined as between 80-100% of patients. The vast majority of these investigators (94%) were confident they would be able to randomize ARDS patients with a PaO<sub>2</sub>/FiO<sub>2</sub> < 150 to a neuromuscular blockade protocol. Similarly, 100% of investigators would be able to follow a neuromuscular blockade protocol in the intervention arm of the study and enforce no routine use of neuromuscular blockade in the control arm.

These survey results demonstrate that neuromuscular blockade is uncommonly used for ARDS patients with a PaO<sub>2</sub>/FiO<sub>2</sub> < 150, and that PETAL sites would be able to effectively perform a randomized study of neuromuscular blockade for ARDS patients with a PaO<sub>2</sub>/FiO<sub>2</sub> < 150.

### 3.6 EARLY NEUROMUSCULAR BLOCKADE FOR ARDS NEEDS REEVALUATION

Despite the encouraging results of the Papazian studies, there are several compelling reasons why the PETAL Network should perform a second study of early neuromuscular blockade for ARDS. First and foremost, the pulmonary and critical care community has clearly learned that clinical trials often require replication and validation before the efficiency of a therapy is proven. In a review of 39 highly cited positive randomized clinical trials, the results were replicated in less than 50% of subsequent studies[14]. Relevant to critical care, the results of several landmark trials including intensive insulin therapy and activated protein C were not replicated in subsequent studies. The high rate of non-replication is a consequence of the ill-founded strategy of claiming conclusive research findings solely on the basis of one study whose  $p$  value  $< 0.05$ . The hesitancy to conclude the efficacy of a treatment based on a single trial may be especially true for studies that appear counterintuitive and question recent paradigms such as the routine use of neuromuscular blockade in critically ill patients. A second large randomized trial with positive results would elevate early neuromuscular blockade for ARDS to the highest GRADE level and the strongest recommendation based on modified Delphi methodology.

Reservations about the Papazian trial were based on the following concerns about study design, statistical analysis, and adverse event reporting.

1. Though the preplanned primary outcome was adjusted mortality, and the adjusted mortality rate was significantly different between the two groups ( $p = 0.04$ ), crude mortality was not significantly different between the groups ( $p = 0.08$ ).
2. The infusion of neuromuscular blockade occurred during the first 48 hours of the study. However, the Kaplan-Meier curves achieved separation after Day 12 in regard to the probability of achieving unassisted breathing, and after Day 18 in regard to mortality. The delay in the observed treatment effect raises concerns about the direct effects of neuromuscular blockade on the positive outcomes in the clinical trial.
3. Variables commonly used to assess the risk of ventilator induced lung injury, such as plateau pressure and tidal volume, were not different between the patients who received neuromuscular blockade and placebo, raising concerns about the biological plausibility of the therapy.
4. A low PEEP strategy was used in both arms of the Papazian trial. For patients with moderate to severe ARDS, meta-analyses suggest that high PEEP strategies may result in improved outcomes including mortality [15]. Based upon the likelihood that atelectrauma may be more common with lower PEEP strategy, neuromuscular blockade may have a different effect for patients receiving a high PEEP strategy.
5. All patients in the control arm of the Papazian trial received heavy sedation defined as a Ramsay score of six. The routine use of heavy sedation is associated with several deleterious outcomes including prolonged length of mechanical ventilation. Based on the results of our survey of PETAL investigators, 86% of respondents reported that the routine sedation goal for ARDS patients is not heavy sedation. Therefore, it is plausible that the positive results of the Papazian trial are related to the harmful and uncommon use of a heavy sedation strategy in the control arm.

6. Safety-related outcomes are commonly underreported in randomized controlled clinical trials resulting in misinterpretation and inadequate conclusions concerning the benefits of the intervention [16, 17]. The assessment of neuromuscular dysfunction was determined using only the MRC score to define weakness. In addition, the potential effects of neuromuscular blockade on the development of symptoms of post-traumatic stress disorder and paralysis recall were not determined. A better understanding of the long term risk associated with the use of neuromuscular blockade would allow clinicians to make a more informed decision about its utility in ARDS.
7. Based on the strength of the previous clinical trials and the need to replicate their results, we propose to test the safety and efficacy of a 48 hour infusion of neuromuscular blockade for reducing mortality in patients with early ARDS. *We hypothesize that early neuromuscular blockade will result in improved clinical outcomes, specifically hospital mortality prior to discharge home before day 90 in patients with moderate-severe ARDS.*

### 3.7 ROSE IS AN EARLY TREATMENT TRIAL

The goal of ROSE is to test early administration of neuromuscular blockade for 48 hours as close to the initial onset of moderate to severe ARDS as possible. All efforts will be made to emphasize very rapid enrollment as soon as this severity of ARDS is diagnosed. We believe early administration is crucial. Neuromuscular blockade is most likely to be effective in mediating lung injury and lung-injury induced non-pulmonary effects and inflammation, if administered early. In addition, though neuromuscular blockade is sporadically used in routine clinical practice, systematic early treatment is not widespread. Thus, if the null hypothesis of ROSE is rejected, this trial will significantly alter and improve current clinical care, leading to increased early treatment with neuromuscular blockade.

Our approach will be to leverage the new PETAL infrastructure and philosophy to screen and enroll patients early using a suite of techniques adapted from prior successful early intervention trials, including Emergency Department trials (Section 4.1). We will also monitor time from inclusion criteria being met to enrollment, overall and by site, and regularly discuss with sites strategies to encourage very early enrollment.

### 3.8 OBJECTIVES

#### **Primary Objective**

To assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS, in comparison to a control group with no routine early neuromuscular blockade.

#### **Primary Hypothesis**

Early neuromuscular blockade will improve mortality prior to discharge home before day 90, in patients with moderate-severe ARDS.

## 3.9 END POINTS

Analyses will be conducted on an intention to treat basis.

### 3.9.1 PRIMARY OUTCOME

The primary outcome is all-cause mortality prior to discharge home before day 90.

### 3.9.2 SECONDARY OUTCOMES

#### 1. ICU acquired weakness

- a. Manual muscle strength testing will be attempted at study day 7, and then every 7 days thereafter, until hospital discharge or day 28 (whichever comes first). Patients will be defined as having ICU acquired weakness if their Medical Research Council (MRC) score is < 48 (or mean MRC < 4 for each muscle group tested)[18, 19].
- b. Highest level of mobility will be assessed on study days 1-7 using the ICU Mobility Scale [20], and then every 7 days thereafter, until hospital discharge or day 28 (whichever comes first).

#### 2. IL-6 levels (plasma)

We will measure interleukin-6 (IL-6) at study entry and at 48 hours. A proposed mechanism of benefit of neuromuscular blockade is decreased ventilator-induced lung injury. Interleukin-6 is a pro-inflammatory cytokine that decreased in patients treated with a lung-protective low tidal volume ventilation strategy compared to control patients.[7] Furthermore, in pilot studies neuromuscular blockade was associated with decreased levels of IL-6.[13] Here, we hypothesize that compared to control subjects, subjects receiving neuromuscular blockade for 48 hours will have lower levels of IL-6, reflecting decreased ventilator-induced lung injury. As in the ARDS Network trials, analysis of covariance (ANCOVA) will be used to examine the impact of treatment with neuromuscular blockade on biomarker levels at 48 hours.

#### 3. Hospital mortality to day 28

#### 4. Ventilator free days to day 28

Ventilator free days to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.



5. Organ failure free days to day 28

Organ failure is defined as present on any date when the most abnormal vital signs or clinically available lab value meets the definition of clinically significant organ failure according to SOFA scores (Appendix K).[21] Patients will be followed for development of organ failures to death, hospital discharge or study day 28, whichever comes first. Each day a patient is alive and free of a given organ failure will be scored as a failure-free day. Any day that a patient is alive and free of all organ failures will represent days alive and free of all organ failure.

6. ICU-free days at day 28

7. Hospital-free days at day 28

8. Physiologic measures to include:

- a) Oxygenation Index on study days 1-4,7
- b) PaO<sub>2</sub> / FiO<sub>2</sub> ratio on study days 1-4, 7
- c) Level of PEEP on study days 1-4, 7
- d) Plateau pressure on study day 1-4, 7
- e) Development of pneumothorax through day 7

9. Long term outcome assessments

We will assess seven measures after hospitalization:

- a) Disability: using Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities of Daily Living Scale (IADL) plus two additional Nagi items
- b) Health-Related Quality of Life (including utilities): EuroQol (EQ-5D-5L)
- c) Self-rated health: 1 standard item
- d) Pain-interference: 1 standard item
- e) Post-traumatic Stress-like Symptoms: Post-Traumatic Stress Symptoms (PTSS-14)
- f) Cognitive function: Montreal Cognitive Assessment (MoCA-Blind) or, via proxy, the Alzheimer's Disease 8 (AD8)
- g) Subsequent return to work, hospital and ED use, and location of residence

These measures will be collected through telephone interviews with patients or their LARs (Appendix G).

10. Use of rescue procedures

Rescue procedures will be chosen according to the practice at the clinical site. We will record the use of the following rescue procedures (yes/no) through study day 28: prone positioning, nitric oxide, epoprostenol sodium, high frequency ventilation, and ECMO.

11. Paralysis recall, in-hospital

Paralysis recall assessment will be monitored once during hospitalization in all patients, using a modified Brice questionnaire [22, 23].

12. Supraventricular tachycardia (SVT) or new onset atrial fibrillation (the occurrence of one or more episodes during the ICU stay will be recorded)

### 3.9.3 SUBGROUPS

A priori subgroups will include: pre-randomization PaO<sub>2</sub>/FIO<sub>2</sub> < 120, and time from meeting ARDS severity criteria for study enrollment to start of cisatracurium infusion.

## 4 STUDY POPULATION AND ENROLLMENT

### 4.1 NUMBER/SOURCE/SCREENING

The trial will accrue a maximum of 1408 patients. Patients will be recruited from the emergency departments, intensive care units and other acute care areas of the PETAL Network Clinical Centers. The overall strategy is to screen and enroll early, every newly intubated, acutely ill or post-operative, patient at each site, using clinically obtained pulse oximetry and blood gases.

Tactics will include:

- i. Follow up each screened patient on a daily basis

Epidemiological studies have demonstrated that 90% of at risk patients will develop ARDS within 5 days. Prior ARDS Network trials have successfully used this “screen and follow” strategy in facilitating early enrollment of eligible patients.

- ii. Emergency Department (ED) screening and ICU hand-off

In the Emergency Department (ED), every intubated patient will be assessed for inclusion and exclusion criteria. This assessment will either be in person or through electronic screening. If a long ICU bed wait time is predicted, patients can be enrolled in the ED. We will facilitate ED-ICU handoff with use of a unified screening log (to be used for both ED and ICU screening), joint inservice training by site PIs to ED and ICU faculty, and coordination by research staff for enrolled patients. When patients are enrolled in the ED, research staff in the ED will call the ICU research staff to report name, medical record number, diagnoses, destination, and time of administration of study drug. This communication will occur before patients leave the ED.

- iii. ICU screening

Every new ICU admission receiving mechanical ventilation will be screened. This will include but not be limited to admissions from the ED, wards, and operating room. We will also assess patients transferred from outside hospitals. The enrollment window for these patients will include the time elapsed since admission at the outside hospital including during transfer.

- iv. Study clinician availability for consent

Each site will have dedicated study physicians and coordinators who are certified and trained in human subjects protection and understand the study protocol.

