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Protocolized Post-Extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Clinical Trial

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Protocolized Post-Extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Clinical Trial

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ABSTRACT:

Introduction: Following extubation from invasive mechanical ventilation, nearly 1 in 7 critically ill adults requires reintubation. Reintubation is independently associated with increased mortality. Post-extubation respiratory support (non-invasive ventilation or high flow nasal cannula applied at the time of extubation) has been reported in small-to-moderate sized trials to reduce reintubation rates among hypercapnic patients, high-risk patients without hypercapnia, and low-risk patients without hypercapnia. It is unknown whether protocolized provision of post-extubation respiratory support to every patient undergoing extubation would reduce the overall reintubation rate, compared to usual care.

Methods and Analysis: The Protocolized Post-Extubation Respiratory Support (PROPER) trial is a pragmatic, cluster-crossover trial being conducted between October 1, 2017 and March 31, 2019 in the medical intensive care unit of Vanderbilt University Medical Center. PROPER compares usual care versus protocolized post-extubation respiratory support (a respiratory therapist-driven protocol that advises the provision of non-invasive ventilation or high flow nasal cannula based on patient characteristics). For the duration of the trial, the unit is divided into two clusters. One cluster receives protocolized support and the other receives usual care. Each cluster crosses over between treatment group assignments every three months. All adults undergoing extubation from invasive mechanical ventilation are enrolled except those who received less than 12 hours of mechanical ventilation, have “Do Not Intubate” orders, or have been previously reintubated during the hospitalization. The anticipated enrollment is approximately 630 patients. The primary outcome is reintubation within 96 hours of extubation.

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Ethics and dissemination: The trial was approved by the Vanderbilt Institutional Review Board. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. The trial was registered with ClinicalTrials.gov (NCT03288311) on September 20, 2017, prior to the enrollment of the first patient on October 1, 2017.

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ARTICLE SUMMARY

Strengths and limitations of this study

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between protocolized post-extubation respiratory support and usual care following extubation of critically ill adults
- The broad inclusion criteria will increase generalizability and the moderately large size will provide the opportunity to examine subgroups of interest
- The trial is being conducted at a single center
- The nature of the study intervention does not allow blinding

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INTRODUCTION

Up to 40% of patients admitted to an intensive care unit require invasive mechanical ventilation [1]. Protocols for low tidal volume ventilation, daily spontaneous awakening trials, and daily spontaneous breathing trials have considerably shortened the duration of invasive mechanical ventilation and improved outcomes for these patients [2,3]. Despite these improvements, the period of time following extubation remains high risk, with rates of reintubation between 10 and 15% in the first 96 hours after extubation [4–8]. Reintubation is associated with increased rates of nosocomial infection [9] and is independently associated with an increased risk of death [7,10,11]. Despite significant improvements in the management of patients receiving invasive mechanical ventilation, the rate of reintubation has not changed meaningfully over the last 20 years [12–14]. The only post-extubation therapy suggested to potentially reduce the rate of reintubation is respiratory support with either non-invasive ventilation (NIV) or high flow nasal cannula (HFNC).

For patients with respiratory failure from an acute exacerbation of chronic obstructive pulmonary disease (COPD) [15] and cardiogenic pulmonary edema [16], NIV can prevent the need for the initial intubation, improve the safety for those progressing to intubation [17], and decrease mortality. Among patients who experience respiratory failure after extubation, however, the data have been disappointing. “Rescue” NIV, applied when a patient develops respiratory failure hours or days after extubation, delays the time to reintubation and may be associated with an increase in ICU mortality [18,19]. Post-extubation respiratory support with NIV, started at the time of extubation

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as prevention, not as treatment for recurrent respiratory failure after extubation, has had more promising initial results.

In unselected ICU populations, several trials failed to demonstrate significant benefit of post-extubation respiratory support with NIV [20,21], but success has been observed in targeted sub-populations, specifically those presumed to be at high risk. These trials have defined risk of re-intubation using various criteria, including duration of ventilation, age greater than 65, Acute Physiology and Chronic Health Evaluation (APACHE) II score exceeding 12 on the day of extubation, congestive heart failure, hypercapnia, weak cough, upper airway stridor, and co-morbidities. For these high-risk patients, post-extubation support with NIV may decrease the rate of reintubation [5,22]. For patients who are hypercapnic during a spontaneous breathing trial, post-extubation support with NIV appears to reduce reintubation and improve 90-day mortality [23]. Recent national guidelines for management following extubation recommend post-extubation respiratory support with NIV for patients at high risk of reintubation [3]. While “high-risk” was not defined in these guidelines, it was suggested that the criteria may include hypercapnia, COPD, congestive heart failure, or other serious comorbidities.

HFNC, a device capable of providing 100% oxygen at flow rates that exceed peak inspiratory flow rates, decreases work of breathing, provides a low level of continuous positive airway pressure, washes out dead space, and improves patient comfort and secretion management [24–28]. HFNC may decrease mortality in non-intubated patients with hypoxemic respiratory failure [29]. In non-hypercapnic patients undergoing extubation in a medical ICU, post-extubation respiratory support with HFNC, started at the time of extubation and continued for 24 to 48 hours, has been reported to reduce

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the rate of reintubation in high risk patients, low risk patients, and a general population of ICU patients [30–32].

In combination, these studies raise the hypothesis that all critically ill adults undergoing extubation from invasive mechanical ventilation might benefit from some form of post-extubation respiratory support, either NIV or HFNC. Concerns remain, however, that results of recent studies may not generalize to the broader population of patients extubated in intensive care units outside of the settings in which the studies were conducted. Rates of reintubation in reported trials range from 14.4% in "low risk" patients [31] to 19.1% for "high-risk" patients [32], considerably higher than the 10% reintubation rate cited by large national registries [8]. Use of any form of post-extubation respiratory support during routine clinical practice remains uncommon at many centers.

