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Design and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade Trial for Acute Respiratory Distress Syndrome

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Abstract

The Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial is a multicenter, randomized trial designed to assess the efficacy and safety of early neuromuscular blockade in patients with moderate to severe acute respiratory distress syndrome. This document provides background for interpretation of the trial results, and highlights unique design approaches that may inform future trials of acute illness. We describe the process by which ROSE was chosen as the inaugural trial of the multidisciplinary Prevention and Early Treatment of Acute Lung Injury Network, provide the trial methodology using the Consolidated Standards of Reporting Trials framework, and discuss key design challenges and their resolution. Four key design issues proved challenging—feasibility, choice of sedation depth in the control group, impact of emphasizing early treatment on enrollment criteria and protocol execution, and choice of positive end-expiratory pressure strategy. We used literature, an iterative consensus model, and internal surveys of current practice to inform design choice. ROSE will provide definitive, Consolidated Standards of Reporting Trials adherent data on early neuromuscular blockade for future patients with acute respiratory distress syndrome. Our multidisciplinary approach to trial design may be of use to other trials of acute illness.

Clinical trial registered with www.clinicaltrials.gov (NCT02509078).

Keywords: respiratory distress syndrome, adult; clinical trial; methods; interdisciplinary communication

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*The participating individuals and institutions of the National Institutes of Health/National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung injury Network are listed in Appendix 1.

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The acute respiratory distress syndrome (ARDS) is a common, life-threatening syndrome characterized by acute inflammatory lung injury, hypoxemic respiratory failure, and bilateral lung opacities on chest radiography (1). In 2010, the ARDS et Curarisation Systematique (ACURASYS) trial reported that early neuromuscular blockade improved adjusted survival for moderate to severe ARDS in a 340-patient trial conducted in 20 French intensive care units (ICUs) (2). Although intriguing, this approach has not been widely adopted (3). Reasons include physician reticence to accept

a single study, given lack of replicability of prior ICU trials, small sample size, unclear mechanism, and lack of long-term follow up for paresis and other outcomes (2, 4). In addition, the ACURASYS control group received deep sedation, inconsistent with current clinical practice (5–8). As a result, many have recommended a definitive phase III trial (4, 9).

In 2014, the National Heart, Lung, and Blood Institute (NHLBI) launched the Prevention and Early Treatment of Acute Lung injury (PETAL) Network to conduct phase III trials to test treatments with the potential to improve clinical outcomes of patients with or at risk of developing ARDS. PETAL succeeds and builds on the NHLBI ARDS Clinical Trial Network (ARDSNet), with a new focus on early treatment and prevention through multidisciplinary collaboration among pulmonologists/intensivists, emergency physicians, trauma and sepsis experts, and other acute care specialists.

In January 2016, PETAL launched the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial (clinicaltrials.gov identifier: NCT02509078). The objective is to assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate to severe ARDS in comparison to a control group with no routine early neuromuscular blockade. We hypothesize that early neuromuscular blockade will improve mortality before discharge home before Day 90. Here, we describe the process by which ROSE was chosen as the inaugural PETAL trial, provide the trial methodology using the Consolidated Standards of Reporting Trials (CONSORT) framework (10, 11), and discuss key design challenges and their resolution. Our goal is to provide background for interpretation of ROSE results, and highlight unique design approaches that may inform future trials of acute illness.

Methods

PETAL Network

The PETAL Network is comprised of 12 clinical centers and one PETAL Clinical Coordinating Center (CCC), all in the United States (Figure 1). The PETAL steering committee is composed of a chairperson, an ICU investigator, and a second investigator from a different acute care specialty (e.g., emergency medicine, surgery, anesthesiology) from each clinical center, the CCC, and NHLBI project officers (Appendix 1). Each clinical center consists of a lead academic medical center, with one or more affiliated satellite recruiting institutions, for a total of 48 hospitals. The NHLBI chose centers based on intensivist and emergency physician (or other acute care specialist) collaboration, ability to screen and enroll, including pre-ICU and at satellite institutions, and strength of submitted trial proposals.

Trial Selection Process

Each clinical center submitted two trial proposals with their Network application. After centers were chosen, the PETAL steering committee developed selection criteria (evidence of potential therapeutic value, preliminary data in humans, feasibility, probability of changing clinical practice, relevance to the most patients), and selected six proposals for in-person discussion. The Pittsburgh and Denver centers both proposed an early neuromuscular blockade trial in their applications, and jointly presented ROSE. Four prevention (granulocyte-macrophage colony–stimulating factor, vitamin C, checklist implementation, no sedation) and one other early treatment (prone positioning) trial were also proposed. After two voting rounds by the PETAL steering committee, ROSE was selected as its first trial in September 2014. The Network then formed a ROSE protocol committee consisting of several steering committee members, which developed a protocol. After multiple rounds of review and revision, an NHLBI-appointed Protocol Review Committee, Data and Safety Monitoring Board, and central Institutional Review Board approved the protocol. In January 2016, ROSE began enrollment.

