Reevaluation Of Systemic Early neuromuscular blockade

Statistical Analysis Plan

ACRONYM: ***ROSE***

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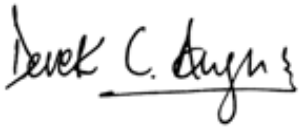

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Introduction

The following document is the Statistical Analysis Plan for the ROSE Study. It describes the study and the statistical methods used to analyze the primary and secondary outcomes in the study. Appendix A is a list of all variables that will be analyzed in the study along with their classification, and analysis method. Appendix B is the definition of all derived and composite variables, and the data imputation rules for all variables where imputation is used.

1. Trial Summary

1.1 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. 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) 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.

1.2 Inclusion Criteria

1. Age $\geq$ 18 years
2. Presence of all of the following conditions for $\leq$ 48 hours
   i. (I) PaO2/FiO2 < 150 with PEEP $\geq$ 8 cm H2O.[a,b,c]

      OR, IF ABG NOT AVAILABLE

      SpO2/FiO2 ratio that is equivalent to a PaO2/FiO2 < 150 with PEEP $\geq$ 8 cm H2O (Appendix A1), and a confirmatory SpO2/FiO2 ratio between 1-6 hours after the initial Sp02/Fi02 ratio determination. [c,d]
   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)

[a] If altitude >1000m, then PaO2/FiO2 < 150 x (PB/760).
[b] These inclusion criteria ensure a non-transient, established hypoxia that persists despite elevated PEEP and time. Initial, post-intubation, PEEP is typically < 8 cm H2O.
[c] The qualifying PaO2/FiO2 or the SpO2/FiO2 must be from intubated patients receiving at least 8 cm H2O PEEP.
d. When hypoxia is documented using pulse oximetry, a confirmatory SpO2/FiO2 ratio is required to further establish persistent hypoxia. Qualifying SpO2/FiO2 must use SpO2 values less than or equal to 96% Qualifying SpO2 must be measured at least 10 minutes after any change to FiO2.

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 SpO2/FiO2 (not the confirmatory SpO2/FiO2) is used determine this time window.

1.3 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 PaCO2 > 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 ≥ 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. PaO2/FiO2 (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

1.4 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.

1.5 Efficacy

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

1. Secondary Outcomes:

    - ICU Acquired Weakness
    - IL-6 levels (plasma)
    - 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
    - Physiologic measures
    - Long term outcome assessments
    - Use of rescue procedures
    - Paralysis recall, in-hospital
    - Supraventricular tachycardia and new onset atrial fibrillation

1.6 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.

2. Data Analysis Plan

2.1 Study Population

There is only one study population. All analyses will be by intention to treat

2.2 Primary Outcome

The primary outcome is intention to treat 90 day all cause in-hospital mortality, where in-hospital includes study hospital and LTAC. Patients who are discharged home (defined as residence prior to admission) prior to day 90 will be assumed to be alive at day 90. If the study does not cross a stopping boundary all patients will be followed for 90 days and the data can be analyzed using Pearson's chi-square test. However, at each interim analysis it is necessary to take into account patients who are still in the hospital with less than 90 days of 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. The 90 mortality estimates in the two treatment groups will be compared by a Z-test using Greenwood's standard error [1].

The number of interim looks and stopping boundaries are given in the protocol. At each interim look the stopping boundaries will be updated using SAS PROC SEQTEST (SAS Institute Inc.,

Cary, NC, USA.) with the information time defined by the Cutler and Ederer effective sample size [2].

The hypothesis regarding the primary outcome is a two-sided superiority hypothesis. The overall type one error is a two sided p-value of 0.05 corrected for the group sequential design as described in the protocol.

2.3 Analysis Methods for: Secondary Outcomes, Descriptive Variables, Safety Outcomes, Patient Characteristics

Continuous secondary outcomes will be compared between treatment groups using a t-test. Ordinal secondary outcomes (defined as outcomes with ordinal levels such as none, mild, moderate…) will be compared between groups using the Cochran-Mantel-Haenszel ANOVA (row mean score) test. Categorical secondary outcomes will be compared between treatment groups using a Chi-square or Fisher's exact test as appropriate to the sparseness of the data**.** All tests will use a two sided p=0.05 significance level. There will be no correction for multiple comparison.