Given the potential benefits for post-extubation respiratory support for multiple patient populations, the low uptake in current usual care in many settings, and concerns about generalizability from prior explanatory trials, an effectiveness trial among critically ill adults undergoing extubation from mechanical ventilation is warranted. We designed the Protocolized Post-Extubation Respiratory Support (PROPER) Trial to determine the overall effect of a protocolized approach to post-extubation support (protocolized support) on reintubation among a broad population of critically ill adults receiving invasive mechanical ventilation.

METHODS AND ANALYSIS

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This manuscript was prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Fig. 1; SPIRIT checklist in online supplement, section 1). [33]

Study Design

The Protocolized Post-Extubation Respiratory Support (PROPER) Trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted between October 1, 2017 and March 31, 2019 in the medical intensive care unit of Vanderbilt University Medical Center in Nashville, TN, USA. PROPER compares the rate of reintubation within 96 hours of extubation between patients provided protocolized support (a respiratory therapist-driven protocol that advises the provision of non-invasive ventilation or high flow nasal cannula based on patient characteristics), to usual care (where post-extubation management is at the discretion of treating clinicians). Consistent with the concept of a pragmatic clinical trial [34], the eligibility criteria are broad and the study procedures are embedded into routine care and executed by clinical personnel. The goal is to evaluate the effectiveness of protocolized support when applied to “real-world” practice. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB 170650). The trial is investigator-initiated with funding provided by the Vanderbilt Institute for Clinical and Translational Research through a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences (UL1 TR000445). The trial protocol was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifier: NCT03288311).

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Patient and Public Involvement

Patients and the public were not involved in identifying the research question or the design of the study. The results of the study will be disseminated to the public at the completion of the trial.

Study Site and Population

The trial is being conducted in the 35-bed medical intensive care unit at Vanderbilt University Medical Center.

The inclusion criteria are:

1. Patient is located in a participating unit
2. Patient undergoing extubation from mechanical ventilation
3. Patient has been receiving mechanical ventilation for at least 12 hours
4. Age ≥ 18 years old

The exclusion criteria for the trial are:

1. Patient is receiving ventilation via a tracheostomy
2. Patient is being extubated to comfort measures or has "Do Not Reintubate" order in place at the time of extubation
3. Patient has required reintubation after a prior attempt at extubation during this hospitalization
4. Unplanned or self-extubation, where immediate reintubation is deemed necessary by the clinical team

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The time of enrollment is considered to be the time of extubation. A patient flow diagram describing the number of patients screened for the trial (all patients who received invasive mechanical ventilation in the study unit), the number who did not meet inclusion criteria (e.g. died before extubation), and the number who were excluded, will be provided in the manuscript reporting the results of the trial (template of flow diagram is provided as supplementary Figure S1).

Randomization and Treatment Allocation

The medical intensive care unit is divided into two geographic clusters (the front hallway and the back hallway), each of which is staffed by a respiratory therapist. During each three-month block of the study, patients in one cluster receive protocolized support delivered by one respiratory therapist while patients in the other cluster receive usual care delivered by another respiratory therapist. The assigned treatment group alternates every three months over the course of the trial so that each cluster will experience an equal number of months of protocolized support and usual care (Fig. 2). A single randomization was performed to determine which cluster would receive protocolized support during the first block.

The rationale for dividing the study unit into two clusters by geographic location of the beds was so that all patients assigned to a given respiratory therapist's cluster will receive the same treatment. A respiratory therapist caring for patients in the cluster assigned to protocolized support receives education on post-extubation respiratory support and structured feedback on his or her performance at the practice level. Assigning some patients cared for by a respiratory therapist protocolized support and

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some patients to usual care was expected to introduce contamination because the respiratory therapist would be more likely to deliver post-extubation respiratory support to patients in their care assigned to the usual care arm. Given the nature of the intervention, patients, treating clinicians, and investigators are not blinded to group assignment.

Study Interventions

Protocolized Support

Patients in the protocolized support group are assigned to receive post-extubation respiratory support starting at the time of extubation. The choice between non-invasive ventilation and high-flow nasal cannula is made using a standardized protocol for post-extubation respiratory support and is implemented by the patient's respiratory therapist (Fig. 3).

Based on the results of previous trials, the protocol for post-extubation respiratory support recommends NIV immediately upon extubation via a full facemask for all patients in the protocolized support group who have suspected hypercapnia [22,23] or are intubated for an acute exacerbation of COPD [35]. Because arterial blood gases are not routinely performed during spontaneous breathing trials in the study unit, suspected hypercapnia is defined as known chronic hypercapnic respiratory failure, known obesity hypoventilation syndrome, or an arterial blood gas with a partial pressure of arterial carbon dioxide (PaCO2) >45 mmHg on a spontaneous breathing trial. Recommended initial settings for NIV include initiation with an initial inspiratory positive airway pressure of 14 cmH_2O, an expiratory positive airway pressure of 8 cmH_2O, and a

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backup respiratory rate of 12 breaths per minute. Settings are titrated to maintain a minute ventilation between 5.0 and 10.0 liters per minute and a respiratory rate below 30 breaths per minute, with a maximum inspiratory positive airway pressure of 20 cmH_2O. Inspired fraction of oxygen is titrated to maintain an oxygen saturation > 90% (Fig. S2). Removal of NIV for up to one hour at a time for patient comfort and to allow patients to eat or drink is encouraged and administration of sedatives to increase patient tolerance of NIV is discouraged. Protocol recommendations may be altered at the discretion of the respiratory therapist or the clinical team.