Trial Methodology and Rationale

We summarize trial methods in Tables 1–5. The following CONSORT methods sections provide additional context (10), and the complete protocol is provided in Appendix 5. Key design differences between ACURASYS and ROSE are summarized in Table 6.

Trial Design

ROSE is a patient-level, equal-randomized, parallel-group, superiority trial of two management strategies of neuromuscular blockade for ARDS—early blockade versus no routine early blockade. To facilitate early enrollment, our goal is to screen every newly intubated, acutely ill, or postoperative patient. We recruit from all acute care areas, including emergency departments (EDs), inpatient floors, and ICUs.

Participants

Inclusion criteria. We seek to enroll adult patients with ARDS with a confirmed and established ratio of Pa_{O_2}/FI_{O_2} less than 150, following the threshold in ACURASYS (2) (Table 1).

Confirmed and established hypoxemia. There is no consensus on how long and under what conditions hypoxemia is considered confirmed and established. Hypoxemia can be transient due to atelectasis, suctioning, and other factors. Past ARDS trials have used various criteria, ranging from a single Pa_{O_2}/FI_{O_2} on any ventilator settings (12, 13) to requiring a second, confirmatory Pa_{O_2}/FI_{O_2} on specific ventilator settings after a set interval (14, 15).

We chose two criteria to ensure persistent hypoxemia. First, we require the Pa_{O_2}/FI_{O_2} measured on at least 8 cm H_2O of positive end-expiratory pressure (PEEP). Initial postintubation PEEP is typically less than 8 cm H_2O. Thus, this inclusion criterion ensures hypoxemia that persists despite increased PEEP and time. Second, as detailed under *Exclusion criteria*, we exclude patients whose oxygenation substantially improves after initially meeting inclusion criteria.

Pulse oximetry. The Berlin ARDS definition requires a Pa_{O_2}/FI_{O_2}. However, arterial blood gas use is declining in ED and ICU practice (16–20), which may result in missed or delayed diagnosis of ARDS. We therefore use oxyhemoglobin percent saturation measured with pulse oximetry (Sp_{O_2}) to impute Pa_{O_2} (21, 22) (Appendix 2), with several criteria to ensure confirmed and established hypoxemia. First, imputation of Pa_{O_2}/FI_{O_2} from Sp_{O_2}/FI_{O_2} is only used if a blood gas

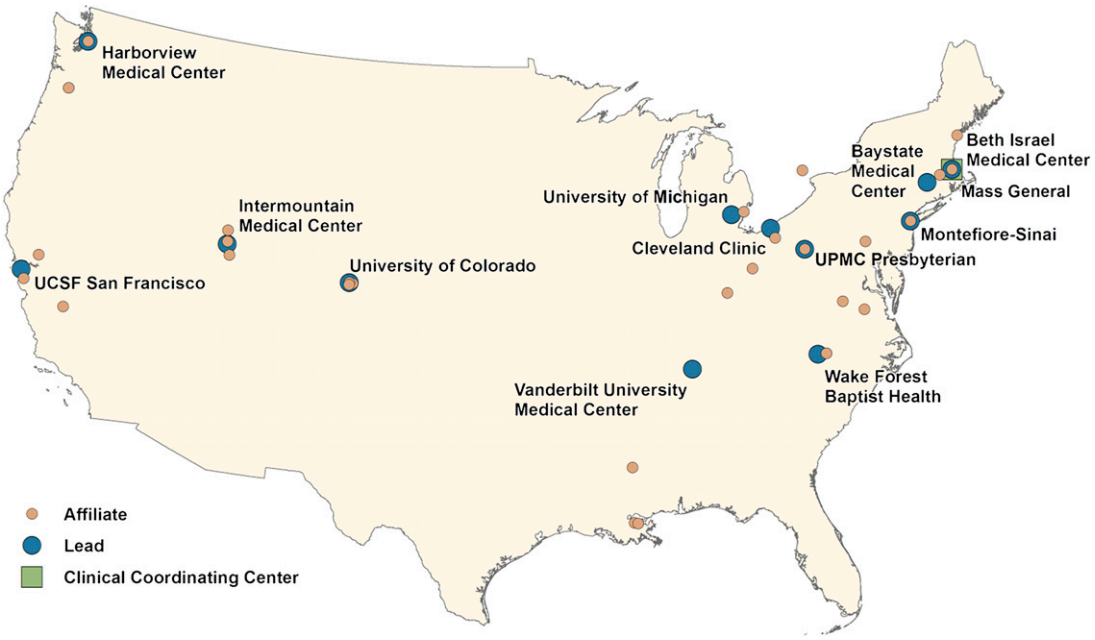

Figure 1. The Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. Each of the 12 clinical centers is comprised of a lead academic medical center, with one or more affiliated satellite recruiting institutions, for a total of 48 Network hospitals, and are overseen by one Clinical Coordinating Center (CCC). The PETAL Steering Committee is composed of a chairperson, an intensive care unit investigator, and a second investigator from a different acute care specialty (e.g., emergency medicine, surgery, anesthesiology) from each clinical center, the CCC, and NHLBI project officers (map courtesy of Dr. David J. Wallace, University of Pittsburgh, Pittsburgh, PA).