2.4 On Study Variables

Variables that are measured daily, such as fluid balance, will be compared between treatment groups on each study day that they are measured.

2.5 Adverse Events

Adverse events will be analyzed using weighted Poisson regression with non-serious events weighted by one and serious events weighted by two. Events rather than patients will be the unit of analysis. Adverse events will be grouped and analyzed separately by MeDRA system organ classes, and MedDRA preferred term.

2.6 Subgroup Analysis

Three statistical tests will be performed for each subgroup. The treatment difference in the subgroup, the treatment difference for patients not in the subgroup and a test for interaction of subgroup status and treatment. The following are the planned subgroup analysis:

1. The primary outcome will be compared between treatment groups in the cohort of patients with pre-randomization PaO2/FIO2 < 120 and in the cohort of patients with pre-randomization PaO2/FIO2 ≥ 120.
2. Time from meeting ARDS severity criteria for study enrollment to randomization divided into two groups using the median value**.**
3. We will do a subgroup analysis using *routine use of NMB* in the study hospital as a grouping criterion. We will rank hospitals in terms of the number of sole exclusions for prior NMB use divided by the hospital's total enrollment. We will then form three roughly equal sized patient subgroups, based on the rank of their treating hospital.
4. We will conduct the required subgroup analysis of groups defined by race, ethnicity and gender.

2.7 Missing Data

Analysis is based on all available data with no imputation of missing data with a few rare exceptions which are noted in Appendix B. All our proposed analyses are valid under Missing at Random(MAR) data.

2.8 Long Term Follow Up Data

Six month and one year survival, for each treatment group, will be calculated using a multistate model. Patients will be classified in terms of the following states, 1-Study Hospital, 2-Other Hospital,3-Home 4-Dead, with possible transitions of 1-2, 1-3,1-4,2-3,2-4. The time duration of each transition that is known will be calculated. Then this model will be used to estimate the 6 and 12 month survival, and it's standard error for each treatment group separately[3]. The test of a treatment effect will then be the difference in the survival estimates divided by the pooled standard error. The method of estimation is based on the multiplication of probabilities. For instance, suppose a patient went home at 100 days but only has 120 follow up at the time of analysis or is lost to follow up at 120 days. Then the probability of death for this patient is probability of a transition from 3 to 4, for a patient who has been home for 20 days.

The primary analysis of continuous and ordinal follow up data on patient's functional status will be a comparison of the distribution of these data using the methods described in the analysis methods section 2,3. The primary issue with this choice of analysis is that the treatment difference is difficult to interpret if there is a mortality difference. In that case we will conduct several sensitivity analyses described below.

The problem is that we are measuring follow up variables, for instance the Euro QOL, denoted here as QOL, in some patients on the better treatment who would have died on the worse treatment. When there is a survival difference the simple comparison does not measure the potential harm or benefit of the intervention on QOL. What we seek to estimate, is the *survival average causal effect*, defined as the difference in QOL among patients who would have survived both treatments. We will assume that patients who would survive on the worse treatment will also survive on the better one. In that case, the mean value of QOL on the worse treatment among patients who would have survived on both treatments is just the ordinary mean of QOL on that treatment.

To estimate the mean value of QOL on the best treatment among patients who would have survived both treatments, we need to take a weighted mean of QOL with weights equal to the probability of survival on the worst treatment given the value of QOL on the best treatment. Unfortunately, these weights cannot be estimated, but one can look at the difference in QOL on the two treatments as a function of how the weights are assigned in a sensitivity analysis. Note that our primary analysis assumes all these weights are equal.

We propose three sensitivity analysis of these variables ascertained among survivors. The first assumes that all the patients with the worst values of QOL would have died on the worst treatment. In terms of weights, all the weights are one except for the *m* worst QOL values where *m* is the difference of mortality rates on the two treatments. This was suggested by Permutt, T. and Li, F [4].