Given previous data suggesting that post-extubation support with HFNC may be superior to conventional oxygen in low-risk patients [31] and equivalent to NIV in non-hypercapnic high-risk patients [32], the protocol for post-extubation respiratory support recommends HFNC for all patients in the protocolized support group who were not intubated for an acute exacerbation of COPD and who do not have suspected hypercapnia. Additionally, HFNC is recommended for patients who have a contraindication to NIV (facial or cranial trauma or surgery, recent gastric or esophageal surgery, inability to protect the airway, active emesis or upper gastrointestinal bleeding, excessive amount of respiratory secretions, or lack of cooperation). Patients who are extubated to NIV but are unable to tolerate it may be transitioned to HFNC.

For patients in the protocolized support group without suspected hypercapnia or a COPD exacerbation, HFNC is initiated immediately upon extubation. Recommended initial settings for HFNC and titration and weaning parameters include initial flow rates of at least 40 liters per minute, adjustment of flow rates in increments of 5 liters per minute, titration to patient comfort and a respiratory rate less than 30, a maximum flow rate of

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60 liters per minute, and titration of the fraction of inspired oxygen to maintain an arterial oxygen saturation > 90% (Fig. S3).

Post-extubation respiratory support is provided from the time of extubation until 5AM on the day following extubation. At 5AM on the day following extubation, a respiratory therapist assesses for readiness for weaning from post-extubation respiratory support. This timing was designed to allow patients to transfer out of the ICU on the day following extubation if clinically appropriate. Based on timing of extubation during the year preceding this trial, patients are expected to receive a median of 17 hours of respiratory support, and no less than five hours of respiratory support prior to being evaluated for weaning.

If the patient meets weaning criteria (Fig S2, S3) at the time of their assessment, the device is removed and the patient may be initiated on conventional oxygen therapy through a nasal cannula or face mask if needed. Post-extubation respiratory support with NIV or HFNC may be continued at the discretion of the treating clinicians, in which case subsequent titration and weaning is determined by the treating clinicians. Post-extubation respiratory support may be discontinued prior to 5AM on the day following extubation if the patient is transferred out of the ICU, the patient declines further post-extubation respiratory support, or the treating clinicians determine that discontinuation is needed for the optimal care of the patient.

The decision to use HFNC or NIV as rescue treatment for post-extubation respiratory failure is made by treating clinicians and is prospectively recorded but is not encouraged. For patients in the protocolized support group, treating clinicians may decide to use invasive mechanical ventilation, NIV, HFNC, or conventional oxygen

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therapy at any time, regardless of group assignment, if felt to be needed for the safe care of the patient.

Usual Care

All aspects of post-extubation management for patients in the usual care arm are determined by treating clinicians. Treating clinicians may elect to use NIV or HFNC as post-extubation respiratory support for those patients they believe will benefit from these therapies. No guidance is provided by the study regarding patient selection, device selection, titration or weaning parameters, or timing of removal of support. In the study ICU in the year prior to the trial, 8.3% of patients received post-extubation respiratory support during routine clinical care; 7.1% received NIV and 1.2% received HFNC.

For patients in the usual care group, treating clinicians may decide to use invasive mechanical ventilation, NIV, HFNC, or conventional oxygen therapy at any time, regardless of group assignment, if felt to be needed for the optimal care of the patient.

Co-interventions

Study group assignment determines only the approach to post-extubation respiratory support. Treating clinicians determine all management prior to extubation, including the approach to sedation, timing of spontaneous breathing and awakening trials, and readiness for extubation. The study ICU has established clinical protocols for the care of patients receiving invasive mechanical ventilation including:

1. Critical Care Pain Observation Tool (CPOT score) [36]

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2. Daily spontaneous awakening trial (SAT) safety screen, SAT performance, spontaneous breathing trial (SBT) safety screen, and SBT performance [2]
3. Richmond Agitation and Sedation Scale (RASS score) [37,38]
4. Choice of analgesia and sedation
5. Confusion Assessment Method for the ICU (CAM-ICU) [39,40]
6. Early Mobility [41]

The clinical protocols used in the study unit can be found in the supplementary appendix.

Following extubation, all clinical care decisions, other than use of NIV and HFNC for post-extubation respiratory support until 5AM the day following extubation, are made by treating clinicians, including use of diuretics, intravenous fluids, antibiotics, corticosteroids, airway clearance measures, and breathing treatments.

Training

The protocols for initiation, titration, and weaning of NIV and HFNC were developed by consensus with local respiratory therapy leaders using best-practice recommendations from professional societies [3], protocols from prior randomized trials, and local protocols regarding the provision of non-invasive respiratory support. In addition to these materials, all respiratory therapists received a 30-minute lecture on the delivery of post-extubation respiratory support prior to caring for patients assigned to the protocolized support group. Ongoing education on post-extubation respiratory support is provided by study staff throughout the trial.

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Data Collection

Data are prospectively collected from the electronic health record by trained study personnel. Data are stored in a secure, online database [42]. Collected data include:

Characteristics: Age; gender; height; weight; body mass index; race; chronic comorbidities; indication for intubation; APACHE II score at ICU admission

Baseline (i.e. time of extubation): APACHE II score; length of mechanical ventilation; last known left ventricular ejection fraction; active medical problems; failure of more than one spontaneous breathing trial; last known Glasgow Coma Score [43]; last known Richmond Agitation and Sedation Score [37]; last known CAM-ICU score [39]; highest FiO2 delivered in the 6 hours prior to extubation; lowest oxygen saturation during a spontaneous breathing trial; highest respiratory rate in the 6 hours prior to extubation; highest respiratory rate during a spontaneous breathing trial; highest heart rate in the 6 hours prior to extubation; highest heart rate during a spontaneous breathing trial; use of vasopressors in the 6 hours prior to extubation; results of any arterial blood gas obtained during a spontaneous breathing trial.