## 4.2 INCLUSION CRITERIA

1. Age  $\geq$  18 years
2. Presence of all of the following conditions for  $\leq$  48 hours:
  - i. (I)  $\text{PaO}_2/\text{FiO}_2 < 150$  with  $\text{PEEP} \geq 8$  cm H<sub>2</sub>O.<sup>a,b,c</sup>

### OR, IF ABG NOT AVAILABLE

$\text{SpO}_2/\text{FiO}_2$  ratio that is equivalent with a  $\text{PaO}_2/\text{FiO}_2 < 150$  with  $\text{PEEP} \geq 8$  cm H<sub>2</sub>O (Appendix A1), and a confirmatory  $\text{SpO}_2/\text{FiO}_2$  ratio between 1-6 hours after the initial  $\text{SpO}_2/\text{FiO}_2$  ratio.<sup>c,d</sup>

- ii. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
- iii. Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present (Appendix L)

<sup>a</sup> If altitude  $>1000\text{m}$ , then  $\text{PaO}_2/\text{FiO}_2 < 150 \times (\text{PB}/760)$ .

<sup>b</sup> These inclusion criteria ensure a non-transient, established hypoxia that persists despite elevated PEEP and time. Initial, post-intubation, PEEP is typically  $< 8$  cm H<sub>2</sub>O.

<sup>c</sup> The qualifying  $\text{PaO}_2/\text{FiO}_2$  or the  $\text{SpO}_2/\text{FiO}_2$  must be from intubated patients receiving at least 8 cm H<sub>2</sub>O PEEP.

<sup>d</sup> When hypoxia is documented using pulse oximetry, a confirmatory  $\text{SpO}_2/\text{FiO}_2$  ratio is required to further establish persistent hypoxia. Qualifying  $\text{SpO}_2/\text{FiO}_2$  must use  $\text{SpO}_2$  values less than or equal to 96%. Qualifying  $\text{SpO}_2$  must be measured at least 10 minutes after any change to  $\text{FiO}_2$ .

The 48-hour enrollment time window begins when criteria i-iii are met. Criteria may be met at either the Network or referring hospital. The first qualifying  $\text{SpO}_2/\text{FiO}_2$  (not the confirmatory  $\text{SpO}_2/\text{FiO}_2$ ) is used determine this time window.

## 4.3 EXCLUSION CRITERIA

1. Lack of informed consent
2. Continuous neuromuscular blockade at enrollment
3. Known pregnancy
4. Currently receiving ECMO therapy
5. Chronic respiratory failure defined as  $\text{PaCO}_2 > 60$  mm Hg in the outpatient setting
6. Home mechanical ventilation (non-invasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing
7. Actual body weight exceeding 1 kg per centimeter of height
8. Severe chronic liver disease defined as a Child-Pugh score of 12-15 (Appendix A2)
9. Bone marrow transplantation within the last 1 year
10. Expected duration of mechanical ventilation  $< 48$  hours

11. Decision to withhold life-sustaining treatment; except in those patients committed to full support except cardiopulmonary resuscitation
12. Moribund patient not expected to survive 24 hours; if CPR provided, assess for moribund status  $\geq 6$  hours from CPR conclusion
13. Diffuse alveolar hemorrhage from vasculitis
14. Burns  $> 70\%$  total body surface
15. Unwillingness to utilize the ARDS Network 6 ml/kg IBW ventilation protocol
16. Previous hypersensitivity or anaphylactic reaction to cisatracurium
17. Neuromuscular conditions that may potentiate neuromuscular blockade and/or impair spontaneous ventilation (Appendix A2)
18. Neurologic conditions undergoing treatment for intracranial hypertension
19. Enrollment in an interventional ARDS trial with direct impact on neuromuscular blockade and PEEP
20. PaO<sub>2</sub>/FiO<sub>2</sub> (if available)  $>200$  after meeting inclusion criteria and before randomization  
Oxygenation may improve during the 48 hour enrollment window. This exclusion criterion ensures *that patients with mild ARDS are not included in the study.*
21. Endotracheal ventilation for  $> 5$  days (120 hours) See Appendix A2 for specific exclusion criteria definitions.
22. Patient has completed lung transplant evaluation and has been officially listed for lung transplant by UNOS

#### 4.3.1 REASONS FOR EXCLUSIONS

Patients  $<18$  years old are excluded because of limited clinical trial data with cisatracurium in these individuals. In addition, we will only be enrolling patients from adult ICUs, and the staff may be less well-trained in sedation and neuromuscular blockade practices in children. Patients with ARDS for  $>48$  hours or on mechanical ventilation for  $> 120$  hours are excluded because the PETAL network is charged to test early treatment. In addition, previous trials that suggested benefit from neuromuscular blockade used a 48 hour time interval. Criteria 2 and 4 exclude patients who are already receiving or likely to receive neuromuscular blockers as part of their clinical care. Exclusion criterion 3 is included because there are not sufficient data to support the use of cisatracurium in pregnant women during treatment for severe ARDS. Criteria 5, 6, 7, 8, 9, 10, 11, 12, 17 and 22 exclude patients who may not survive to important study endpoints or whose underlying condition or ventilator management complicates assessment of the secondary endpoint of ventilator free days. Patients with diffuse alveolar hemorrhage (criterion 13) are excluded because the mechanism of lung injury is different from ARDS due to other causes. Patients with large burns (criterion 14) are also excluded as conservative fluid management may be contraindicated.

#### 4.4 RANDOMIZATION, AND STUDY INITIATION TIME WINDOW

All patients must be randomized within 48 hours of meeting inclusion criteria. The window for randomization begins at the time of meeting all inclusion criteria, regardless of patient location.

After randomization, the low tidal volume protocol must be initiated within two hours (if not already being used). In the intervention arm, deep sedation followed by neuromuscular blockade must be initiated within four hours of randomization.

#### 4.5 INFORMED CONSENT

Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in the trial. No study procedures will be done prior to obtaining informed consent.

Permission to approach patients and/or LARs will be requested from the attending physicians. All patients meeting inclusion criteria will be entered on a screening log. If the patient is not enrolled, the screening log will include information explaining why enrollment did not occur (e.g., exclusion criteria, attending physician denial, patient refusal) and a minimum data set to the extent allowed (Appendix F).

#### 4.6 RANDOMIZATION

After obtaining a signed and dated informed consent from the subject or the subject's LAR, the subject will be randomized via the coordinating center web based randomization system. Each research coordinator will have a unique Personal Identification Number (PIN) to access the randomization system. Each subject will receive a computer-generated study ID number and study arm assignment to neuromuscular blockade or control. An emailed confirmation will follow to the study site. Randomization will be stratified by institution at study entry.

#### 4.7 MINORITIES AND WOMEN

Gender and racial patient subsets were considered by the NHLBI in selecting the PETAL Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate patient population contains representative proportions of minorities and women. Recruitment of minorities and women will be monitored by the PETAL Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

### 5 STUDY PROCEDURES

Trials should be conducted in a setting reflective of best practice that can be clearly described and reproduced in a clinical non-trial setting. We therefore (i) selected centers already providing high quality standardized ICU care, (ii) will document the use of protocols and order sets at each center, (iii) monitor the provision and results of key processes of care, and (iv) implement strict protocols (with training, monitoring, and feedback) for the use of neuromuscular blockade and mechanical ventilation. Almost all PETAL centers have existing protocols and order sets for routine sedation management, glucose control, septic shock resuscitation, deep venous thrombosis prophylaxis, and other aspects of background care.

## 5.1 EARLY NEUROMUSCULAR BLOCKADE GROUP

### 5.1.1 INITIATION AND DOSAGE

Study staff will ensure a Ramsay score of 5-6 (RASS of -4 to -5, or Riker of 1-2) is achieved and documented prior to initiation of neuromuscular blockade and that patients are receiving controlled modes of mechanical ventilation. We do not mandate sedative type or dose.

Initiation of neuromuscular blockade must begin within 4 hours of randomization. Patients randomized to the early neuromuscular blockade arm will receive a cisastracurium besylate bolus of 15 mg, followed by a continuous infusion of 37.5 mg/hour for 48 hours (Appendix J).

We chose this fixed, relatively high dosage for simplicity (train of four titration imperfect and with limited evidence base [24-26]) and to help ensure effective neuromuscular blockade (clinical observation and train of four monitoring can lead to under-dosing). This dosage is the same as used in the ACURASYS trial. We chose cisatracurium as its metabolism is independent of hepatic and renal function.

In the rare circumstance that neuromuscular blockage is deemed inadequate, (i) check the patient and the ventilator to confirm the correct reading, (ii) check the infusion rate and drug to confirm correct, (iii) rebolus, using the below recommendation and call the CCC for further direction as needed.

Recommendation: If the end-inspiratory plateau pressure remains greater than 32 cm of water for at least 10 minutes, it is recommended that the patient receive the administration of increasing doses of sedatives and decreasing tidal volume and positive end-expiratory pressure (if tolerated) before considering using open-labeled cisatracurium. If the treating physician still wants to administer a neuromuscular blocking agent, an open-label, rapid, intravenous injection of 20 mg of cisatracurium will be recommended for patients in the control or treatment arms of the study. If this rapid, intravenous injection results in a decrease of the end-inspiratory plateau pressure by less than 2 cm of water, a second injection of 20 mg of cisatracurium will be allowed. If after injection, the end-inspiratory plateau pressure does not decrease or decreases by less than 2 cm of water, cisatracurium boluses should not be administered again during the following 24-hour period.

We chose to not blind cisatracurium administration as patients under neuromuscular blockade will have easily identifiable clinical characteristics such as absence of any movement. Therefore, true blinding of the study physicians and research coordinators is unlikely to occur. PETAL investigators are familiar with the performance of unblinded studies including the recent EDEN trial.[3] As the primary outcome variable is an objective measure (mortality), the risk of systematic bias with an unblinded study design is low.

We will prepare and recommend safety plans to patients receiving neuromuscular blockade that include eye care, positioning, and pressure ulcer monitoring.

### 5.1.2 SEDATION

The sedation dosage required to achieve Ramsay of 5-6 (RASS of -4 to -5, or Riker of 1-2) prior to cisatracurium administration should be continued for the 48 hour neuromuscular blockade period. After neuromuscular blockade ceases, sedation should be as in the control arm. We do not mandate sedative type or dose.

### 5.1.3 STOPPING RULES FOR NEUROMUSCULAR BLOCKADE

#### During the 48 hour study intervention period

Neuromuscular blockade can be stopped if ventilator weaning criteria are met for PEEP/FiO<sub>2</sub> criteria of FiO<sub>2</sub> ≤ 0.40 and PEEP ≤ 8 cm (Appendix D), and maintained for at least 12 hours. If after the discontinuation of neuromuscular blockade, the oxygenation significantly worsens (≥ 2 rightward steps on PEEP/FiO<sub>2</sub> table required), neuromuscular blockade should be resumed. Neuromuscular blockade can also be stopped for investigator or clinician safety concerns. Stoppages for any other reasons will be recorded as protocol violations.

In the rare event that extubation and reintubation occurs during the 48 hour time window (e.g., unplanned extubation, rapid clinical improvement prompting early extubation), neuromuscular blockade should be resumed after reintubation.

#### After the 48 hour study intervention period

Treating clinicians will be informed when the 48h period ends and that the cisatracurium infusion will be stopped at that time as a study intervention, while continuing sedation. After the 48 hour study intervention period, decisions on further use of neuromuscular blockade, including type of and dosing of the agent, will be as per the treating clinicians.