The second method is to assume weights of the form exp(b Y), where Y is QOL, and then vary b, note that b can be interpreted as the relative effect on mortality per unit Y. Finally, we can use weights based on patient covariates, using the model specified in the ALVEOLI Trial [5] to estimate the weights. For the first two analysis significance, will be tested by calculating the standard error of each mean. For the last, we can use the methods described by Hayden, Pauler and Schoenfeld [6]. In addition, in order to give a graphical representation of these data, one can used these methods to estimate the distribution, for instance the probability that Y<K in in the better treatment which is the weighted mean of the indicator functions I(Y<K) weighted by the same weights described above. We will assume that if we are missing an observation for reasons other than death it is missing at random(MAR) if the proportion of patients missing in this way is high we will conduct a sensitivity analysis of the MAR approach.

2.9 Treatment for Non-Compliance

For the primary endpoint, and for secondary end points that are significantly affected by treatment assignment we will estimate the causal effect of the actual treatment given using an instrumental variable approach [7].

2.10 Heterogeniety of Treatment Effects

We will use a model fit on the ARMA 6ml/kg data and previously published [5] to develop a risk score for each patient in the study. The variables used were age, APACHE, pplat, missing pplat, number of organ failures, hospital days prior to enrollment, and AADO2**.** Then as a statistical test we will fit a logistic model with terms for treatment, risk score and a treatment risk score interaction. The significance of the interaction term will test for Heterogeneriety of Treatment Effects. In addition as a graphical display of the data we will divide the patients into 10 equal sized group by risk score and plot the mortality difference as a function of risk score group.

Appendix:

Appendix A1: Outcome Variables

Variable	Category	Scale	Method
All-cause mortality prior to discharge home before day 90	Primary Outcome	Binary	Wald-test from 90 day KM estimate
ICU acquired weakness	Secondary Outcome	Binary	Monte Carlo Fisher's Exact Test
IL-6 levels (plasma)	Secondary Outcome	Continuous	T-test
Hospital mortality to day 28	Secondary Outcome	Binary	Chi-square Test
Ventilator free days to day 28	Secondary Outcome	Continuous	T-test
Organ failure free days to day 28	Secondary Outcome	Continuous	T-test
ICU-free days at day 28	Secondary Outcome	Continuous	T-test
Hospital-free days at day 28	Secondary Outcome	Continuous	T-test
Oxygenation Index on study days 1-4,7 PaO2 / FiO2 ratio on study days 1-4, 7 Level of PEEP on study days 1-4, 7 Plateau pressure on study day 1-4, 7 Development of pneumothorax through day 7	Physiologic measure	Continuous Continuous Continuous Continuous Binary	T-test T-test T-test T-test Fisher's Exact Test
Disability: using Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities of Daily Living Scale (IADL)	Long term outcome assessments	Binary	Chi-square Test

plus two additional Nagi items			
Health-Related Quality of Life (including utilities): EuroQol (EQ-5D-5L)		Continuous	T-test
Self-rated health: 1 standard item		Continuous	T-test
Pain-interference: 1 standard item		Continuous	T-test
Post-traumatic Stress-like Symptoms: Post-Traumatic Stress Symptoms (PTSS-14)		Binary (Part B Score >= 45)	Chi-square Test
Cognitive function: Montreal Cognitive Assessment (MoCA-Blind)		Continuous Binary (< 26)	T-test Chi-square Test
Via proxy, the Alzheimer's Disease 8 (AD8)		Continuous	T-test
Subsequent return to work, hospital and ED use, and location of residence		Categorical	Fisher's Exact Test
Use of rescue procedures	Safety	Binary	Fisher's Exact Test

Paralysis recall, in-hospital	Safety	Binary	Fisher's Exact Test
Supraventricular tachycardia (SVT) or new onset atrial fibrillation	Safety	Binary	Fisher's Exact Test