Data from 0 to 96 hours: The need for reintubation within 96 hours; time to reintubation; indication for reintubation; presence of laryngeal edema requiring reintubation; amount of time spent receiving HFNC and NIV in the first 24 hours post-extubation; the amount of time spent receiving prophylactic post-extubation respiratory support from 0-96 hours post-extubation; the highest and lowest levels of respiratory support (flow rate; FiO2; IPAP; EPAP) at three time points

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(0-6, 6-12, and 12-24 hours post-extubation); the highest and lowest respiratory rate, heart rate, SaO2; and FiO2 at three timepoints (0-6, 6-12, and 12-24 hours post-extubation); the presence of delirium at any timepoint from 0-96 hours post-extubation (as determined by CAM-ICU score).

Clinical Outcomes: Reintubation between baseline and the first of either hospital discharge or 28-days; in-hospital mortality; time to death; ICU-free days and ventilator-free days in the 28 days after enrollment.

Primary Outcome

The primary outcome is reintubation in the 96 hours following enrollment. Reintubation is defined as placement of an endotracheal tube or tracheostomy tube in the trachea for any reason.

Death may be a competing event for the outcome of reintubation. Among the patients who would have met criteria for enrollment in the year prior to the trial, every patient who died within 96 hours of extubation experienced reintubation prior to death. In the event that any patient in the trial dies in the 96 hours following enrollment without experiencing reintubation, they will be classified in the primary analysis as having met the primary outcome. Patients who are discharged from the hospital before 96 hours following enrollment without having experienced reintubation will be classified as not meeting the primary outcome.

Any decision to reintubate will be made by the clinical team. Prior studies have attempted to protocolize the decision to reintubate [29,31,32]. Because the goal of the PROPER study is to evaluate the performance of protocolized support when applied to

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a broad population of critically ill adults in “real-world” practice, we deliberately deferred all decisions regarding management of post-extubation respiratory failure and reintubation to the clinical team with no involvement or guidance from the research team.

Secondary Outcome

The single, pre-specified, secondary outcome is the number of ICU-free days in the 28 days following enrollment. This is defined as the number of whole calendar days alive and not admitted to an intensive care unit beginning at midnight on the day of extubation to 28 days following enrollment. Patients who are never discharged from the intensive care unit will receive a value of 0. Patients who die before day 28 will receive a value of 0. For patients who return to an ICU and are subsequently discharged prior to day 28, ICU-free days will be counted as the number of whole calendar days from midnight on the day following the final ICU discharge to 28 days following enrollment. All data collection will be censored at the first of hospital discharge or 28 days.

Exploratory Outcomes

- All-cause in-hospital mortality
- Ventilator-free days in the 28 days following enrollment (defined in the online supplement)
- Time from enrollment to reintubation
- Indication for reintubation (respiratory indication, laryngeal edema, other)
- Delirium in the 96 hours following enrollment

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- Lowest SpO2/FiO2 ratio in the 24 hours following enrollment
- Highest respiratory rate in the 0-6 hours, 6-12 hours, and 12-24 hours following enrollment

Statistical Analysis and Reporting

Sample Size Estimation

Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment [44], the incidence of reintubation within 96 hours after extubation was 12.1%. Similar rates have been reported in previous observational studies of extubation in the ICU [6,7]. Prior randomized trials have reported that prophylactic post-extubation respiratory support with NIV may reduce the relative risk of reintubation by 49% to 66% in high risk patients [5,22], while post-extubation respiratory support with HFNC may reduce the relative risk of reintubation by 81% in high risk patients and 60% in low risk patients [30–32]. Based on the results of these prior randomized trials, we estimated that protocolized support would reduce the relative risk of reintubation by at least 55%. This is equivalent to an absolute risk reduction of 6.7%, from 12.1% in the usual care group to 5.4% in the protocolized support group.

Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, the intra-cluster correlation, intra-period correlation, and intra-cluster intra-period correlation for the primary outcome were all <0.001 assuming a cluster-crossover design with two clusters and three-month periods. Using PS version 3.1.2 with the above assumptions and a chi-squared test of the primary hypothesis with an alpha level of 0.05, we calculated that enrolling 566 patients (283 per group) would

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achieve at least 80% statistical power. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, 8.3% received post-extubation respiratory support during usual care. In order to account for loss of statistical power due to use of post-extubation respiratory support in the usual care group during the trial, we increased our sample size estimate by 10% to 623 patients. Based on data from the study ICU in the year prior to the trial, we anticipated that enrollment of at least 630 patients would require a study duration of 18 months.

Data and Safety Monitoring Board and Interim Analysis

For this 18-month, single-center study comparing a minimal risk intervention with usual care, a data and safety monitoring board was not appointed and an interim analysis is not planned.

Statistical Analysis Principles

All analyses will be conducted at the level of the individual patient during an individual hospitalization on an intent-to-treat fashion, unless otherwise specified. Continuous variables will be reported as median and IQR; categorical variables will be reported as frequencies and proportions. Given the cluster cross-over design, all comparisons between the protocolized post-extubation respiratory support group and the usual care group will take into account the cluster and period level correlations. With only one primary outcome and one secondary outcome, a two-sided p-value of 0.05 will be considered statistically significant.

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Comparison of primary outcome between groups

We will compare the binary primary outcome of reintubation within 96 hours between the protocolized support group and the usual care group. It is possible to estimate a marginal effect, which is interpreted as the population effect of implementing a general policy of post intubation ventilatory support, or a conditional effect, which is interpreted as the effect on an individual patient given the values of the covariates for that patient [45]. Since our intervention may be applied at both the unit level as a general policy, or at the patient level as an individual intervention, both may be of interest. We will use a generalized estimating equation (GEE) approach to estimate the marginal effect, and we will use a generalized linear mixed model with logit link function to estimate the conditional effect. Group assignment will be a fixed effect, and cluster and period will be included as random effects [46,47]. We will report both adjusted and unadjusted comparisons; for the purposes of declaring success on the primary endpoint, we will consider the unadjusted marginal effect.