### 5.1.4 CONFIRMATION OF NEUROMUSCULAR BLOCKADE

In addition to the bedside clinical nurses' routine monitoring of patients while on neuromuscular blockade infusion, research staff will assess these patients daily, and record set and actual ventilator rates, infusion rate and boluses.

## 5.2 CONTROL GROUP

Patients randomized to control will receive care as per their treating clinicians except for aspects of care outlined in section 5.3.

### 5.2.1 MINIMIZING NEUROMUSCULAR BLOCKADE

We will encourage sites to minimize neuromuscular blockade use in the control arm.

Our goal is to respect clinician autonomy and protect patient safety, while preserving separation of treatment between arms. We will encourage non-neuromuscular blockade interventions for refractory hypoxia such as recruitment maneuvers, proning without neuromuscular blockade, deeper sedation, and consider a trial of diuresis. The threat of higher use of these interventions



in the control arm is outweighed by the necessity of having a separation in neuromuscular blockade treatment between arms.

**Recommendation:** If the end-inspiratory plateau pressure remains greater than 32 cm of water for at least 10 minutes, it is recommended that the patient receive the administration of increasing doses of sedatives and decreasing tidal volume and positive end-expiratory pressure (if tolerated) before considering using open-labeled cisatracurium. If the treating physician still wants to administer a neuromuscular blocking agent, an open-label, rapid, intravenous injection of 20 mg of cisatracurium will be recommended for patients in the control or treatment arms of the study. If this rapid, intravenous injection results in a decrease of the end-inspiratory plateau pressure by less than 2 cm of water, a second injection of 20 mg of cisatracurium will be allowed. If after injection, the end-inspiratory plateau pressure does not decrease or decreases by less than 2 cm of water, cisatracurium should not be administered again during the following 24-hour period.

### 5.2.2 SEDATION

We provide sedation score targets; we do not mandate sedative type or dose.

#### For patients not on neuromuscular blockade

- TITRATE sedation as per clinician discretion
- RECOMMEND: Ramsay of 2-3 (RASS 0 to -1 or Riker 3 to 4) OR absence of respiratory distress, and/or daily sedation breaks if no contraindication
- DOCUMENT: reasons for sedation given for RASS < -1

#### For patients that receive neuromuscular blockade

Ramsay of 5-6 (RASS of -4 to -5, or Riker of 1-2) should be achieved prior to neuromuscular blockade and continued for the 48 hour infusion.

## 5.3 COMMON STRATEGIES FOR BOTH STUDY GROUPS

### 5.3.1 STUDY STARTUP PROCEDURES

In both groups, we will use the following standardized, step-wise, startup procedures to collect hemodynamic safety data (Section 6.3.1) in the first 6 hours following randomization. These procedures will allow comparison of hemodynamics during study startup between groups, and will avoid simultaneous PEEP and sedation titration, which would render interpretation of hypotensive episodes challenging. Close oversight of study initiation should be provided by an intensive care attending and/or designee.

1. Initiate low tidal volume ventilation within 2 hours, as per Section 5.3.3.).
2. Adjust sedation to target sedation score (if not already at target) – deep sedation in the early neuromuscular blockade group, recommendation of light sedation in control group.



3. If in the neuromuscular blockade arm, start cisatracurium within 4 hours of randomization, as per section 5.1.1.
4. Before increasing PEEP, a PETAL investigator or designee will determine hemodynamic appropriateness for PEEP increase using the following as guidelines: MAP > 55 or SBP > 80, no fluid bolus or vasopressor increase for greater than 15 minutes.
5. Peep will be gradually up-titrated as per Appendix D1.

### 5.3.2 PRONING

We will recommend sites wait at least 12 hours (as per PROSEVA[1]) before proning, and to avoid automatic use of neuromuscular blockade with proning.

Based on the results of our survey of PETAL investigators, we expect modest use of proning in either arm of this study. Overall, half of the investigators reported that proning was initiated in less than 40% of ARDS patients with a P/F < 150.

### 5.3.3 VENTILATOR PROCEDURES

We will protocolize low tidal volume ventilation, weaning, and a high PEEP strategy (Appendix D).

#### Low tidal volume ventilation

We will use a simplified version of the ARDS network 6 ml/kg PBW lung protective ventilation protocol except that controlled modes of ventilation will be required during the period of neuromuscular blockade. If not already being used, a low tidal volume protocol for mechanical ventilation must be initiated within two hours of randomization in all patients.

#### Weaning

Since the time a patient achieves unassisted ventilation affects some secondary endpoints, and because recent evidence-based consensus recommendations have identified a best practice for weaning, a weaning strategy will also be controlled by protocol rules in accordance with these evidence-based recommendations. This will assure similar weaning methods and provide potential benefit to both study groups. This weaning strategy is a simplified version of the protocolized weaning strategy used in prior ARDS Network studies (Appendix D).

#### PEEP

As a study procedure, all study patients will receive a high PEEP strategy based on previously deployed PEEP protocols [27-30]. The use of the high PEEP protocol will be required for up to 5 days after randomization. We selected to protocolize high PEEP in all patients for the following reasons:

1. To mitigate the possibility of differential PEEP use between arms.
2. A presumptive physiologic benefit of neuromuscular blockade is reduction of atelectrauma, barotrauma, volutrauma, and heterogeneity in alveolar expansion. A

higher PEEP strategy will limit atelectrauma and heterogeneity of alveolar expansion. It is also unknown if neuromuscular blockade adds additional protection over a higher PEEP strategy alone.

3. Trials should test novel interventions on a background of “best care”. Secondary analyses and opinion leaders suggest high PEEP strategies may be beneficial in those ARDS patients with higher acuity.[15]

If hypotension occurs with the use of a high PEEP protocol, the recommendation from the fluid management approach will be the administration of fluid boluses. (Appendix E)

We will allow deviation from the high PEEP strategy, for limited situations:

- If there is clinical concern that the use of high PEEP may be worsening oxygenation (e.g., oxygenation worsens with PEEP increases) at a  $FiO_2 \geq 0.5$  for more than 2 hours, clinicians may trial lower PEEP.
- If oxygenation worsens or is unchanged at the lower level of PEEP, the PEEP should be raised back to the previous level.
- If oxygenation improves, the clinicians may choose to leave the PEEP at the lower level. Subsequently the clinician should decrease the  $FiO_2$  as tolerated until a listed combination on the PEEP/ $FiO_2$  chart is reached, and then continue to follow the PEEP/ $FiO_2$  protocol.
- If hypotension, high plateau pressure ( $> 30$  cm H<sub>2</sub>O), and/or severe acidemia ( $pH < 7.15$ ) are present despite further tidal volume reduction, fluid boluses, and/or respiratory rate increase (Section 5.3.3. and Appendix D1), lower PEEP may be used. With the ROSE PEEP table (Appendix D1) as the starting point, reduce PEEP 2 cm H<sub>2</sub>O every 5-15 minutes, until the physiologic parameters of concern have improved, as per the treating clinician and/or responsible investigator (e.g., reduce PEEP to the level that lowers plateau pressure to 30 cm H<sub>2</sub>O). Later, try to return PEEP to a level consistent with the ROSE PEEP table, at least daily through study day 5.

Lower PEEP may also be used if a study participant develops a pneumothorax, or is deemed at high risk for barotrauma (e.g., known multiple pulmonary cysts or bullae).

#### 5.3.4 ON-STUDY FLUID MANAGEMENT

Fluid management during shock will be unrestricted. However, in patients not in shock, a conservative fluid approach will be recommended for all patients enrolled in the study. This conservative fluid management approach will represent a simplification of the algorithm utilized in the ARDS Network FACTT study (see Appendix E)[31].

#### 5.3.5 GLUCOSE CONTROL

Hyperglycemia has been associated with neuromuscular dysfunction. Each site will use their own standard management, including institution-specific insulin drip protocols, to maintain blood

sugars with a target upper blood glucose level  $\leq$  180 mg/dL. This range avoids marked hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target.

### 5.3.6 RESCUE PROCEDURES

If PaO<sub>2</sub>  $\geq$  55 mmHg or SpO<sub>2</sub>  $\geq$  88% with FIO<sub>2</sub> of 1.0 cannot be maintained, clinicians may employ alternate therapies (rescue procedures). Rescue procedures will be chosen according to the practice at the clinical site, and may include repeated recruitment maneuvers, prone positioning, inhaled nitric oxide, inhaled epoprostenol sodium, high frequency ventilation, or ECMO. The participants will continue to be followed and included in the analysis on an intention-to-treat basis. The use of rescue procedures will constitute a secondary outcome.

## 6 DATA VARIABLES AND SPECIMENS

### 6.1 BACKGROUND ASSESSMENTS

1. Demographic and Admission Data (including age, sex, race)
2. Pertinent Medical History and Physical Examination (including Charlson co-morbidity score)
3. Height; gender; measured Body Weight (mBW); calculated predicted body weight (PBW); body mass index (BMI)
4. Time on ventilator prior to enrollment
5. Type and location of endotracheal intubation
  - Pre-hospital, ED, ward, ICU, operation room, referring hospital
6. Location when inclusion criteria met
  - Pre-hospital, ED, ward, ICU, operation room, referring hospital
7. Type and location of ICU Admission
  - Medical
  - Surgical scheduled
  - Surgical unscheduled
  - Trauma
8. Risk factors for ARDS (sepsis, aspiration, trauma, pneumonia, other)
9. Ever smoker (>100 cigarettes in lifetime)?
  - If Yes, current smoker?
  - If ever smoker, estimate pack years [Pack years = (# packs per day) x (number of years smoked)]
  - If former smoker, when quit?

10. Survey of alcohol history (see Appendix I)

11. Basic assessment of prior functioning

## 6.2 BASELINE ASSESSMENTS

The following information will be recorded during the 24-hour interval preceding randomization. If more than one value is available for this 24-hour period, the value closest to the time of randomization will be recorded. If no values are available from the 24 hours prior to randomization, then values will be measured post randomization but prior to initiation of cisatracurium (intervention arm) and within 4 hours (control arm). All values will be derived from clinically available data.

1. History and physical examination

Vital signs: heart rate (beats / min), systemic systolic and diastolic BP (mmHg), body temperature (°C) (APACHE)

2. Ventilator mode, set rate, actual rate, minute ventilation, tidal volume, FiO<sub>2</sub>, PEEP, I:E ratio, plateau, peak, and mean airway pressures

3. Administration of the following medications (name)

a) Intravenous sedatives

b) Intravenous opioids

c) Intravenous or enteral Corticosteroids (>= 20 methylprednisolone equivalents)

4. Presumed site of infection, if sepsis is the etiology of ARDS

5. APACHE III score, including the acute physiology components and laboratory values

6. APACHE III demographics plus history of: hypertension, prior myocardial infarction, congestive heart failure, peripheral vascular disease, prior stroke with sequelae, dementia, chronic pulmonary disease, arthritis, peptic ulcer disease

7. SOFA Score: Cardiovascular, renal, respiratory, hepatic, and hematology organ function will be assessed using the SOFA methodology as described in Appendix K.

8. Pneumothorax at time of randomization (Y/N)

## 6.3 ASSESSMENTS DURING STUDY

### 6.3.1 HEMODYNAMIC MONITORING DURING STUDY STARTUP

For the first 4 hours after randomization, we will record the time that target PEEP/FiO<sub>2</sub> and sedation score are achieved, the time of both the cisatracurium bolus and infusion, as well as the time of any fluid bolus or change in vasopressor use.

Together with SOFA and adverse event data at 48 hours, this hemodynamic monitoring data will be used to report study process safety data to the DSMB.