Appendix A2: Reference Measurements

Variable	Category	Scale	Method
Time and dose of loading dose		Continuous	Descriptive
Time of initiation of cisatracurium infusion		Continuous	Descriptive
Reason and duration of infusion hold during first 48 hours		Binary>=48.5 hours Continuous	Descriptive
Total dose of cisatricurium infusion during first 96 hours		Continuous	Descriptive
Name and total dose of other NMB during first 96 hours		Dose, Continuous	Descriptive
Additional NMB administered after 96 hours (yes/no)		Binary	Descriptive
Name and total dose of any NMB used in the first 96 hours after randomization (Control Arm)		Binary (Yes/ No) Continuous (Total Dose)	Descriptive
Additional NMB administered after 96 hours (yes/no) (Control Arm)		Binary (Yes/ No) Continuous (Total Dose)	Descriptive

If receiving positive pressure ventilation: Ventilator mode		Categorical, Days 1-4 & 7	Monte Carlo Fisher's Exact Test
If receiving positive pressure ventilation: set rate actual rate minute ventilation tidal volume FiO_2 PEEP I:E ratio, plateau, peak, mean airway pressures set peak flow, set inspiratory time		Continuous, Days 1-4 & 7	T-Test
PaO_2, $PaCO_2$, pH, and SpO_2		Continuous, Days 1-4 & 7	T-Test
Serum electrolytes and glucose		Continuous, Days 1-4 & 7	T-Test
Intravenous sedatives Intravenous opioids Enteral or intravenous corticosteroids		Binary, Days 1-4 & 7	Chi-Square Test
Sedation score: If RASS < -1 (or Riker < 3, Ramsay > 3), and sedation given, list reason given		Reasons (Categorical) Scale Used (Categorical) Light/ Deep/ Agitation (Categorical) Mean score (Continuous)	Chi-square Test Chi-square Test Chi-square Test T-test
Was a sedation interruption performed? Y/N		Binary Daily	Chi-square Test

Fluid intake and output/CVP if available		Continuous	T-Test
ICU Mobility Scale	Safety	Binary (Able to sit at edge of bed or greater)	Fisher's Exact Test
Manual Muscle Testing	Safety	Continuous	T-test

Appendix A3: Derived Outcome Variables

Primary Outcome

The primary outcome is intention to treat 90 day all cause in-hospital mortality, where in-hospital includes study hospital and LTAC. Patients who are discharged home (defined as residence prior to admission) prior to day 90 will be assumed to be alive at day 90. It may be necessary to account for patients who are still in the hospital with less than 90 days of 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.

If a patient has no data entered for the primary outcome then a censoring date is determined from the maximum date or study day on the available ACTIVITY, SOFA, VENT, MMT, TERMINATION, ICU History, Study Initiation and Drug Dosage, Protocol Deviation, AE, and BRICE forms.

ICU acquired weakness

Patients will be defined as having ICU acquired weakness if their Medical Research Council (MRC) MMT score is < 48 (or mean MRC < 4 for each muscle group tested).

Hospital mortality to day 28

Death prior to discharge alive from study hospital will be counted as hospital mortality. Patients whose final status is unknown but who are known to be alive on study day 28 based on known event dates on the termination form will be counted as alive. Patients with insufficient follow up to determine this outcome will be treated as missing data.

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.

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. 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.

Variables	SOFA Score				
	0	1	2	3	4
Coagulation Platelets x $10^3/\mu L$	>150	</=150	</=100	</=50	</=20
Liver Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>11.9
Cardiovascular 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‡
Renal 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

*Norepiindicates 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.

We treat post-ICU SOFA as normal (i.e. defining organ dysfunction as abnormal SOFA in an ICU); post-ICU means getting out and staying out of ICU; patients are still at risk and have SOFA scores in intervals between ICU readmissions.

Carry forward until home date, death date, last known date in ICU+1, or day29, whichever comes first; patient status decides organ failure free if both status information and SOFA data are available.

We carry last observation forward for any missing data except baseline P/F. Carry forward vasopressors yes/no if taking any vasopressors and missing y/n. Carry forward vasopressor doses if taking this drug and missing dose.