Adjusted comparisons will include age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, chronic pulmonary disease, and respiratory rate on a spontaneous breathing trial. To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous covariates and the outcome.

Comparison of secondary outcome between groups

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The secondary outcome is the number of ICU-free days in the 28 days following enrollment. We will use a proportional odds model to compare this outcome between groups. As with analysis of the primary outcome, a generalized estimating equation approach will be used to estimate marginal effects and generalized linear model approach will be used to estimate conditional effects, and both unadjusted and adjusted comparisons will be reported. Adjustment will include age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, chronic pulmonary disease, and respiratory rate on a spontaneous breathing trial.

Sensitivity analyses

To assess the impact of design considerations on the outcomes, we will conduct several sensitivity analyses. First, we assumed all patients who died within 96 hours to have required reintubation. We will repeat the analysis of the primary and secondary outcome classifying patients who died within 96 hours without experiencing reintubation as not meeting the primary outcome. Second, we have included all patients who are extubated, regardless of reason. We will repeat the analysis of the primary and secondary outcome excluding patients with an unexpected extubation, such as self-extubation. Finally, it is possible that some patients received less than 5 hours of post-extubation respiratory support due to, for example, a protocol error or patient intolerance. We will conduct a modified intent to treat analysis of the primary and secondary outcomes that excludes these patients.

Exploratory Analyses

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Time to reintubation. In our design, we selected a 96-hour window as being appropriate for capturing re-intubation that might reasonably be associated with the post-extubation respiratory support. Different rates may have been observed if different time windows had been used. To evaluate the relative risk of reintubation over time, we will construct a proportional hazards model. This will also allow us to account for the competing risk of death.

Effect Modification (Subgroup Analyses). We will test for effect modification on the primary outcome by evaluating the interaction between group assignment and pre-specified subgroups. Any interaction term with a p-value less than 0.1 will putatively identify an effect modifier. Subgroup analyses may proceed within levels of a modifying variable. Pre-specified subgroups include:

1. Number of risk factors for reintubation, as defined by Hernandez et al. [32]:
    - Age > 65 years
    - Heart failure as the primary indication for mechanical ventilation
    - Moderate to severe COPD
    - APACHE II score at extubation > 12
    - Body mass index > 30 kg/m^2
    - Failure of one or more spontaneous breathing trials
    - Duration of invasive mechanical ventilation greater than 7 days

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2. Chronic hypercapnia or mechanical ventilation for COPD exacerbation
3. Time of extubation (the effect of "dose" of therapy received will be evaluated using this baseline variable anticipated to correlate with the duration of post-extubation support, as patients are evaluated for removal from protocolized support at 5AM on the day following extubation)
4. Primary indication for mechanical ventilation:
    - Hypoxemic respiratory failure
    - Hypercapnic respiratory failure
    - Altered mental status
    - To facilitate a procedure
    - Other
5. Duration of invasive mechanical ventilation prior to enrollment
6. Chronic pulmonary disease, defined as any of:
    - COPD, interstitial lung disease, asthma, cystic fibrosis, non-cystic fibrosis bronchiectasis, recurrent aspiration, pulmonary sarcoidosis, obstructive sleep apnea, obesity hypoventilation syndrome, pulmonary malignancy, pulmonary hypertension, chronic respiratory infection, or restrictive lung disease due to neuromuscular weakness
7. APACHE II score at extubation

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8. Respiratory rate during a spontaneous breathing trial prior to extubation
9. Failure of more than one spontaneous breathing trial
10. Body mass index

Corrections for multiple testing

We have pre-specified a single primary outcome and a single secondary outcome. Consistent with recommendations of the Food and Drug Administration [48] and the European Medicines Association [49], each will be tested using a two-sided p-value with a significance level of 0.05. For all other analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors* [50], and no corrections for multiple comparisons will be performed.

Handling of missing data

The primary outcome, reintubation within 96 hours, is not anticipated to be missing for any patients. If ventilator status throughout the 96 hours is unavailable, which may occur if the patient is discharged home or transferred to a skilled nursing facility, we will use last known status carried forward. Missing data will not be imputed for the primary outcome, or any of the analyses of secondary or exploratory outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations. We expect that age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, and chronic pulmonary

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disease will not be missing in any patients. Respiratory rate during the spontaneous breathing trial may not be available in all patients, particularly those who undergo unexpected extubations.

Trial Status

PROPER is an ongoing pragmatic trial comparing protocolized respiratory support to usual care following the extubation of critically ill adults. Patient enrollment began on October 1, 2017 and will complete on March 31, 2019.

Ethics and dissemination

IRB Approval

The trial was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center with a waiver of informed consent (IRB# 170650).

Consent

There are no known randomized trials or evidence-based guidelines that advocate for or against the use of protocolized support for all critically ill adults undergoing extubation in a medical intensive care unit. This study was submitted to the IRB as meeting the criteria for minimal risk because:

(1) Respiratory support was used *ad hoc* in the clinical care of patients undergoing extubation in the participating ICU prior to initiating the research.

(2) There are no data asserting the superiority or inferiority of protocolized respiratory support for all patients compared with usual care.

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(3) If needed for the optimal care of a patient, treating clinicians can administer NIV, HFNC, or conventional oxygen therapy to any patient, at any time, regardless of group assignment.

(4) All other activities of the research are limited to collection of data from the medical record with no other participant interaction.

In addition to the criteria for minimal risk, the conduct of the study was thought to be impracticable without an alteration or waiver of informed consent. Obtaining prospective, informed consent from all patients being extubated by each respiratory therapist in each cluster would not be feasible, and would risk systematically excluding patients experiencing urgent or unplanned extubation. Excluding such patients would introduce bias and limit generalizability by neglecting a group at high risk of reintubation.