is unavailable. Second, Sp_{O_2} must be 80–96%, as the Ellis-Severinghaus equation becomes inaccurate outside this range (23). Third, we stipulate that Sp_{O_2} must be measured at least 10 minutes after an FI_{O_2} change. Fourth, we require signed investigator attestation to pulse oximeter waveform adequacy. Last, we require a second, confirmatory Sp_{O_2}/FI_{O_2} 1–6 hours after the initial qualifying Sp_{O_2}/FI_{O_2}. The goal of these steps is to enhance recruitment without diluting the study population with participants less ill than intended.

Exclusion criteria. We use exclusion criteria similar to ACURASYS and past ARDSNet trials (Table 1). We exclude patients with ARDS for greater than 48 hours or on mechanical ventilation for greater than 120 hours as PETAL is charged to test early treatment. Oxygenation may improve during the 48-hour enrollment window. We therefore exclude patients with an available, clinically measured, Pa_{O_2}/FI_{O_2} greater than 200 after meeting inclusion criteria and before randomization. This exclusion criterion ensures that patients with mild ARDS are not enrolled. We also exclude patients not expected to survive 24 hours. In patients who underwent cardiopulmonary resuscitation (CPR), this short-term survival assessment is made 6 hours or longer from CPR conclusion.

Interventions

Study arms: intervention—early neuromuscular blockade. Study staff ensure deep sedation to a Ramsay score of 5–6 (RASS [Richmond Agitation–Sedation Scale] −4 to −5; Riker 1–2) occurs and is documented before neuromuscular blockade initiation (Table 2). The dose required to achieve this sedation target continues while the participant is under blockade. We do not mandate sedative type.

Neuromuscular blockade must begin within 4 hours of randomization, with a cisastracurium besylate bolus of 15 mg, followed by a continuous infusion of 37.5 mg/h for 48 hours. We chose this fixed dose based on ACURASYS, which found it safe and effective for achieving blockade without the need for monitoring (e.g., train of four) (2). Train-of-four monitoring is imperfect, supported by limited evidence (24–26), and may lead to underdosing. We chose cisatracurium for its excellent safety profile, hepatic and renal function–independent metabolism, and to replicate ACURASYS.

We recommend routine safety plans that include eye care, positioning, and pressure ulcer monitoring.

Neuromuscular blockade can be stopped early if ventilator weaning criteria are met with FI_{O_2} of 0.40 or less and PEEP of 8 cm or less, and maintained for at least 12 hours. If oxygenation significantly worsens ($\geq$2 rightward steps on $PEEP/FI_{O_2}$ table; Appendix 3), we recommend that blockade resume. Blockade can also be stopped for safety concerns. Treating clinicians are informed when the 48-hour intervention period ends and that cisatracurium will be stopped as a study intervention. After the 48-hour period, further blockade is per treating clinicians. These steps balance trial intervention fidelity and individual patient clinical need.

Study arms: control—no routine early neuromuscular blockade. All control group care is per the treating clinicians, except for aspects outlined in *Common strategies for both groups*.