### 6.3.2 REFERENCE MEASUREMENTS

The following data will provide the basis for assessing protocol compliance and safety as well as between-group differences in several efficacy variables. Data for each of the variables will be recorded on the days shown in the Time-Events schedule (Appendix B) or until death, or discharge from the intensive care unit. Values will be derived from clinically available data.

1. NMB Dosing
  - a) Intervention Arm
    - i. Time and dose of loading dose
    - ii. Time of initiation of cisatracurium continuous infusion
    - iii. Reason and duration of infusion hold during first 48 hours
    - iv. Total dose of cisatracurium infusion during first 96 hours
    - v. Name and total dose of other NMB during first 96 hours
    - vi. Addition NMB administered after 96 hours (yes/no)
  - b) Control Arm
    - i. Name and total dose of any NMB used in the first 96 hours after randomization
    - ii. Addition NMB administered after 96 hours (yes/no)

#### Reference Measurements (Daily)

The following parameters will be measured and recorded between 4:00 and 10:00 A.M. using the values closest to 8:00 A.M. on the days specified in the Time-Events schedule. The following conditions will be ensured prior to measurements: no endobronchial suctioning for 10 minutes; no invasive procedures or ventilator changes for 30 minutes. All vascular pressures will be zero-referenced to the mid-axillary line.

1. If receiving positive pressure ventilation: Ventilator mode, set rate, actual rate, minute ventilation, tidal volume, FiO<sub>2</sub>, PEEP, I:E ratio, plateau, peak, mean airway pressures, set peak flow, and set inspiratory time
2. PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, and SpO<sub>2</sub>

Values for the following variables will be recorded for the dates shown in the Time-Events Schedule. If the measurements are not obtained during the 6-hour reference interval (4:00 to 10:00 A.M.), then the value obtained closest in time to the reference interval on the respective date will be recorded. If more than one value is obtained during the reference interval, then the value obtained closest to 8:00 A.M. will be recorded.

3. Rescue procedures used
  - a) Proning
  - b) Inhaled nitric oxide
  - c) Epoprostenol sodium
  - d) High frequency ventilation

- e) ECMO
- 4. Serum electrolytes and glucose
- 5. Administration of the following medication infusions:
  - a) Intravenous sedatives
  - b) Intravenous opioids
  - c) Enteral or intravenous corticosteroids ( $\geq$  20 methylprednisolone equivalents)
- 6. Sedation score: If RASS  $<$  -1 (or Riker  $<$  3, Ramsay  $>$  3), and sedation given, list reason given
- 7. Was a sedation interruption performed? Y/N
- 8. Modified SOFA
- 9. Fluid intake and output/CVP if available
- 10. ICU Mobility Scale: Score 0-10 (see Appendix M)

#### Other Reference Measurements

1. Manual muscle strength testing (MMT) screen and assessment on day 7, 14, 21 28 or until hospital discharge.
2. Assessment of gross motor movement on study day 3.
3. Paralysis recall assessment, in both study arms, one time during study hospitalization, using a modified Brice questionnaire [22, 23].

To facilitate the ability of the patient to interact appropriately with the above measures, sedative agents will be titrated according to the institution's sedation protocol. The MMT and the Modified Brice questionnaire will be conducted in patients who meet the awakening and comprehension criteria. Awakening and comprehension will be determined based upon the response of the patient to five commands ("open/close your eyes," "look at me," "open your mouth and stick out your tongue," "nod your head," and "raise your eyebrows when I have counted to five"). If the patient can respond appropriately to all five of these orders, the patient will be considered awake and able to comprehend and the above measures will be attempted to be obtained.

Additionally, prior to conducting the MMT the patient will be assessed for injuries or medical devices that would preclude the MMT assessment and for any safety barriers to strength training such as unstable shock, profound hypoxemia, unstable spine or airway, nonresponsive to verbal command (RASS -4 or -5). The Manual Muscle strength testing uses the MRC (Medical Research Council) score evaluates muscle strength with very good interobserver agreement, and was used in the ACURASYS trial [2, 32]. Introduced in 1970, the Brice questionnaire is a reliable and efficient method of detecting recall after sedation or general

anesthesia. This questionnaire avoids falsely identifying pre-sedation memories and experiences [22, 23].

### 6.3.3 SPECIMEN COLLECTION

Urine and plasma will be collected within 2 hours of randomization, at 24 hours (24 hours after randomization for control arm and 24 hours after starting cisatracurium for active patients), and at 48 hours (48 hours after randomization for control arm and 48 hours after starting cisatracurium for active patients), frozen, and stored for IL-6 measurement (at 2 hours and 48 hours) and at a biorepository for future research. Total blood volume for these draws is approximately 15 ml/day, for a total of approximately 45 ml. When consent obtained, we will also obtain an additional 20 ml of whole blood for future RNA and DNA studies. Study samples will be sent to a central repository to be stored in accordance with good laboratory practices. Samples will be identified by a coded number during shipment and storage in the central repository.

## 6.4 ASSESSMENTS AFTER HOSPITALIZATION

These domains and instruments to assess after hospitalization status were selected by the PETAL Neuromuscular Blockade Protocol Committee in conjunction with the PETAL Long-Term Outcomes Committee.

We will assess seven measures after hospitalization:

1. Disability: using Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities of Daily Living Scale (IADL) plus two additional Nagi items
2. Health-Related Quality of Life (including utilities): EuroQol (EQ-5D-5L)
3. Self-rated health: 1 standard item
4. Pain-interference: 1 standard item
5. Post-traumatic Stress-like Symptoms: Post-Traumatic Stress Symptoms (PTSS-14)
6. Cognitive function: Montreal Cognitive Assessment (MoCA-Blind) or, via proxy, the Alzheimer's Disease 8 (AD8)
7. Subsequent return to work, hospital and ED use, and location of residence

These measures will be collected through telephone interviews with patients or their LARs (Appendix G). Informed consent process will include text to facilitate future ancillary long term follow up studies and data collection. All will be obtained at 3, 6, and 12 months except for post-traumatic stress-like symptoms, which will only be obtained at 6 and 12 months. All will be obtained in English or Spanish, from the patient wherever possible. Most will be obtained from proxies when necessary, except as noted for self-rated health, pain interference and post-traumatic stress-like symptoms.

The assessments after follow-up will provide information about post-discharge deaths faster than is available from other sources, although the National Death Index will be used to verify date of death whenever possible (see below).

The Katz ADL is associated with multiple health outcomes among community-dwelling elders[36], and valid among nursing home residents[37]. The Lawton IADL is probably the most widely used self-report or informant-report IADL instrument. These assess a range of common functional activities, from walking and toileting to managing money and cooking meals. We will use the precise wordings from the NIA-funded Health and Retirement Study for which US (and international) norms are available. These scales have been specifically shown to perform well when assessed by proxies for ICU survivors. [40] We will remove the 3 ADL/IADL items that are duplicative of the EQ-5D questions (using the EQ-5D instead), and will add two items from the Nagi scale [41]as implemented in the HRS.

The EQ-5D[44] has US utilities[45] and is recommended for measurement of health-related quality of life among critical illness survivors.[46] It is quick and feasible in individuals with inattention and fatigue[47]. We will use the EQ-5D-5L version currently used by both the ANZIC RC in Australia and New Zealand and ICNARC in the United Kingdom. We will not use the Visual Analog Scale as these follow-ups will be phone administered and the VAS is not necessary for health economic analysis.

Self-rated health and pain-interference are two common single-item scales that are widely used. We will use the wordings from the SF-12. Because of the highly subjective nature of these domains, these will only be assessed by self-respondents.

The Montreal Cognitive Assessment (MoCA) appears superior to the mini mental status examination and its derivatives for neurocognition assessment in critical illness survivors [48-51], and allows rapid, reliable determination of cognitive impairment [52] in various clinical syndromes.[51, 53-55] The MOCA-Blind version is developed for phone administration. Among community-dwelling older individuals, MoCA scores were lower (more impairment) among patients with elevated levels of inflammatory cytokines.<sup>56</sup> When patients are not able to respond themselves, the validated AD-8 [56]will be used to assess cognitive function by proxy.

We will capture return to work status using the Improving Care of ALI Patients (ICAP) study questionnaire.[59] The Improving Care of Acute Lung Injury Patients employment instrument (ICAP-12) was designed to determine pre- and post-morbid employment status in a multi-center observational study of ARDS survivors[59, 60] and used externally in the NHLBI ARDS Network's ARDS Long-term Outcomes Study (ALTOS) cohorts[61, 62]. We will also ask about recent hospital and Emergency Department use, and whether the patient is residing in a nursing home, at home, or elsewhere.

We will also verify duration of survival for patients lost to follow-up or noted to have died using the Centers for Disease Control and Prevention's National Death Index (NDI) and other federal databases. We will use each patient's social security number (SSN) for an exact NDI match.

We will also collect the patient's Medicare identification number for patients in Medicare to allow assessment of post-discharge health care utilization without any respondent burden back on the



patient. We will collect contact information for the patient and alternative contact information on up to 2 individuals.

#### 6.4.1 TOKENS OF APPRECIATION

Each participant will receive a \$10 token of appreciation after each 3-, 6- or 12-month interview, in the form of a gift card to a national chain of stores. In addition, each participant will be mailed a reminder postcard prior to the 3- and 12-month interviews. Each participant will receive a \$5 token of appreciation for returning the postcard with updated contact information.

Because of the importance of having an excellent response rate, we set aside some funds to avert refusals, specifically an increase from the original \$10 to \$20. This increased amount is based on prior studies[63] as well as conversations with personnel at the University of Michigan Health and Retirement Study (HRS), launched in 1992 and funded by the National Institute on Aging and the Social Security Administration. Their procedures have been well vetted, and are still in use in the 2014 fielding of the HRS. Research has shown that refusal conversions increase cooperation rates significantly for all incentive levels.

Interviewers will be trained on how to avert refusals during the initial participant contact by addressing any concerns that the respondent may have. After gauging participation rates over the course of the study, study staff may find it necessary to offer an incentive of \$20 during the initial contact. This will take place if the participant is hesitant during the initial contact in hopes that participation rates will increase. In the event that a respondent does not wish to participate in subsequent surveys after having completed their first survey, we will then offer an additional incentive of \$10 for a total of \$20. Once a participant is offered the higher incentive, they will receive that amount for each of the remainder of surveys that they complete.

In no case will more than \$20 be offered to avoid any potential for coercion, although examples of much higher incentives certainly exist in the literature. For example, Turnball et al recently published a study with incentives up to \$50, and Robinson et al's recent systematic review noted studies with incentives up to \$160.[64][65]

## 7 STATISTICAL CONSIDERATIONS

***NOTE: please see the detailed statistical analysis plan (SAP) that is a separate document***

### Statistical Methods

The primary outcome is intention to treat 90 day all cause in-hospital mortality, where in-hospital includes study hospital and LTAC. Subjects who are discharged home (defined as residence prior to admission) prior to day 90 will be assumed to be alive and censored at day 91.

Sample size is based on a comparison of binomial proportions with an overall two-sided alpha level of 0.05 and power of 0.90. With 35% mortality rate in controls and 27% rate in NMB the maximum required total samples size is 1408 subjects.

The presumed 35% mortality rate in the control group is based on several recently published clinical trials.[2, 27, 66] In the original Papazian study, mortality prior to discharge home before day 90 was 40.7% in the control group. Similarly in the multi-center clinical trial of high-frequency oscillation for ARDS (OSCILLATE), the in-hospital mortality rate was 35% for the control group. In this study, control subjects received a high PEEP strategy. Finally in the ARDS subjects used to validate the new Berlin definition of ARDS, the mortality in those patients with moderate ARDS, defined as a P/F ratio between 100-200, was 32%. Though recent ARDSNet trials reported lower mortality in their primary outcome (EDEN ~23%, SAILS ~27%), these studies enrolled less severely ill patients (P/F < 300) and used a shorter duration mortality outcome (60 days).