Publication

The results of the trial will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

DISCUSSION

Upon completion, PROPER will provide the most comprehensive data to date on the effect of protocolized post-extubation respiratory support on reintubation in an unselected medical ICU population. Previous trials have suggested that patients with hypercapnia [22,23], non-hypercapnic patients at high risk of reintubation [3,5,22], and non-hypercapnic patients at low risk of reintubation [31] could all potentially benefit from post-extubation respiratory support. The protocolized provision of respiratory support to

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a broad population of ICU patients encompassing each of these previously-examined subgroups in a randomized, controlled trial has yet to be reported.

If our results demonstrate that protocolized respiratory support reduces the rate of reintubation, this would provide compelling evidence that nearly all patients undergoing extubation in a medical intensive care unit should receive respiratory support in the form of either NIV or HFNC at the time of extubation. Conversely, if we demonstrate that protocolized respiratory support does not reduce the rate of reintubation overall, this would allow providers to avoid unnecessarily expending the resources required to provide post-extubation respiratory support to nearly all patients undergoing extubation. Instead, resources might be targeted to those patient subgroups for whom benefit has been previously noted, or for whom benefit is noted in our subgroup analyses. The results may also guide future research toward identifying patients at highest risk of reintubation and those most likely to benefit from respiratory support.

Previous trials have provided 24 to 48 hours of support [5,22,23,31,32]. We elected a lower minimum duration because this support can only be provided in an ICU setting at many centers, and in a population with a low baseline reintubation rate the intervention could potentially lead to longer ICU lengths of stay than necessary. The design of the PROPER trial specifies the provision of post-extubation respiratory support from extubation until at least 5AM the following day, at which point the patient's readiness to wean from post-extubation respiratory support is assessed. This strategy involves a minimum of 5 hours of respiratory support, and our preliminary data suggest a median of 17 hours of support. While shorter than other studies, our approach allows

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removal of support and transfer from the ICU on the day following extubation, if clinically appropriate, or continuation of respiratory support when clinically indicated.

The primary outcome is reintubation, defined as placement of an endotracheal tube or tracheostomy tube in the trachea for any reason, in the 96 hours following enrollment. Previous studies have evaluated reintubation over a broad range of time intervals, from 48 hours [31,32,51] to 7 days [52] and longer [5]. Longer time intervals capture more events but increase the risk that the reintubation is unrelated to the original illness and respiratory function in the immediate post-extubation period. Intubation within 96 hours of extubation was chosen as the primary outcome based on a large observational study assessing time to reintubation in 96,367 adults who received ventilation in an intensive care unit in the United States. That study proposed 96 hours as the optimal time point at which to assess reintubation [8]. While justifiable, selection of a binary endpoint occurring within a defined time window might miss evidence for benefit, and so we have prespecified a survival analysis that considers time to reintubation.

In our design, we have made choices to bias towards the null. This means there are several threats to observing a difference between study groups. Foremost, the anticipated median duration of post-extubation respiratory support of 17 hours is shorter than the 24-48 hours delivered in some prior trials. Some patients may be intolerant of post-extubation respiratory support, which may further limit the average exposure to the study interventions. It is also possible that the use of post-extubation respiratory support in the usual care group may be higher during the study period than prior to the trial due to increasing provider familiarity with post-extubation respiratory support,

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contamination from the unblinded intervention being delivered in the same study location, or both. Another potential possibility is that use of one therapy will be similar between the intervention and usual care groups (e.g., use of NIV) with substantial separation between groups in the other therapy (e.g., use of HFNC). This would require a more nuanced interpretation of the study findings. Treating clinicians are aware of study group assignment and so clinicians may alter the timing of extubation or management of post-extubation respiratory failure based on group assignment. To assess for such bias, we will present baseline characteristics of the two study groups, as well as information about use of rescue respiratory support in the two groups, and we will adjust for these factors or conduct prespecified sensitivity analyses. Finally, group assignment at the level of the cluster with multiple cluster-level crossovers introduces the possibility for intracluster correlation, intraperiod correlation, and intracluster intraperiod correlation, which may confound the relationship between group assignment and outcome. In the PROPER trial, the two clusters are anticipated to be extremely similar, as they are two halves of a single ICU. The periods are relatively short and each cluster alternates between group assignment relatively frequently. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, we measured these correlations and found the effect of intracluster correlation, intraperiod correlation, and intracluster intraperiod correlation to be negligible (see Supplemental methods).

CONCLUSION

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We describe, before the conclusion of enrollment or data un-blinding, our trial design and our approach to analyzing the data from a large, pragmatic, cluster-crossover trial comparing the rate of reintubation between patients receiving protocolized post-extubation respiratory support and those patients receiving usual care. Disseminating this pre-specified framework enhances the rigor and reproducibility of our final report, and will allow readers to better judge the impact of our findings.

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FIGURES

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, Interventions, and Assessments.

Figure 2. Group assignment during the trial. During each three-month period of the study, one cluster is assigned to protocolized support (P), and the other to usual care (U).

Figure 3. Post-extubation respiratory support protocol. Visual summary of study protocol used at the bedside by a respiratory therapist caring for patients assigned to the protocolized support group.