We recommend light sedation to Ramsay 2–3 (RASS 0 to −1, Riker 3–4) or

Table 1. Eligibility criteria

CONSORT	ROSE
Inclusion criteria	⩾18 yr of age Presence of all of the following conditions for ⩽48 h i. $Pa_{O_2}/F_{I_{O_2}} < 150$ with PEEP ⩾ 8 cm H_2O*,†,‡ or if arterial blood gas not available $Sp_{O_2}/F_{I_{O_2}}$ ratio that is equivalent to a $Pa_{O_2}/F_{I_{O_2}} < 150$ with PEEP ⩾ 8 cm H_2O (Appendix 2), and a confirmatory $Sp_{O_2}/F_{I_{O_2}}$ ratio between 1 and 6 h after the initial $Sp_{O_2}/F_{I_{O_2}}$ ratio determination.‡,§ 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 4) The 48-h enrollment time window begins when criteria i–iii are met. Criteria may be met at either the Network or referring hospital. The first qualifying $Sp_{O_2}/F_{I_{O_2}}$ (not the confirmatory $Sp_{O_2}/F_{I_{O_2}}$) is used determine this time window.
Exclusion criteria	Lack of informed consent Continuous neuromuscular blockade at enrollment Known pregnancy Currently receiving ECMO therapy Chronic respiratory failure defined as $Pa_{CO_2} > 60$ mm Hg in the outpatient setting Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for CPAP/BIPAP used solely for sleep-disordered breathing Actual body weight exceeding 1 kg/cm of height Severe chronic liver disease defined as a Child-Pugh score of 12–15 Bone marrow transplantation within the last 1 yr Expected duration of mechanical ventilation <48 h Decision to withhold life-sustaining treatment; except in those patients committed to full support except CPR Moribund patient not expected to survive 24 h; if CPR provided, assess for moribund status ⩾6 h from CPR conclusion Diffuse alveolar hemorrhage from vasculitis Burns >70% total body surface Unwillingness to use the ARDS Network 6 ml/kg IBW ventilation protocol Previous hypersensitivity or anaphylactic reaction to cisatracurium Neuromuscular conditions that may potentiate neuromuscular blockade and/or impair spontaneous ventilation (amyotrophic lateral sclerosis, Guillain-Barre, myasthenia gravis, upper spinal cord injury at C5 or above) Neurologic conditions undergoing treatment for intracranial hypertension Enrollment in an interventional ARDS trial with direct impact on neuromuscular blockade and PEEP $Pa_{O_2}/F_{I_{O_2}}$ (if available) >200 after meeting inclusion criteria and before randomization (oxygenation may improve during the 48-h enrollment window; this exclusion criterion ensures that patients with mild ARDS are not included in the study) Endotracheal ventilation for greater than 120 h (5 d)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BIPAP = bilevel positive airway pressure; CONSORT = Consolidated Standards of Reporting Trials; CPAP = continuous positive airway pressure; CPR = cardiopulmonary resuscitation; ECMO = Extracorporeal Membrane Oxygenation; IBW = ideal body weight; PEEP = positive end-expiratory pressure; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade; Sp_{O_2} = oxyhemoglobin % saturation measured with pulse oximetry

*If altitude >1,000 m, then $Pa_{O_2}/F_{I_{O_2}} < 150 \times (PB/760)$, where PB is barometric pressure.

†These inclusion criteria ensure a non-transient, established hypoxia that persists despite elevated PEEP and time. Initial, postintubation, PEEP is typically <8 cm H_2O.

‡The qualifying $Pa_{O_2}/F_{I_{O_2}}$ or the $Sp_{O_2}/F_{I_{O_2}}$ must be from intubated patients receiving at least 8 cm H_2O PEEP.

§When hypoxia is documented using pulse oximetry, a confirmatory $Sp_{O_2}/F_{I_{O_2}}$ ratio is required to further establish persistent hypoxia. Qualifying $Sp_{O_2}/F_{I_{O_2}}$ must use Sp_{O_2} values ⩽96%. Qualifying Sp_{O_2} must be measured at least 10 minutes after any change to $F_{I_{O_2}}$.

absence of respiratory distress, and/or daily sedation breaks if no contraindication. We document reasons sedation is given if RASS is less than −1 (or equivalent). When control participants receive neuromuscular blockade, we recommend the same deep-sedation approach as in the intervention group.

We encourage sites to minimize early neuromuscular blockade. Our goal is to respect clinician autonomy and protect patient safety, while preserving separation of treatment between arms. For refractory high plateau pressure, we offer the same recommendation used in ACURASYS. If plateau pressure exceeds 32 cm H_2O for 10 minutes or longer, we recommend increasing sedation and decreasing tidal volume and PEEP before considering a 20-mg cisatracurium bolus. If this bolus decreases plateau pressure less than 2 cm H_2O, a second 20-mg cisatracurium bolus is allowed. If the second bolus is also ineffective, we recommend no further cisatracurium for 24 hours.

Common strategies for both groups. In both groups, we protocolize study startup and ventilator procedures, and provide recommendations for key cointerventions.

We follow standardized, step-wise startup procedures to compare hemodynamics during startup between groups, and to avoid simultaneous PEEP and sedation titration, which would render interpretation of hypotensive episodes challenging. Study initiation oversight is provided by an intensivist and/or designee. First, low tidal volume ventilation is initiated following the ARDSNet lung-protective ventilation strategy (27–29). Any controlled ventilation mode capable of delivering the prescribed volume (6 ml/kg predicted body weight) may be used. Second, sedation is adjusted to target sedation score. Third, in the intervention group, cisatracurium is started. Fourth, a PETAL investigator or designee determines hemodynamic appropriateness for PEEP increase, and, if deemed appropriate, PEEP is gradually uptitrated to a high-PEEP strategy based on previously implemented protocols (Appendix 3) (13, 14, 28, 30). We require the high-PEEP protocol for 5 days after randomization.