This trial will stop for superiority of either active or control and is designed with symmetric group sequential flexible stopping boundaries as described in Lan and DeMets (Reference Lan, K. K. G. and DeMets, D. L. (1983), Discrete sequential boundaries for clinical trials. Biometrika 70, 659-663.) They specify that that at each look at the data the cumulative probability of exceeding the upper or lower boundary on that look or previous looks will be  $0.025 t^{-4}$  under the null hypothesis of no difference between the treatments, where  $t$  is the information time, defined as the ratio of the effective sample size at the time of the look to the eventual sample size. We plan to have two interim and one final look that will be approximately evenly spaced. However, the scheduling of the DSMB meetings may alter this schedule.

Table 1 presents an illustration of the stopping boundaries at each of the three looks if they are equally spaced. The table presents stopping boundaries as both a required observed mortality difference and one-sided p-value. The columns under 'Probability of Stopping' present the probability of stopping at each stage under the null and alternative (NMB reduces mortality from 35% to 27%) hypotheses respectively.

**Table 1**

Number of Subjects	Active Superior		Control Superior		Probability of Stopping	
	Observed Mortality Difference Active-Control	P-value*	Observed Mortality Difference Active-Control	P-value*	Under the Null Hypothesis	Under the Alternative Hypothesis
470	-0.146	0.00031	0.146	0.99969	0.001	0.061
938	-0.078	0.00479	0.078	0.99521	0.010	0.528
1408	-0.049	0.02361	0.049	0.97639	0.050	0.900

\* = These are one sided p values for the upper and lower boundaries.

For example, the second stage analyses will take place when approximately 938 patients have been enrolled and the study would be stopped if the 90 day absolute mortality difference

exceeds 0.078. This corresponds to a one-sided p-value of 0.00479. If the alternative hypothesis is true then the probability of stopping at this stage is 0.528.

### Sample size and power under different mortality assumptions

The table below shows the effect of changes in the power of the study as a function of the mortality rate on the treatment with the higher mortality. We calculated the power under two assumptions. The first is that the absolute difference in mortality rates was 8% and the second was that the relative difference was 23% which is approximately 8% of the anticipated mortality of 35%. The second row of the table shows the current assumptions. Whether you fix the absolute or the relative difference, the power is above 80% as long as the null mortality rate is over 25%. The power goes down to 73% if the mortality rate is 20% which is below the mortality rate observed in a ARDSNet studies except the placebo arm of ALTA [67]. Unlike prior ARDSNet studies including ALTA, ROSE seeks to enroll patients at the more severe end of the ARDS severity spectrum.

Both methods of adaption have the problem that the direction of the sample size adjustment depends on whether you consider the absolute difference or the relative difference to be the important parameter. This choice is somewhat arbitrary. From the point of view of the utility of the treatment the absolute difference is important because it is directly related to the number needed to treat. That is,  $NNT=1/D$ . On the other hand, if the sample is diluted by a proportion of patients who are not at risk of death then the relative decrease in mortality would stay the same while the absolute difference would decrease. Adaption based on the overall mortality rate has the additional problem that you don't know whether the reduction is due to the null mortality rate or the alternative mortality rate. Adaption based on both observed mortality rates or the maximum mortality rate might require a p-value adjustment which would reduce the power of the study. If both mortality rates in this study were less than 20% then the DSMB should consider whether we had the right population to study for a treatment like induced neuromuscular blockade.

<b>Null Mortality</b>	<b>Power at 8% Absolute Decrease in Mortality</b>	<b>Power at ~23% Relative Decrease in Mortality</b>
<b>45%</b>	86%	97%
<b>35% *</b>	90%	90%
<b>30%</b>	93%	85%
<b>25%</b>	96%	79%
<b>20%</b>	98%	73%

\*Assumption used in the ROSE Protocol

## **8 DATA COLLECTION AND SITE MONITORING**

**Data Collection:** The research coordinators will collect data and record it either on paper data sheets or in a custom-designed computer database. Data will be transferred to the Clinical

Coordinating Center on a prescribed basis through a web-based data collection program.

Once daily, coordinators will enter data regarding ventilator and fluid management that can be analyzed for consistency with the supportive care protocols. Examples of data that will be recorded are: tidal volume, plateau pressure, PEEP, FiO<sub>2</sub>, fluid balance, blood pressure, use of vasopressors, infusions and bolus doses of diuretics. We will use the algorithms developed by ARDSNet investigators to assess data in PETAL subjects for consistency with protocol rules. For example, if at 22:50 on November 20, 2015 a tidal volume is within the range of 5.5-6.5 ml/kg predicted body weight and plateau pressure is  $\leq$  30 cm H<sub>2</sub>O, then tidal volume for that date and time will be deemed "on-target." If the tidal volume is  $>$  6.5 ml/kg PBW and pH is  $>$  7.15, then tidal volume for that date and time will be deemed "off-target." We will also assess FiO<sub>2</sub>, PEEP, plateau pressure, and fluid and diuretic management for consistency with protocol rules.

The Clinical Coordinating Center will calculate a "%-on-target" value for each center for each of the monitored variables ( $\#$  of dates on-target for a specific variable/ $\#$  of opportunities to be on-target for that specific variable). Principal Investigators and Co-Investigators at each Center will receive monthly reports of (1) % on-target for each of the specific variables in the most recent month, (2) % on-target for each of the variables since the beginning of a trial, and (3) a list of dates/times from the past month, the specific data that were entered for those dates/times, and determinations of on- or off-target.

Investigators will use these reports to identify aspects of protocol management that can be improved at their Centers. The on-target performances of all centers will also be included, allowing investigators at each center to know how their center is performing relative to other PETAL Centers. On-target performances will be discussed during regular meetings of the Steering Committee. The Institutional Support Committee will provide advice and assistance to Centers that are not performing up to expectations. On-target data for the specific variables according to study group will be included in the primary reports of the results of the individual trials.

**Site Monitoring:** Data quality will be reviewed remotely using front end range and logic checks at the time of data entry and back-end monitoring of data using SAS reports. Additionally, Clinical Center on site visits will be performed on a regular basis by the Clinical Coordinating Center to ensure that all regulatory requirements are being met and to monitor data quality. Patient records and case report forms will be examined on a spot check basis to evaluate the accuracy of the data entered into the database and monitor for protocol compliance.

## 9 RISK ASSESSMENT

This study involves randomization to early neuromuscular blockade, or a control arm with no routine neuromuscular blockade, for the first 48 hours. Compared to not being part of the study,

patients may have a higher, lower, or the same risk of death. In addition, all patients will receive a high PEEP strategy with specific exceptions detailed in Section 5.3.2. Neuromuscular blockade and high PEEP carry potential risks and potential offsetting benefits.

## 9.1 RISKS OF NEUROMUSCULAR BLOCKADE

Potential risks of cisatracurium are bradycardia (developed in 1 of 340 patients in ACURASYS; 0.4% incidence per FDA package insert), hypersensitivity reaction (~0.2%) and ICU acquired weakness. The true risk and relationship between neuromuscular blockade and paresis is unclear and have been recently challenged<sup>12</sup>. An increased risk for the development of ICU acquired weakness was not observed in patients randomized to neuromuscular blockade in the ACURASYS trial. The accompanying deep sedation that is always given with neuromuscular blockade may result in hypotension requiring vasopressor support and/or a longer total period of sedation. The neuromuscular blockade and the accompanying deep sedation may decrease risk of pain or discomfort, but may also render detection of pain or discomfort more difficult.

## 9.2 RISKS OF HIGH PEEP

Historical risks of high levels of PEEP include pneumothorax and hypotension. However, in recent large randomized trials, no significant differences in pneumothorax or barotrauma, nor vasopressor use or circulatory and other organ failures were noted.[27-30]

## 9.3 RISKS OF BLOOD DRAWS

All patients will have blood drawn for research purposes. As almost all patients will have invasive lines placed for clinical purposes, risk of blood draws are essentially nil, as blood can be easily obtained from these lines. In the rare case an invasive line is not present, the risks of drawing blood are uncommon and include bleeding and bruising. Commonly, drawing blood is painful, and rarely, drawing blood can lead to infections at the site of the blood draw.

## 9.4 RISK OF DEATH

It is possible that one treatment arm may lead to more deaths; mortality will be monitored during the course of the study.

## 9.5 MINIMIZATION OF RISKS

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. There are several elements of study design inherent in the present protocol that meet this human subject protection requirement. Neuromuscular blockade is clinically used in ARDS; this trial studies early use. We limit study blockade to 48 hours; ICU acquired weakness has been most associated with long, uninterrupted infusion. Exclusion criteria prohibit participation of patients who might be at increased risk of prolonged paresis or harm from cisatracurium (e.g., myasthenia gravis, previous hypersensitivity reaction). We will assess for ICU acquired weakness in all study participants. The protocol entrains deep sedation prior to starting neuromuscular blockade to prevent paralysis recall. Neuromuscular blockade will be stopped for sustained severe

bradycardia. We will use a high PEEP protocol based on those used in multiple large clinical trials, that were shown safe, feasible, and of potential clinical benefit for the intended population or moderate to severe ARDS. The DSMB will be reviewing data as outlined above and will examine not only efficacy but safety (inclusive of mortality) and will reserve the right to halt the study at any time.

## 9.6 POTENTIAL BENEFITS

Study subjects may or may not receive any direct benefits from their participation in this study. High PEEP has been shown to improve oxygenation in ARDS, to be safe in multiple large trials, and of potential benefit in moderate-severe ARDS. Early neuromuscular blockade may result in lower mortality.

## 9.7 RISKS IN RELATION TO ANTICIPATED BENEFITS

Federal regulations at 45 CFR 46.111 (a)(2) require that “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits.

**Procedures** – blood draws. The risks associated with these common clinical practices are small, however the knowledge gained in furthering our understanding of the pathophysiology and potentially leading to better and targeted therapy may be substantial.

**PTSS-14 Survey:** There is a potential risk for identifying underlying mental health issues such as PTSD in the PTSS-14 survey. For subjects that are identified as having symptoms of PTSD, the research assistant will provide them information about national resources for additional mental health services. **Treatments** – High PEEP and neuromuscular blockade are clinically used in clinical practice. There is potential for benefit to society and individual patients should neuromuscular blockade prove to be of benefit. Should neuromuscular blockade, again consistent with clinical practices, prove to be harmful, the benefit will be in avoiding such therapies for future patients with ARDS.

## 10 HUMAN SUBJECTS

Each study participant or a LAR must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study. PETAL will use a central IRB.

### 10.1 SELECTION OF SUBJECTS

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The EDs, ICUs, and other acute care areas of PETAL sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests or procedures will be performed as part of the screening process. If any subjects meet criteria for



study enrollment, then the attending physician will be asked for permission to approach the patient or his/her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

## 10.2 JUSTIFICATION OF INCLUDING VULNERABLE SUBJECTS

The present research aims to investigate the safety and efficacy of a type of treatment for patients with ARDS. Due to the nature of ARDS and its risk factors (e.g., sepsis, trauma), the vast majority of these patients will have impaired decision-making capabilities. This study cannot be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

## 10.3 INFORMED CONSENT

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each prospective subject or the subject's LAR. We anticipate almost all consents will be from the subject's LAR, and thus the remainder of this section will focus on LARs. The one obtaining consent is responsible for ensuring that the LAR understands the risks and benefits of participating in the study, and answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to permit the subject's continued participation in the trial. The consentor will make every effort to minimize coercion. All study participants or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the patient is entered into the study, and to document that the LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each LAR. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including administration of study agent.