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	STUDY PERIOD				
	Allocation	**Enrollment**	**On-Study**		**On-Study**
TIMEPOINT	**Admission**	**Extubation**	***0-24 hrs post-extubation***	**24-96 hours post-extubation**	***Discharge or 30 days after enrollment***
ENROLLMENT:		X			
Eligibility screen	X	X			
Allocation		X			
INTERVENTIONS:					
Protocolized Support			X		
Screening for contraindications	X	X	X		
Usual Care			X		
Screening for contraindications	X	X	X		
ASSESSMENTS:					
Baseline Variables	X	X			
Peri-procedural variables		X	X	X	
Clinical Outcomes			X	X	X

Baseline variables are obtained from electronic medical record and include: indication for intubation, duration of invasive mechanical ventilation, risk factors for reintubation, respiratory rate at extubation, APACHE II score at ICU admission and at extubation, chronic hypercapnia, history of pulmonary disease, history of congestive heart failure, failure of previous spontaneous breathing trial, age, BMI, and other demographic details. Post-extubation variables include: the amount of time spent receiving prophylactic post-extubation respiratory support from 0-96 hours postintubation, the level of support provided with these devices, and the need for rescue treatment with NIV or HFNC to prevent reintubation within 96 hours of extubation. Clinical outcomes include: the need for reintubation within 96 hours (the primary outcome), time to reintubation, indication for reintubation, vital status, number of ventilator-free days to 28 days, and number of ICU-free days to 28 days.

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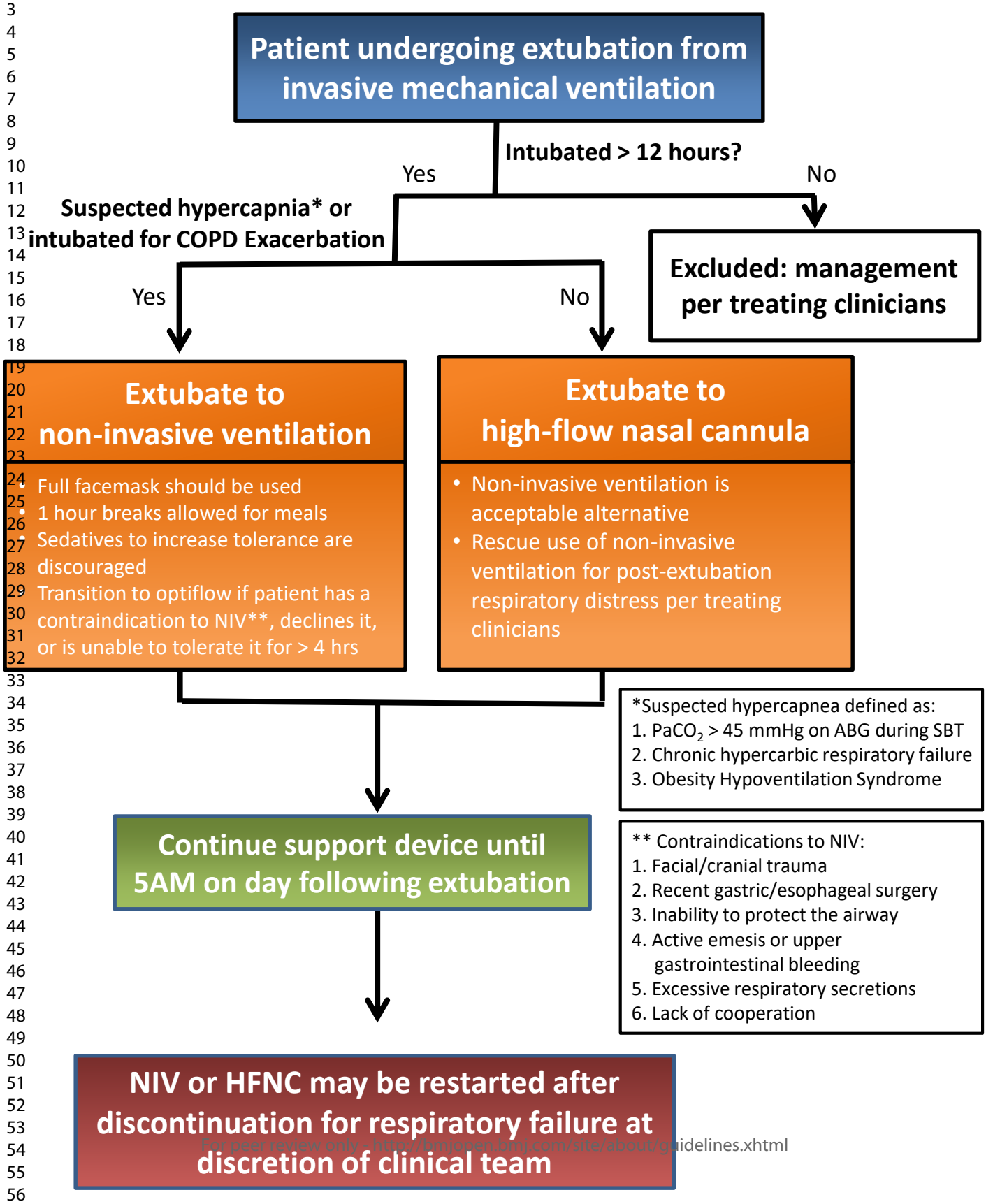
	Oct '17	Nov '17	Dec '17	Jan '18	Feb '18	Mar '18	Apr '18	May '18	Jun '18	Jul '18	Aug '18	Sep '18	Oct '18	Nov '18	Dec '18	Jan '19	Feb '19	Mar '19
Cluster A	U	U	U	P	P	P	U	U	U	P	P	P	U	U	U	P	P	P
Cluster B	P	P	P	U	U	U	P	P	P	U	U	U	P	P	P	U	U	U

Post-Extubation Support Protocol



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ONLINE SUPPLEMENT TO:

Protocolized Post-extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Randomized Trial

Jonathan D. Casey, Erin M. Vaughn, Bradley D. Lloyd, Peter A. Bilas, Eric J. Hall, Alexandra H. Toporek, Kevin G. Buell, Ryan M. Brown, Roger K. Richardson, J. Craig Rooks, Li Wang, Chris J. Lindsell, E. Wesley Ely, Wesley H. Self, Gordon R. Bernard, Todd W. Rice, Matthew W. Semler for the Pragmatic Critical Care Research Group.