We allow protocol deviation for worsening of oxygenation after PEEP increase, pneumothorax, or high barotrauma risk (e.g., pulmonary bullae), similar to the Oscillation for Acute Respiratory Distress Syndrome Treated

Table 2. Interventions

CONSORT	ROSE
Study arms	
Intervention	Early neuromuscular blockade group i. Low tidal volume ventilation (≤6 ml/kg, plateau pressure ≤30 cm H_2O) ii. Deep sedation (Ramsay 5–6, RASS −4 to −5, or Riker 1–2) iii. Cisatracurium 15-mg bolus, then 37.5 mg/h infusion for 48 h iv. High PEEP strategy (Appendix 3)
Control	No routine early neuromuscular blockade group i. Low tidal volume ventilation (≤6 ml/kg, plateau pressure ≤30 cm H_2O) ii. Light sedation (Ramsay 2–3, RASS 0 to −1, or Riker 3–4; recommended) iii. High PEEP strategy (Appendix 3)
Standardization	Standardized teaching material used at start-up and refresher meetings, frequently asked questions, access to coordinating center and trial physician 24/7 Twice-yearly, in-person PETAL Steering Committee meetings, study website Regular site visits and news letters Site monitoring Regular adherence and on-target reports and feedback to individual centers
Adherence	Computerized audits to ensure study protocol is being followed, combined with regular center specific feedback and monitoring, center initiation, standardized operating procedures, 24/7 coordinating center and trial physician support

Definition of abbreviations: CONSORT = Consolidated Standards of Reporting Trials; PEEP = positive end-expiratory pressure; PETAL = Prevention and Early Treatment of Acute Lung Injury; RASS = Richmond Agitation–Sedation Scale; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade. Kilogram values are in terms of predicted body weight.

Early trial (14). We also allow protocol deviation if hypotension, plateau pressure greater than 30 cm H_2O, and/or severe acidemia ($pH < 7.15$) are present despite tidal volume reduction, fluid boluses, and/or respiratory rate increase. In these situations, with the high-PEEP protocol as the starting point, PEEP is reduced gradually until the physiologic parameters of concern improve. Later, we attempt to return to high PEEP, at least daily through Study Day 5 (Appendix 5).

We recommend that clinicians wait at least 12 hours before proning, as per the Proning Severe ARDS Patients trial (15), conservative fluid management using a simplification of the ARDSNet Fluids and Catheters Treatment Trial algorithm (31), and glycemic control with a target upper blood glucose level less than or equal to 180 mg/dl (32). Rescue procedures for refractory hypoxemia are per clinician discretion.

Standardization

To standardize protocol delivery, the PETAL CCC provides standardized training and materials and continuous support to the clinical centers. The CCC conducts twice-yearly, in-person meetings, holds regular conference calls, maintains a website with multiple resources, and reviews detailed, monthly "on target" performance reports (33). The CCC and protocol leaders train each center's principal investigators and coordinators in the rationale and steps of study interventions, who then train their coinvestigators and other personnel.

Adherence

Protocol adherence is promoted by frequent monitoring of intervention delivery conduct and feedback. The CCC and protocol leaders field questions regarding protocol specifics, such as patient eligibility and protocol delivery, and conduct monthly calls with centers to identify and solve challenges with protocol adherence.

Outcomes

Primary. The primary outcome is all-cause mortality before discharge home before Day 90 (Table 3, Appendix 5). Home is defined as the level of residence or healthcare facility where the patient was residing before hospital admission. Participants still in a healthcare facility at Day 91 are considered alive.

This outcome includes death in *any* healthcare facility before discharge home until Day 90. We chose this outcome to increase patient centeredness, as death after hospital discharge, but before returning home, is common for critically ill patients (e.g., long-term acute care hospitals) (34), and to account for mortality attributable to ARDS and ARDS risk factors months after the acute event (35).

Secondary. Key secondary outcomes (Table 3, Appendix 5) are: (*1*) process and safety measures; (*2*) physiologic measures; (*3*) early outcomes; and (*4*) long-term outcomes.

Process and safety measures include hemodynamic monitoring during study initiation, rescue procedures, achieved mobility level (36), and paralysis recall (37, 38). Physiologic measures include weekly manual muscle strength testing on participants who pass a safety and attention screen (until hospital discharge or Day 28, whichever comes first), and respiratory physiology assessments. We measure plasma IL-6 at study entry and 48 hours, and collect a biorepository of plasma and urine at multiple time points. The biorepository and clinical database will be made available to the scientific community through the NHLBI Biologic Specimen and Data Repository Information Coordinating Center after the trial ends (https://biolincc.nhlbi.nih.gov/home/).

For early outcomes, we measure survival and days without various supports (e.g., ventilator-free days) at Day 28. For long-term outcomes, we will query federal databases (e.g., National Death Index), and perform telephone interview assessments at 3, 6, and 12 months. We assess vital status and several domains, including disability, quality of life, and cognition. Interviews are conducted in English or Spanish from a central call center, first with participants, and, if unavailable, a proxy respondent. We chose survey instruments based on robustness, comparability with past work, power to detect outcome differences, and brevity (target interview time 20 min or less).