If a patient has missing data at baseline, then the patient would have missing SOFA components, but the total will be the sum of available components scores instead of missing.

Notes: LOCF carries forward each sofa variable rather than carrying forward the computed scores.

ICU-free days at day 28

Patient will be followed until death, study hospital discharge or study 28, whichever comes first. Any day a patient is alive and out of ICU will be scored as an ICU-free day. There is no penalty for readmission.

Hospital-free days at day 28

Hospital free days are counted from hospital discharge through day 28. A patient who is discharged from the study hospital on day 28 is assigned one hospital free day. A patient who is discharged from the study hospital after day 28 is assigned zero hospital free days. A patient who dies prior to day 29 is assigned zero hospital free days.

Paralysis recall, in-hospital

Paralysis recall assessment will be monitored once during hospitalization in all patients, using a modified Brice questionnaire. Paralysis recall will be counted if a patient answered “Yes” to “Do you remember anything between going to sleep and waking up?” and "unable to move or breathe”. Paralysis recall can be indicated in both AE and Brice forms. We gather information from both places and treat missing as “NO” if a patient has an open BRICE form.

Long Term Outcomes

Disability: using Katz Activities of Daily Living (ADL)/Lawton Instrumental Activities of Daily Living Scale (IADL) plus two additional Nagi items

ADL/IADL assessments are administered at baseline, months 3, 6 and 12. 2 additional NAGI items were collected at months 3, 6, and 12. The total score is a summation of the all the times. Possible 8 maximum points at baseline and 10 maximum points at follow up. Any missing items are allotted 0 points.

Health-Related Quality of Life (including utilities): EuroQol (EQ-5D-5L)

EQ-5D-5L assessment is given to either the subject or the proxy at baseline, month 3, month 6 and month 12. Scores are calculated by mapping the 5-digit code generated from the answers to the U.S. EQ-5D-5L lookup table. Any missing items will result in a missing score.

Self-rated health: 1 standard item

Assessed at months 3, 6, and 12 and only if the patient is available.

Pain-interference: 1 standard item

Assessed at months 3, 6, and 12 and only if the patient is available.

Post-traumatic Stress-like Symptoms: Post-Traumatic Stress Symptoms (PTSS-14)

Assessed at months 3, 6, and 12 by the subject or the proxy. Part A score was calculated as a sum of all the questions answered as “Yes”. The part B score was a sum of all the answers (rated from 1 to 7) with a maximum score ranging from 14 to 98.

Cognitive function: Montreal Cognitive Assessment (MoCA-Blind)

MoCA-blind is assessed at 3, 6 and 12 months post-randomization if the subject is available. The 22-point score for the MoCA-blind is scaled up to 30 points. If information regarding a high school degree (>12 years of education) is missing, assume subject has a high school degree.

The additional points allotted to <12 years of education is added after converting to the 30-point scale. If any question is incomplete, then the patient is not given a total MoCA score.

Via proxy, the Alzheimer's Disease 8 (AD8)

AD8 is assessed at 3, 6, and 12 months through the proxy if the subject is unable to be contacted. Total score is a sum of all the AD8 items. Missing answers allotted 0 points.

Subsequent return to work, hospital and ED use, and location of residence

Collected at months 3, 6, and 12 from the subject or proxy survey (if subject is unavailable).

Additional Derived Variables

Barotrauma

Barotrauma includes pneumothorax and pneumomediastinum, which can be indicated in both AE and Termination forms. We gather the information from both places and treat missing as "NO".

Intervention Arm: Total dose of cisatricurium infusion during first and second 48 hours

Total dose was calculated from cisatricurium infusion duration times rate plus boluses plus additional doses.

Intervention Arm: Total dose of other NMB during first and second 48 hours

Total dose was calculated from infusion duration times rate plus boluses plus additional doses of any neuromuscular blocker.

Control Arm: Total dose of any NMB used in the first and second 48 hours after randomization

Total dose was calculated as the sum of all doses of any neuromuscular blocker.

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