## 10.4 CONTINUING CONSENT

Subjects for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital, will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent will be obtained.

## 10.5 WITHDRAWAL OF CONSENT

Patients may withdraw or be withdrawn (by the LAR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn. If a patient or LAR requests termination of the trial drug during the treatment period, the drug will be stopped but the patient will continue to be

followed up as part of the trial. If a patient or LAR withdraws consent during trial treatment, the trial drug will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or LAR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

## 10.6 IDENTIFICATION OF LEGALLY AUTHORIZED REPRESENTATIVES

Many of the patients approached for participation in this research protocol will invariably have limitations of decision-making abilities due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's legally authorized representative (LAR).

Regarding proxy consent, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research...unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a legally authorized representative (LAR) as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for subject participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the PETAL central IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee (NBAC)), an investigator should accept a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place [68]. Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study [69].

## 10.7 JUSTIFICATION OF SURROGATE CONSENT

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that person with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and research ethics commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting [70]. Several U.S. task



forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." [71]. Finally, NBAC stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that "the potential subject's LAR gives permission..." [68]

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is **similar** to that available in the clinical setting, with the exception of the additional blood draws.

## 10.8 ADDITIONAL SAFEGUARDS FOR VULNERABLE SUBJECTS

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45CFR46.111 (b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) assessment of the potential subject's capacity to provide informed consent, b) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; c) augmented consent processes. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

## 10.9 CONFIDENTIALITY

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. The coded number will be generated by a computer, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office. Study information will not be released without the written permission of the patient, except as necessary for monitoring by the National Heart, Lung, and Blood Institute, and the PETAL Clinical Coordinating Center.

# 11 ADVERSE EVENTS

## 11.1 SAFETY MONITORING

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will determine daily if any adverse events occur during the period from enrollment through **study day 7** (five days after infusion of study drug) or ICU discharge, whichever occurs first.

The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events
- Nonserious adverse events that are considered by the investigator to be related to study drug or study procedures or of uncertain relationship (Appendix C2)
- Adverse events that lead to permanent discontinuation of the study drug infusion
- Hypersensitivity reactions to cisatracurium, severe prolonged bradycardia (heart rate < 50 for > 30 minutes), and paralysis recall
- Hypotension or pneumothorax, considered by the investigator to be related to high PEEP, or of uncertain relationship.

A clinical trial adverse event is any untoward medical event associated with the use of a drug or study procedure in humans, whether or not it is considered related to a drug or study procedure.

After randomization, adverse events related to protocol procedures or occurring after the patient receives the first dose of study drug must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the CCC their assessment of the potential relatedness of each adverse event to protocol procedure or study drug via electronic data entry. Investigators will assess if there is a reasonable possibility that the study drug or procedure caused the event, based on the criteria outlined in Appendix C2. Investigators will also consider if the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

## 11.2 SERIOUS ADVERSE EVENTS

Serious adverse event collection begins after the patient or surrogate has signed informed consent and has received study drug or undergone study procedures. If a patient experiences a serious adverse event after consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the CCC of any **serious and study drug or study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix C for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs)

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Deaths

- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or rehospitalization

As per <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Persistent or significant disability/incapacity

As per <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

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

Serious adverse events will be collected during the first **7 study days** or until ICU discharge, whichever occurs first, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

## 12 APPENDICES

### A1 S/F RATIO INCLUSION CRITERIA

Table 2 displays an equivalence table that determines the estimated P/F ratio from the FiO<sub>2</sub> and SpO<sub>2</sub>. This data was generated by investigators at the University of Utah, on a cohort of critically ill patients with pneumonia.[72-78].

Table 2: Imputed PaO<sub>2</sub>/FiO<sub>2</sub> for combination of SpO<sub>2</sub> (rows) and FiO<sub>2</sub> (columns)

SPO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

For altitude adjustment, we would recommend the practice from ARDS Network studies of multiplying the qualification threshold P/F by the ratio of average ambient to sea level barometric pressure (for Utah, it is  $0.86 \times 150 = 129$ ; for Denver it is  $0.84 \times 150 = 126$ ).

Additional requirements for the use of the S/F ratio include:

1. SpO<sub>2</sub> between 80-96%
2. SpO<sub>2</sub> should be measured at least 10 minutes after any change in FiO<sub>2</sub>.
3. PEEP  $\geq$  8 cm H<sub>2</sub>O
4. An adequate pulse oximeter waveform tracing

## A2 EXCLUSION DEFINITIONS

### Child-Pugh Score [79]

Premorbid values within 1 year of enrollment should be used.

<u>Points</u>	<u>Class</u>
5-6	A
7-9	B
≥ 10	C

Measurement	Numerical Score for Increasing Abnormality		
	1	2	3
Ascites	None	Present	Tense
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/L)	> 35	28-35	< 28
Prothrombin time (sec. prolonged)	1-4	4-10	> 10

NOTE: If using INR instead of Prothrombin time for Child-Pugh calculation, points for INR are as follows:

<1.7 = 1point

1.7-2.3 = 2points

>2.3 = 3points

### Neuromuscular Disease That May Potentiate Neuromuscular Blockade or Impair Spontaneous Ventilation

1. Amyotrophic lateral sclerosis
2. Guillain-Barré Syndrome
3. Myasthenia gravis
4. Upper spinal cord injury at level C5 or above

## B TIME-EVENTS SCHEDULE

Measurement/Event	Day 0	1	2	3	4	5	6	7	14	21	28	90
Demographics, History and Physical	X											
Etiology of ARDS	X											
APACHE III	X											
HCG (females)	X											
Alcohol Use/Smoking History	X											
CXR (number of quadrants)	X											
Study NMB Administration	X	X	X									
Baseline LTO	X											
Non-protocol NMB administration	X	X	X	X	X							
Level of Sedation	X	X	X	X	X	X	X	X				
Sedation Interruption (y/n)	X	X	X	X	X	X	X	X				
Gross motor assessment				X								
ICU Mobility Scale		X	X	X	X	X	X	X	X	X	X	
Ventilator Parameters#†	X	X	X	X	X			X				
Arterial Blood Gases	A	A	A	A	A			A				
K+, HCO <sub>3</sub> , glucose	A	A	A	A	A			A				
Pneumothorax (y/n)*	X										X	
Use of rescue procedures (y/n)*											X	
Fluids (intake/output)	X	X	X	X	X	X	X	X				
Central Venous Pressure	A	A	A	A	A	A	A	A				
On-study meds: sedative, opioid, corticosteroid administration (y/n)	X	X	X	X	X			X				
SOFA Score (modified) <sup>B</sup>	X	X	X	X	X	X	X	X	X	X	X	
Manual Muscle Testing (with screening)								X	X	X	X	
Paralysis recall assessment**											X	
Plasma Collection	X	X	X									
Urine Collection	X	X	X									
Whole Blood collection for DNA/RNA	X		X									
Vital Status§											X	X

X=Required

A=When available

†= Data gathered at times indicated or until 48 hours UAB, whichever occurs first

\*\*=Collected once during study hospitalization

<sup>B</sup>=Records clinically available creatinine, platelets, bilirubin, SBP and vasopressor use

~=Data gathered on days 0-28 or until d/c from study hospital

#=Measure during reference period (0600-1000); other values may be obtained closest to 0800 on the specified calendar date

§=Also measure at 6 and 12 months as part of Long Term Outcome.

\*= Assessed for days 1-28 once on day 28 or discharge

## C ADVERSE EVENT REPORTING AND UNANTICIPATED PROBLEMS

As noted in section 11.2, investigators will report all adverse events that are serious and study drug or study procedure related to the CCC within 24 hours. The CCC will then notify the NHLBI and cIRB.

The Medical Monitor at the CCC will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study drug or procedure, as outlined in 21 CFR 312.32(a)(1)I, and below (Appendix C2). The Medical Monitor will also determine if the event is unexpected. An adverse is considered “unexpected” if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). For this study, the cisatracurium (Nimbex®) package insert and the ACURASYS Study<sup>2</sup> serve as the investigator brochure. If a determination is made that a serious adverse event has a reasonable possibility of having been caused by the drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The CCC will report all unexpected and study related deaths, SAEs, and SUSARs to the DSMB, NHLBI, and cIRB within 7 days after receipt of the report from a clinical site. A written report will be sent to the NHLBI, DSMB and the cIRB within 15 calendar days. All unexpected and study related deaths and life threatening SUSARS will be reported to the FDA within 7 days; all other SUSARS will be reported to the FDA within 15 days. The DSMB will also review all adverse events and clinical outcomes during scheduled interim analyses, including frequency of additional neuromuscular blockade use in both study groups, for the first 48 hours. If the DSMB determines that the overall rate of adverse events is higher in the cisatracurium group than the control group the cIRB and the FDA will be notified within 15 days of this determination (via an IND safety report (21 CFR 312.32(c)(1)(i)(A))). The CCC will distribute the written summary of the DSMB’s periodic review of adverse events to the cIRB in accordance with NIH guidelines (<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>).

### C1. UNANTICIPATED PROBLEMS (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with the study drug or study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or

recognized.

## **C2. DETERMINING RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG OR PROCEDURES**

Investigators will be asked to grade the strength of the relationship of an adverse event to cisatracurium or study procedures as follows:

- **Definitely Related:** The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
- **Probably or Possibly Related:** The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- **Probably Not Related:** The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- **Definitely Not Related:** The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- **Uncertain Relationship:** The event does not meet any of the criteria previously outlined.