Data quality methods. The CCC safeguards data quality monitoring via web-based data collection, monthly query reports, and site visits, and provides

Table 3. Outcomes

CONSORT	ROSE
Outcomes	
Primary	All-cause mortality before discharge home before Day 90. (Home is defined as the level of residence or health care facility where the patient was residing before hospital admission.)
Secondary	Process and safety measures Hemodynamic monitoring during study initiation (fluid boluses, vasopressors) Rescue procedures Achieved mobility (ICU Mobility Scale) Paralysis recall, in hospital Physiologic measures ICU-acquired weakness Respiratory physiology and ventilator measurements (to include oxygenation index, Pa_{O_2}/FI_{O_2}, PEEP, plateau pressure on Study Days 1–4, 7; and development of pneumothorax through Day 7) Supraventricular tachycardia and new onset atrial fibrillation IL-6 (plasma) Early outcomes (to Day 28) Hospital mortality to Day 28 Ventilator free days to Day 28 Organ failure free days to Day 28 ICU-free days at Day 28 Hospital-free days at Day 28 Long-term outcomes (3, 6, and 12 mo) Disability: Katz Activities of Daily Living/Lawton Instrumental Activities of Daily Living Scale harmonized with the Health and Retirement Study Health-related quality of life (including utilities): EuroQol (EQ-5D-5L) Self-rated health: 1 standard item Pain interference: 1 standard item Posttraumatic stress-like symptoms: Post-Traumatic Stress Symptoms-14 (at 6 & 12 mo only; no proxy respondents allowed) Cognitive function: Montreal Cognitive Assessment-Blind. For proxy respondents, the Alzheimer's Disease 8 Subsequent return to work, hospital and emergency department use, location of residence Late mortality via both follow-up survey and linkage to National Death Index
Data quality methods	Standardized data collection and recording Web-based DCF with built-in logic checks, automatic data queries, and streamlined user interface Periodic DCF checks to monitor data irregularities and protocol compliance Detailed center study coordinator DCF training and periodic conference calls Center monitoring visits and independent, random review of source documents

Definition of abbreviations: CONSORT = Consolidated Standards of Reporting Trials; DCF = data collection form; ICU = intensive care unit; PEEP = positive end-expiratory pressure; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade.

structured data collection training to centers before study initiation.

Sample Size

Determination. Sample size is based on a comparison of binomial proportions, with an overall two-sided α of 0.05 and power of 0.90, to detect an absolute mortality difference half that assumed by ACURASYS. With a 35% mortality rate in control and a 27% rate in intervention, the maximum required sample size is 1,408 participants. (Table 4, Appendix 5). The presumed 35% control mortality rate is based on the control mortality rates in the ACURASYS (41%) and Oscillation for Acute Respiratory Distress Syndrome Treated Early (35%) trials of moderate to severe ARDS (2, 14), and the observed mortality (32%) for moderate ARDS in the Berlin ARDS definition validation cohort (39). Though the most recent ARDSNet trials reported lower mortality in their primary outcome (Early Versus Delayed Enteral Nutrition [EDEN], ~23%; Statins for Acutely Injured Lungs from Sepsis [SAILS], ~27%), these trials enrolled less severely ill patients ($Pa_{O_2}/FI_{O_2} < 300$) and used a shorter-duration mortality outcome (60 d) (12, 40).

Interim analyses and stopping rules. We will submit data to the independent Data and Safety Monitoring Board (DSMB) for two interim analyses and one final look with *a priori* stopping rules. ROSE will stop for superiority of either group, and is designed with symmetric group sequential flexible stopping boundaries as per Lan and DeMets (41). The boundaries specify that, at each data look, 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 groups, 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. Before trial completion, only the DSMB and designated study statisticians will see outcome data per arm; the DSMB may recommend stopping enrollment for efficacy, harm, or futility. Pre-established statistical plans and oversight committee charters mitigate concerns of spurious early cessation (42).

Randomization

Sequence generation. ROSE randomizes at the patient level, with 1:1 study arm allocation using a computer-generated permuted block design, and stratification by institution (Table 5). The CCC and protocol leaders provide continuous access for randomization backup.

Allocation concealment. We assure concealment via an automated, centralized assignment system. Only after enrollment does the system assign a study arm.

Implementation. Each coordinator has a unique personal identification number to access the CCC web-based randomization system. Each participant receives a computer-generated study

Table 4. Sample size determination and interim analyses

CONSORT	ROSE
Sample size*	1,408
Determination	Hypothesis: early neuromuscular blockade will improve mortality before discharge home before Day 90 (primary outcome) in patients with moderate to severe ARDS[†] 8% absolute risk reduction of primary outcome rate Assumes 35% primary outcome rate in control group ⩾90% power, two-sided α of 0.05
Interim analyses and stopping rules	Two interim analyses and one final look, approximately evenly spaced Symmetric group sequential flexible stopping boundaries, Lan and DeMets design

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CONSORT = Consolidated Standards of Reporting Trials; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade.
*The trial will enroll a maximum of 1,408 participants, and may stop early, per statistical stopping rules and Data Safety Monitoring Board recommendations.
[†]Participants who are discharged home (defined as the level of residence or healthcare facility where the patient was residing before hospital admission) before Day 90 will be assumed to be alive and censored at Day 91.

identification number and study arm assignment. An e-mailed confirmation is automatically generated and sent to the study site.

Blinding

We chose to not blind cisatracurium administration, as patients under neuromuscular blockade have easily identifiable clinical characteristics, such as absence of movement. PETAL investigators are familiar with unblinded trials, including the recent ARDSNet enteral feeding trial (40). The potential for clinician knowledge of randomization assignment to bias treatment is real, but modest. Risk of assessment bias is low, as the primary outcome is objective (mortality), and statistical analysis and long-term outcome assessment staff are blinded to study arm. We restrict access to unblinded data to designated study statisticians and oversight committees.

Statistical Methods

We will conduct an intention-to-treat analysis, with two-tailed significance testing at an α of 0.05, with no adjustment for multiple comparisons. We will analyze adverse events using weighted Poisson regression with nonserious events weighted by one, and serious events weighted by two. Events will be the unit of analysis, and will be grouped by Medical Dictionary for Regulatory Activities organ classes. We will report results in accordance with CONSORT. We will use standard analytic methods based on all available data with no imputation, with two exceptions.

For the primary outcome, participants not discharged home before Day 90 are followed for 90 days, and the primary mortality outcome is analyzed using Pearson's chi-square test to compare the proportion deceased before hospital discharge. However, at each interim analysis, it is necessary to account for patients still in hospital with less than 90 days follow up. This will be accomplished using the Kaplan-Meier Day 90 mortality point estimates with all patients who are discharged home or still alive at Day 90 censored at Day 91, which is beyond the last possible day of death. We will then compare Day 90 mortality estimates in the two study arms using a Z test with Greenwood's standard error (43). In the absence of censoring (before Day 90), this Z test is equivalent to Pearson's chi-square test.

Randomized treatment comparisons for endpoints defined only for survivors (e.g., quality of life) cannot be performed, because these endpoints are only defined in the nonrandom subgroup of survivors. We will therefore analyze long-term outcomes among survivors using a method that corrects for covariate imbalance due to differential causes of mortality in each study arm. This potential bias will be corrected by estimating the survivor average causal effect, as per Hayden and colleagues (44), which weights each participant's outcome by the estimated probability of survival on the other treatment. These probabilities are estimated from the observed covariates using logistic regression under the assumption that all relevant confounders have been measured.

Table 5. Randomization, blinding or masking, and statistical methods

CONSORT	ROSE
Randomization	
Sequence generation	Patient-level, permuted block design Stratified by institution Randomized equally to each study arm
Allocation concealment	Central Web-based randomization, accessible 24 h/d
Implementation	Local center staff enroll patients via Web-based randomization system Web-based system then assigns patients to trial arm, based on computer generated allocation sequence
Blinding	Statistical analysis and long-term outcome assessment staff are blinded to study arm Aggregate outcome data restricted to unblinded statistician and data safety monitoring board
Statistical methods	Intention to treat Primary data analysis, including sub-group analyses, to be carried out according to pre-established analysis plan

Definition of abbreviations: CONSORT = Consolidated Standards of Reporting Trials; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade.

Discussion

We wrestled with four key design challenges. We made decisions based on previous research, an iterative consensus model when data were less rigorous, and internal surveys of existing practice to assess feasibility and inform design. We detail these challenges and decisions subsequently here.

Table 6. Key design differences between the ACURASYS and ROSE trials

Design element	ACURASYS	ROSE	Rationale
Hypoxemia inclusion criterion	$Pa_{O_2}/FI_{O_2} < 150$ on PEEP ≥ 5	$Pa_{O_2}/FI_{O_2} < 150$ on PEEP ≥ 8, or if arterial blood gas unavailable, equivalent Sp_{O_2}/FI_{O_2}	Pa_{O_2}/FI_{O_2} imputation from Sp_{O_2}/FI_{O_2} allows enrollment when arterial blood gas unavailable
PEEP	Lower PEEP (27)	Higher PEEP (13, 14, 28, 30)	Mitigate differential PEEP between arms, limit atelectrauma, unknown if neuromuscular blockade, beneficial over higher PEEP alone; higher PEEP may be optimal in moderate-severe ARDS (45)
Blinding	Yes	No	Neuromuscular blockade easily identifiable
Sedation, control arm	Deep	Light	Light sedation currently universally recommended, in absence of specific indication; deep sedation may be harmful (6–8)
Sample size	340	1,408	ROSE powered for 1/2 the effect size ACURASYS assumed
Long-term outcomes	None	3-, 6-, and 12-mo phone interviews	Critical illness and interventions can have long-term consequences

Definition of abbreviations: ACURASYS = Acute Respiratory Distress Syndrome et Curarisation Systematique; ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; ROSE = Reevaluation of Systemic Early Neuromuscular Blockade; Sp_{O_2} = oxyhemoglobin percent saturation measured with pulse oximetry.