## **C3. CLINICAL OUTCOMES THAT MAY BE EXEMPT FROM ADVERSE EVENT REPORTING**

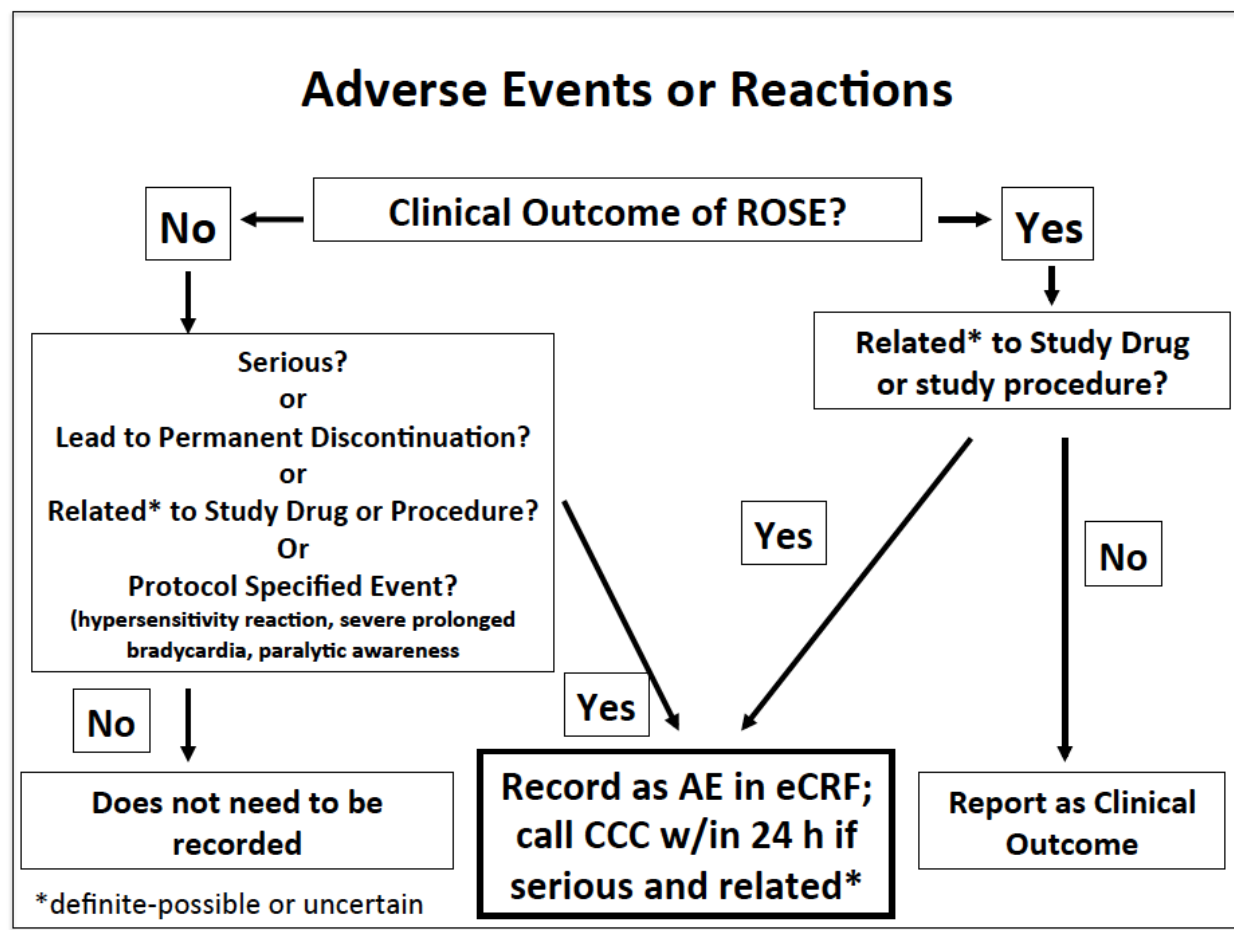
Study-specific clinical outcomes of ARDS, as outlined in Sections 3.8.1 and 3.8.2 (Primary and Secondary Outcomes) and Section 6.3 (Assessments During the Study) are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship). The following are examples of events that will be considered study specific clinical outcomes

- Death not related to the study drug or procedures.
- Cardiovascular events: need for vasoactive drugs or fluids for hypotension or hypotension.
- Respiratory events: decreased PaO<sub>2</sub>/FiO<sub>2</sub>, hypoxia, worsening acute respiratory distress syndrome, or respiratory failure.
- Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin.
- Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine.
- Hematologic/coagulation events: coagulopathy, disseminated intravascular coagulation, thrombocytopenia, or thrombocytosis.



Note: Arrhythmias such as heart block, ventricular tachycardia or ventricular fibrillation are not considered study specific clinical outcomes and should be recorded as adverse events if they are serious events, are considered by the investigator to be related to study drug, or lead to discontinuation of the study drug infusion.

#### C4. DECISION TREE FOR DETERMINING IF AN ADVERSE EVENT IS REPORTABLE



Adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. Epub 2012 May 22. PubMed PMID: 22616830

## D VENTILATOR PROCEDURES

### D.1 VENTILATOR MANAGEMENT

A modified, simplified version of the ARDS Network lung protective lower tidal volume strategy will be used in this trial. This strategy, which was associated with unprecedented low mortality rates in three previous ARDS Network trials (ARMA, ALVEOLI, and FACTT), will ensure that study subjects receive the beneficial effects of lung protection as part of their participation in this trial [7, 30, 31]. For those patients who remain hospitalized and on mechanical ventilation, the ventilator and weaning protocols will be implemented up to day 90 of hospitalization.

We will also use a modified version of the higher PEEP strategy used in several trials (ALVEOLI, LOV, EXPRESS, OSCILLATE). The use of the high PEEP protocol will be required for up to 5 days after randomization. This strategy has been repeatedly shown to improve oxygenation and to be safe.

PETAL Network personnel have substantial experience in the application of both strategies from the completed trials noted above.

1. Controlled modes of ventilation will be required during the period of neuromuscular blockade. Following neuromuscular blockade, any mode of ventilation capable of delivering the prescribed tidal volume (6ml/kg PBW, +/- 2ml/kg) may be used, provided the  $V_T$  target is monitored and adjusted appropriately. During APRV, tidal volume is defined as the sum of the volume that results from the ventilator pressure-release and an estimation of the average spontaneous  $V_T$ .
2. Tidal Volume ( $V_t$ ) Goal: 6 ml / kg PBW

Predicted body weight (PBW) is calculated from age, gender, and height (heel to crown) according to the following equations:

$$\text{Males: PBW (kg)} = 50 + 2.3 [\text{height (inches)} - 60]$$

$$\text{Females: PBW (kg)} = 45.5 + 2.3 [\text{height (inches)} - 60]$$

3. Measure and record inspiratory plateau pressure (Pplat) according to ICU routine (at least every four hours and after changes in  $V_t$  and PEEP recommended).
4. If Pplat > 30 cm H<sub>2</sub>O, reduce  $V_T$  to 5 ml / kg and then to 4 ml / kg PBW if necessary to decrease Pplat to ≤ 30 cm H<sub>2</sub>O.
5. If  $V_T$  < 6 ml / kg PBW and Pplat < 25 cm H<sub>2</sub>O, raise  $V_T$  by 1 ml / kg PBW to a maximum of 6 ml / kg.
6. If "severe dyspnea" (more than 3 double breaths per minute or airway pressure remains at or below PEEP level during inspiration), then raise  $V_T$  to 7 or 8 ml / kg PBW if Pplat remains below 30 cm H<sub>2</sub>O. If Pplat exceeds 30 cm H<sub>2</sub>O with  $V_T$  of 7 or 8 ml / kg PBW, then revert to lower  $V_T$  and consider more sedation.
7. If pH < 7.15,  $V_T$  may be raised and Pplat limit suspended (not required).

8. Oxygenation target: 55 mmHg < PaO<sub>2</sub> < 80 mm Hg or 88% < SpO<sub>2</sub> < 95%. When both PaO<sub>2</sub> and SpO<sub>2</sub> are available simultaneously, the PaO<sub>2</sub> criterion will take precedence.
9. Minimum PEEP = 5 cm H<sub>2</sub>O
10. Adjust FiO<sub>2</sub> or PEEP upward within 5 minutes of consistent measurements below the oxygenation target range
11. Adjust FiO<sub>2</sub> or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.
12. The below high PEEP strategy FiO<sub>2</sub>/PEEP table, modified from the ALVEOLI trial , should be used in all patients. See Section 5.3.3 for when deviation is permitted.

FiO <sub>2</sub>	.30	.40	.40	.40	.40	.40	.40	.40	.40	.50	.50	.50	.60	.70	.80	.80	.90	1.00	1.00
PEEP	5	5	6	8	10	12	14	16	16	18	20	20	20	20	22	22	22	22	24

If a patient's PEEP/FiO<sub>2</sub> is not compatible with the PEEP/FiO<sub>2</sub> scale immediately after randomization **either PEEP or FiO<sub>2</sub> (or both) will be adjusted in steps, at intervals of 5-15 minutes until the PEEP/FiO<sub>2</sub> is compatible with the scale.**

**NOTE: A step is equal to 2 cm H<sub>2</sub>O of PEEP and/or FiO<sub>2</sub> of 0.1.**

(Levels of PEEP in these FiO<sub>2</sub> / PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.)

13. No specific rules for respiratory rate, but incremental increase in the RR to maximum set rate of 35 if pH < 7.30.
14. No specific rules about I:E. Recommend that duration of Inspiration be ≤ duration of Expiration.
15. Bicarbonate is allowed (neither encouraged nor discouraged) if pH < 7.30.

Changes in more than one ventilator setting driven by measurements of PaO<sub>2</sub>, pH, and Pplat may be performed simultaneously, if necessary.

## D.2 WEANING

### Commencement of weaning

Patients will be assessed for the following weaning readiness criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to six hours. Patients can be assessed for weaning readiness criteria twice a day.

1. At least 12 hours since enrollment in the trial.
2. FiO<sub>2</sub> ≤ 0.40 and PEEP ≤ 8 cm

3. Values of both PEEP and  $FiO_2 \leq$  values from previous day (comparing Reference Measurement values, section 6.3).
4. Systolic arterial pressure  $\geq 90$  mm Hg without vasopressor support ( $\leq 5$  mcg / kg / min dopamine will not be considered a vasopressor).

### **Spontaneous breathing trial (SBT) procedure and assessment for unassisted breathing**

If criteria 1-4 above are met, first the neuromuscular blocking agent will need to be discontinued if the medication is still being infused. When the neuromuscular blocking agent has worn off and the patient is having spontaneous respirations, then initiate a trial of up to 120 minutes of spontaneous breathing with  $FiO_2 \leq 0.5$  using any of the following approaches:

1. Pressure support  $\leq 5$ cm H<sub>2</sub>O, PEEP  $\leq 5$ cm H<sub>2</sub>O
2. CPAP  $\leq 5$  cm H<sub>2</sub>O
3. T-piece
4. Tracheostomy mask

Monitor for tolerance using the following:

1.  $SpO_2 \geq 90\%$  and / or  $PaO_2 \geq 60$  mmHg
2. Mean spontaneous tidal volume  $\geq 4$  ml / kg PBW (if measured)
3. Respiratory Rate  $\leq 35$  / min
4.  $pH \geq 7.30$  (if measured)
5. No respiratory distress (defined as 2 or more of the following):
  - a. Heart rate  $\geq 120\%$  of the 0600 rate ( $\leq 5$  min at  $> 120\%$  may be tolerated)
  - b. Marked use of accessory muscles
  - c. Abdominal paradox
  - d. Diaphoresis
  - e. Marked subjective dyspnea.

If any of the goals 1-5 are not met, revert to previous ventilator settings or to PS + 10 cm H<sub>2</sub>O with Positive End-expiratory Pressure and  $FiO_2 =$  previous settings and reassess for weaning the next morning.

The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

### **Decision to remove ventilatory support**

For intubated patients, if tolerance criteria for spontaneous breathing trial (1-5 above) are met for at least 30 minutes, the clinical team may decide to extubate. However, the spontaneous breathing trial can continue for up to 120 minutes if tolerance remains in question. If any of criteria 1-5 are not met during unassisted breathing (or 120 minutes has passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean will be restored and the patient will be reassessed for weaning (see section D.2) the following day.

### **Definition of unassisted breathing**

- a) Extubated with face mask, nasal prong oxygen, or room air, OR
- b) T-tube breathing, OR
- c) Tracheostomy mask breathing, OR
- d) CPAP  $\leq 5$  without PS or IMV assistance
- e) Use of CPAP or BIPAP solely for sleep apnea management
- f) Use of a high flow oxygen system

### **Completion of ventilator procedures**

Patients will be considered to have completed the study ventilator procedures if any of the following conditions occur:

- a. Death
- b. Hospital discharge
- c. Alive 28 days after enrollment

If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures will resume unless the patient was discharged from the hospital or > 28 days elapsed since enrollment.