First, we sought to develop a protocol that would both fulfill our study objectives and be feasible to deploy. In November 2014, we surveyed PETAL hospitals to determine neuromuscular blockade and sedation practices, their ability to randomize into ROSE, and proning use. Only one reported routinely (80–100% of patients) using neuromuscular blockade as per ACURASYS. All but two reported ability to randomize a majority of qualifying patients, and all reported ability to follow a specific neuromuscular blockade and sedation protocol in an intervention group. Regarding control group design, respondents expected baseline low neuromuscular blockade use in control, and that they could encourage low use of such. Regarding proning, half reported almost never doing so, and only two reported routine use, with the remainder reporting intermittent use with wide variation. Hospitals also reported commonly waiting 12–24 hours to prone, and the feasibility of proning without neuromuscular blockade. Based on these results, we believed our design feasible, would result in separation of neuromuscular blockade use between arms, and that proning would minimally confound results.

Second, choice of sedation depth in control was challenging. Deep sedation is clinically entrained with neuromuscular blockade to prevent paralysis recall. However, ACURASYS protocolized deep sedation in both groups. We considered this approach, which would have eliminated sedation as a potential confounder. However, excess sedation has been associated with harm (5), and our internal survey found that, in the absence of neuromuscular blockade, 75% of PETAL hospitals titrated to light sedation or to avoid ventilator dyssynchrony, with only five providing deep sedation as a usual goal. Moreover, light sedation is universally recommended when neuromuscular blockade is not used and ventilator dyssynchrony, respiratory distress, or other specific indications are absent (6–8). We therefore chose a control arm design consistent with current thinking and practice for sedation—light sedation in the absence of specific indications in control, and entrained deep sedation while under neuromuscular blockade in intervention.

Third, emphasizing early treatment creates complexities in both enrollment criteria and protocol execution, not seen in past ARDSNet and other ICU-based trials, but common in ED-based trials. Defining confirmed and established hypoxemia early in a patient's course was complicated by less-frequent arterial blood gas use in the ED versus most ICUs (17–19), and potentially transient hypoxemia immediately after intubation. However, our overarching hypothesis as a Network is that early intervention improves outcomes, and our charge is to test this hypothesis. We therefore crafted criteria to allow early enrollment while ensuring true hypoxemia.

For protocol execution, initiating deep sedation, neuromuscular blockade, and high PEEP can cause hypotension, and many patients with moderate to severe ARDS will have hemodynamic instability, especially early in their course. As our goal is to provide definitive guidance in exactly such patients, we chose not to exclude or significantly delay enrollment of hemodynamically unstable patients, as doing so would diminish the clinical relevance of our results, and challenge our Network charge to test early treatment. Furthermore, in routine clinical use, neuromuscular blockade is not delayed for hemodynamic instability. Its use is instead often accelerated in the sickest patients to facilitate acute control of pathophysiology. Therefore, with the DSMB, we took several measures to both mitigate risk and facilitate early protocol execution. We protocolize step-wise initiation of startup procedures and gradual PEEP uptitration, wait at least 6 hours after CPR before considering enrollment, mandate PETAL investigator or designee determination of hemodynamic appropriateness for high PEEP, and allow for delay in high-PEEP administration for hypotension and other physiologic concerns.

Lastly, we chose to protocolize high PEEP in all participants for the following reasons. First, to mitigate the possibility of

differential PEEP use between arms. Second, a presumptive physiologic benefit of neuromuscular blockade is reduction of atelectrauma, barotrauma, volutrauma, and alveolar expansion heterogeneity. High PEEP also reduces atelectrauma and alveolar expansion heterogeneity. It is unknown if neuromuscular blockade adds additional protection over high PEEP alone. Third, trials should test novel interventions on a background of "best care." Secondary analyses, including a patient-level meta-analysis of three trials, suggest that high PEEP improves survival in patients with ARDS with greater hypoxemia (45).

Conclusions

ROSE will provide definitive early neuromuscular blockade data for future patients with ARDS by providing a CONSORT-adherent design with large sample size, background care consistent with current best practice, and extensive long-term outcomes. Our multidisciplinary approach to trial design may be of use to other trials of acute illness. ■

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