### **Removal from the ventilator management protocol**

Patients may be removed from the 6 ml / kg tidal volume ventilation requirement if they develop neurologic conditions where hypercapnia would be contraindicated (e.g., intracranial bleeding, GCS  $\leq 8$ , cerebral edema, mass effect [midline shift on CT scan], papilledema, intracranial pressure monitoring, fixed pupils).

## E CONSERVATIVE FLUID MANAGEMENT APPROACH

A modified conservative fluid protocol will be used based on the findings from FACTT that conservative fluid management increased ventilator free days. This protocol is recommended for all enrolled patients, to be used until UAB or study day 7, whichever occurs first.

1. Discontinue maintenance fluids.
2. Continue medications and nutrition.
3. Manage electrolytes and blood products per usual practice.
4. For shock, use any combination of fluid boluses<sup>#</sup> and vasopressor(s) to achieve MAP  $\geq$  60 mmHg as fast as possible. Wean vasopressors as quickly as tolerated beginning four hours after blood pressure has stabilized.
5. Withhold diuretic therapy in renal failure<sup>§</sup> and until 12 hours after last fluid bolus or vasopressor given.

This protocol is a simplified modification of the conservative protocol used in FACTT. For patients without a CVC, no fluid gain over the first 7 study days is recommended once patients' blood pressure has stabilized. Stable blood pressure is defined as no requirement for either vasopressors or a fluid bolus to support blood pressure for 12 or more hours.

CVP (recommended)	PAOP (optional)	MAP $\geq$ 60 mm Hg AND off vasopressors for $\geq$ 12 hours	
		Average urine output < 0.5 ml/kg/hr	Average urine output $\geq$ 0.5 ml/kg/hr
>8	> 12	Furosemide* Reassess in 1 hour	Furosemide* Reassess in 4 hours
4-8	8-12	Give fluid bolus as fast as possible <sup>#</sup> Reassess in 1 hour	No intervention Reassess in 4 hours
< 4	< 8		

§ Renal failure is defined as dialysis dependence, oliguria with serum creatinine > 3mg/dl, or oliguria with serum creatinine 0-3 with urinary indices indicative of acute renal failure.

# Recommended fluid bolus= 15 mL / kg crystalloid (round to nearest 250 mL) or 1 Unit packed red cells or 25 grams albumin

\* Recommended Furosemide dosing = begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg / day. Also, if patient has heart failure, consider treatment with dobutamine.

## F DE-IDENTIFIED DATA ELEMENTS FOR SCREENED, NON-ENROLLED SUBJECTS

The following data elements will be collected on screened subjects who met the inclusion criteria but were not enrolled.

- Did frontal CXR show bilateral infiltrates consistent with pulmonary edema?
- Number of quadrants with opacities?
- Is patient intubated?
- PaO<sub>2</sub>
- SpO<sub>2</sub>
- FiO<sub>2</sub>
- Was there evidence of left atrial hypertension?
- Month of the year that patient met screening criteria (1-12).
- Gender
- Ethnicity
- Age (if age >89, 89 will be entered for age)
- Patient location (e.g. MICU, SICU, etc.) and if regularly screened
- Reason(s) patient excluded from study.
- If not excluded, not enrolled, why?
- Lung injury category (e.g. sepsis, pneumonia)
- If sepsis, site of infection

## G NEUROMUSCULAR AND LONG TERM OUTCOMES

### Phone Interviews for Survivors from All PETAL Study Sites

We will perform phone interviews for vital status and the domains noted in Section 6.4. Centralized vs site-level administration of phone surveys will be determined by the PETAL Steering Committee.

Interviews will be performed by basic research staff using detailed scripts appropriate for each survey instrument. Manuals of Operations will be developed for training, reference and quality assurance review.



## H DATA AND SAFETY MONITORING BOARD

The principal role of the DSMB is to assure the safety of patients in the ROSE trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the NHLBI with respect to:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

Two interim analyses will be conducted at approximately 33% and 67% target enrollment accrual.

The NHLBI PETAL Network DSMB is appointed by the Director, NHLBI and makes recommendations to the NHLBI Director. The DSMB reviews all protocols for safety following review by an independent NHLBI Protocol Review Committee. The DSMB will consist of members with expertise in acute lung injury, emergency medicine, biostatistics, ethics, and clinical trials. An NHLBI staff member not associated with PETAL will serve as Executive Secretary. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and the Medical Monitor of the CCC will be responsible for the preparation of all DSMB and adverse event reports and may review unblinded data. The DSMB will develop a charter and review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the CCC. When appropriate, conference calls may be held in place of face-to-face meetings. Recommendations to end, modify, or continue the trial will be prepared by the DSMB executive secretary for review by Director, NHLBI. Recommendations for major changes, such as stopping, will be reviewed by the NHLBI Director and communicated immediately. Other recommendations will be reviewed by the NHLBI director and distributed in writing to the CCC, which will distribute to the PETAL steering committee with instructions for reporting to local IRBs when appropriate.

Details of the NHLBI policies regarding DSMBs can be found at the following URL:

[http://www.nhlbi.nih.gov/funding/policies/dsmb\\_inst.htm](http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm)

The PETAL Network Steering Committee is comprised of the Principal Investigators and Co-investigators of all the Clinical sites, the CCC, and the NHLBI Project Officer who represents the NHLBI. All sites have two votes and the CCC has one.

# I AUDIT QUESTIONNAIRE

## The Alcohol Use Disorders Identification Test [80]

The Alcohol Consumption Questionnaire is important to administer because there is a common association between alcohol abuse and ARDS[81]. It will be important to have this information for a subgroup analysis. Knowledge of alcohol abuse will also help the primary team better care for the patient and improve patient outcome, as there are alcohol specific disorders in critically ill patients that often are not diagnosed and therefore not treated effectively. This survey will not be completed on subjects less than 18 years of age.

We will use the modified AUDIT questionnaire (first three questions) as this simplified version has good performance characteristics and is less time consuming.

<p>1. How often do you have a drink containing alcohol?</p> <p>(0) Never [Skip to Qs 9-10]            (1) Monthly or less            (2) 2 to 4 times a month            (3) 2 to 3 times a week            (4) 4 or more times a week</p> <input type="checkbox"/>	<p>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <input type="checkbox"/>
<p>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</p> <p>(0) 1 or 2            (1) 3 or 4            (2) 5 or 6            (3) 7, 8, or 9            (4) 10 or more</p> <input type="checkbox"/>	<p>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <input type="checkbox"/>
<p>3. How often do you have six or more drinks on one occasion?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <p><i>Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0</i></p> <input type="checkbox"/>	<p>8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <input type="checkbox"/>
<p>4. How often during the last year have you found that you were not able to stop drinking once you had started?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <input type="checkbox"/>	<p>9. Have you or someone else been injured as a result of your drinking?</p> <p>(0) No            (2) Yes, but not in the last year            (4) Yes, during the last year</p> <input type="checkbox"/>
<p>5. How often during the last year have you failed to do what was normally expected from you because of drinking?</p> <p>(0) Never            (1) Less than monthly            (2) Monthly            (3) Weekly            (4) Daily or almost daily</p> <input type="checkbox"/>	<p>10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?</p> <p>(0) No            (2) Yes, but not in the last year            (4) Yes, during the last year</p> <input type="checkbox"/>
<p style="text-align: right;">Record total of specific items here <input type="checkbox"/></p> <p><i>If total is greater than recommended cut-off, consult User's Manual.</i></p>	

## J CISATRACURIUM PACKAGE INSERT AND ACURASYS STUDY PUBLICATION

NIMBEX (cisatracurium besylate) is a nondepolarizing skeletal muscle relaxant for intravenous administration. Compared to other neuromuscular blocking agents, it is intermediate in its onset and duration of action. Cisatracurium besylate is one of 10 isomers of atracurium besylate and constitutes approximately 15% of that mixture. Cisatracurium besylate is [1R-[1 $\alpha$ ,2 $\alpha$ (1'R\*,2'R\*)]-2,2'-[1,5-pentanediy]bis[oxy(3-oxo-3,1-propanediy)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzenesulfonate. The molecular formula of the cisatracurium parent bis-cation is C<sub>53</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub> and the molecular weight is 929.2. The molecular formula of cisatracurium as the besylate salt is C<sub>65</sub>H<sub>82</sub>N<sub>2</sub>O<sub>18</sub>S<sub>2</sub> and the molecular weight is 1243.50.

The full package insert and the ACURASYS study primary publication, which together will serve as the Investigator Brochure for this trial, can be found here:

Cisatracurium package insert:

<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3db3b76c-3e5a-456e-46a8-456fde1e6195>

ACURASYS study: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1005372>

Note: The mean measured body weights in ACURASYS (+/- SD) were 77 (+/-18 kg; range 43 to 126 kg) in the placebo group and 78 (+/-19 kg; range 30 to 185 kg) in the cisatracurium group (reference 2a)

## K SOFA SCORING SYSTEM

Variables	SOFA Score				
	0	1	2	3	4
<b>Coagulation</b> Platelets x 10 <sup>3</sup> /μL	>150	≤150	≤100	≤50	≤20
<b>Liver</b> Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>11.9
<b>Cardiovascular</b> Hypotension	No hypotension	Mean arterial pressure <70 mmHg	Dop ≤5 or dob (any dose) ‡	Dop >5, epi ≤0.1, or norepi ≤0.1‡	Dop >15, epi >0.1, or norepi >0.1‡
<b>Renal</b> Creatinine, mg/dL or urine output, ml/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>4.9 or <200

\*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine, Epi, epinephrine.

†Values are with respiratory support.

‡Adrenergic agents administered for at least one hour (doses given are in μg/kg/min)

We define a clinically significant organ failure as a new SOFA score of ≥ 2.

## L COMMON RISK FACTORS FOR ARDS

### Direct

Pneumonia

Aspiration of gastric contents

Inhalational injury

Pulmonary contusion

Drowning

### Indirect

Non-pulmonary sepsis

Major trauma

Pancreatitis

Severe burns

Non-cardiogenic shock

Drug overdose

Multiple transfusions or transfusion associated acute lung injury (TRALI)

Source: Supplementary Online Content, eTable 1. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA. doi:10.1001/jama.2012.5669.

## L ICU MOBILITY SCALE [20]

	Classification	Definition
0	Nothing (lying in bed)	Passively rolled or passively exercised by staff, but not actively moving
1	Sitting in bed, exercising in bed	Any activity in bed including rolling, bridging, active exercises, cycle ergometry and active assisted exercises; not moving out of bed or over edge of bed
2	Passively moving to chair (no standing)	Hoist, passive lift or slide transfer, to the chair, with no standing or sitting on the edge of the bed
3	Sitting over edge of bed	May be assisted by staff, but involves actively sitting over the edge of the bed with some trunk control
4	Standing	Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table.
5	Transferring bed to chair	Able to step or shuffle through standing to the chair. This involves actively transferring the weight from one leg to the other to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device).
6	Marching on spot (at bedside)	Able to walk on the spot by lifting alternate feet (must be able to step at least 4 times, twice on each foot), with or without assistance.
7	Walking with assistance of 2 or more people	Walking away from bed/chair by at least 5 m (5 yards) assisted by 2 or more people
8	Walking with assistance of 1 person	Walking away from bed/chair by at least 5 m (5 yards) assisted by 1 person
9	Walking independently with a gait aid	Walking away from bed/chair by at least 5 m (5 yards) with a gait aid but no assistance from another person. In a wheelchair bound person, this activity involves wheeling the chair 5m (5 yards) away from the bed/chair.
10	Walking independently without a gait aid	Walking away from bed/chair by at least 5 m (5 yards) without a gait aid, or assistance from another person.

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