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Supplemental Methods

1. Definitions

Study Intervention

Post-extubation respiratory support: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started immediately following extubation to prevent subsequent respiratory failure

Rescue therapy: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started minutes, hours, or days after extubation as treatment for respiratory failure

Hours to discontinuation of post-extubation respiratory support: number of hours from extubation to the permanent discontinuation of post-extubation respiratory support. Use of NIV or HFNC as rescue therapy will not be included.

Duration of respiratory support within the first 24 hours: number of hours spent receiving either NIV or HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

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Duration of HFNC within the first 24 hours: number of hours spent receiving HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

Duration of NIV within the first 24 hours: number of hours spent receiving NIV as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

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Outcomes:

Ventilator Free Days (VFD): Ventilator-free days are defined as the number of days alive and breathing without assistance from [illegible] breathing to 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. If a patient survives to discharge and is never reintubated after enrollment, VFD is 28. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

In-hospital mortality: In-hospital mortality will be defined as death from any cause prior to hospital discharge.

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2. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist:

Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3, 8
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 9
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
	5a	Names, affiliations, and roles of protocol contributors	1

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Roles and responsibilities	5b	Name and contact information for the trial sponsor	1, 2, 9
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 2
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	6-8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9

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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18, 19

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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19-20
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	19-20

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10, 11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, 11
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	10, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for [illegible]	5

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	2
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-26
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	26, 27

Methods: Monitoring

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20, 21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16, 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9, 28
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	S19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	27, 28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27, 28
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	S20

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2, 9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	29
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group Attribution-NonCommercial-NoDerivs 3.0 Unported

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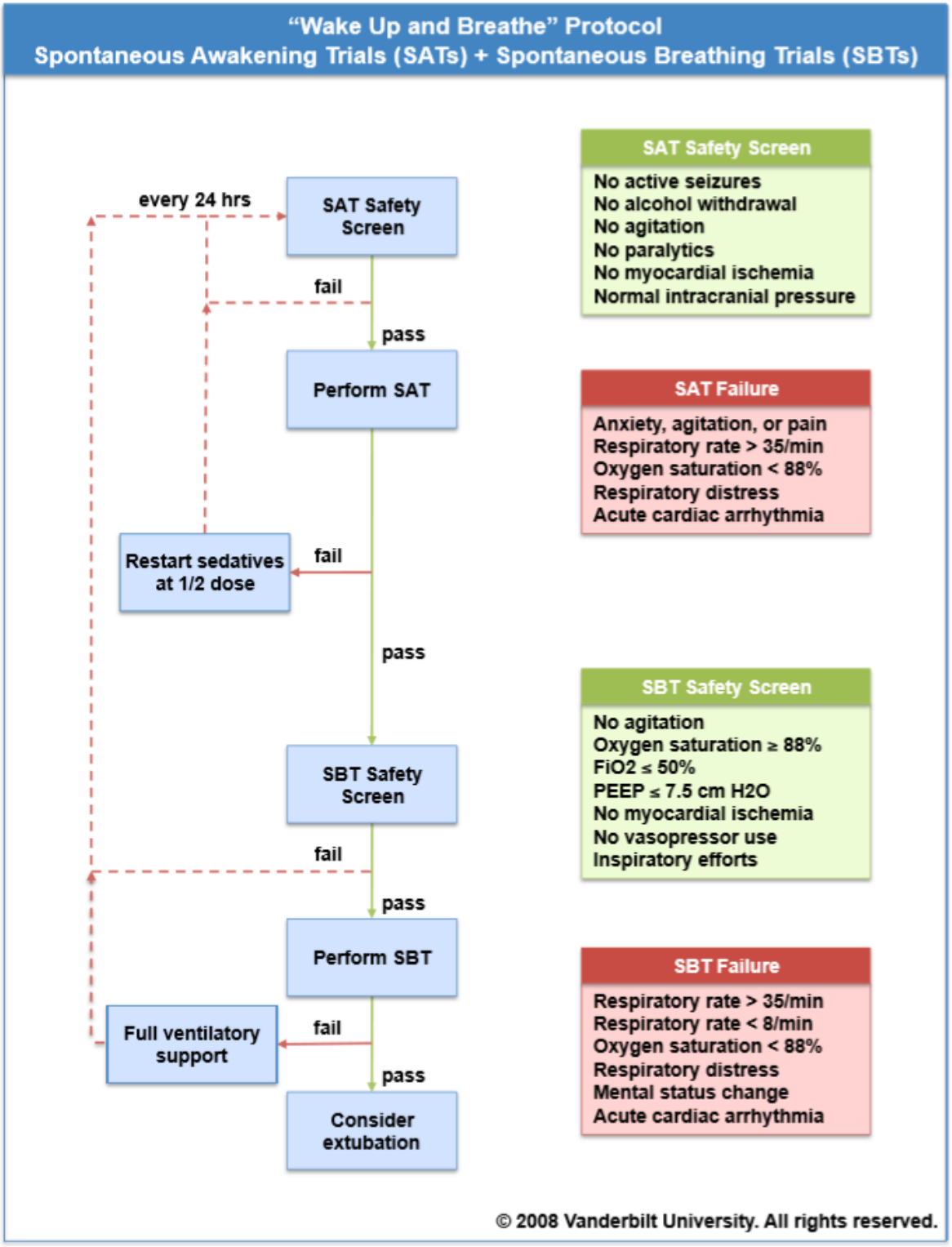
3. Protocol for Daily Spontaneous Awakening Trial (SAT) Safety Screen, SAT Performance, Spontaneous Breathing Trial (SBT) Safety Screen, and SBT Performance



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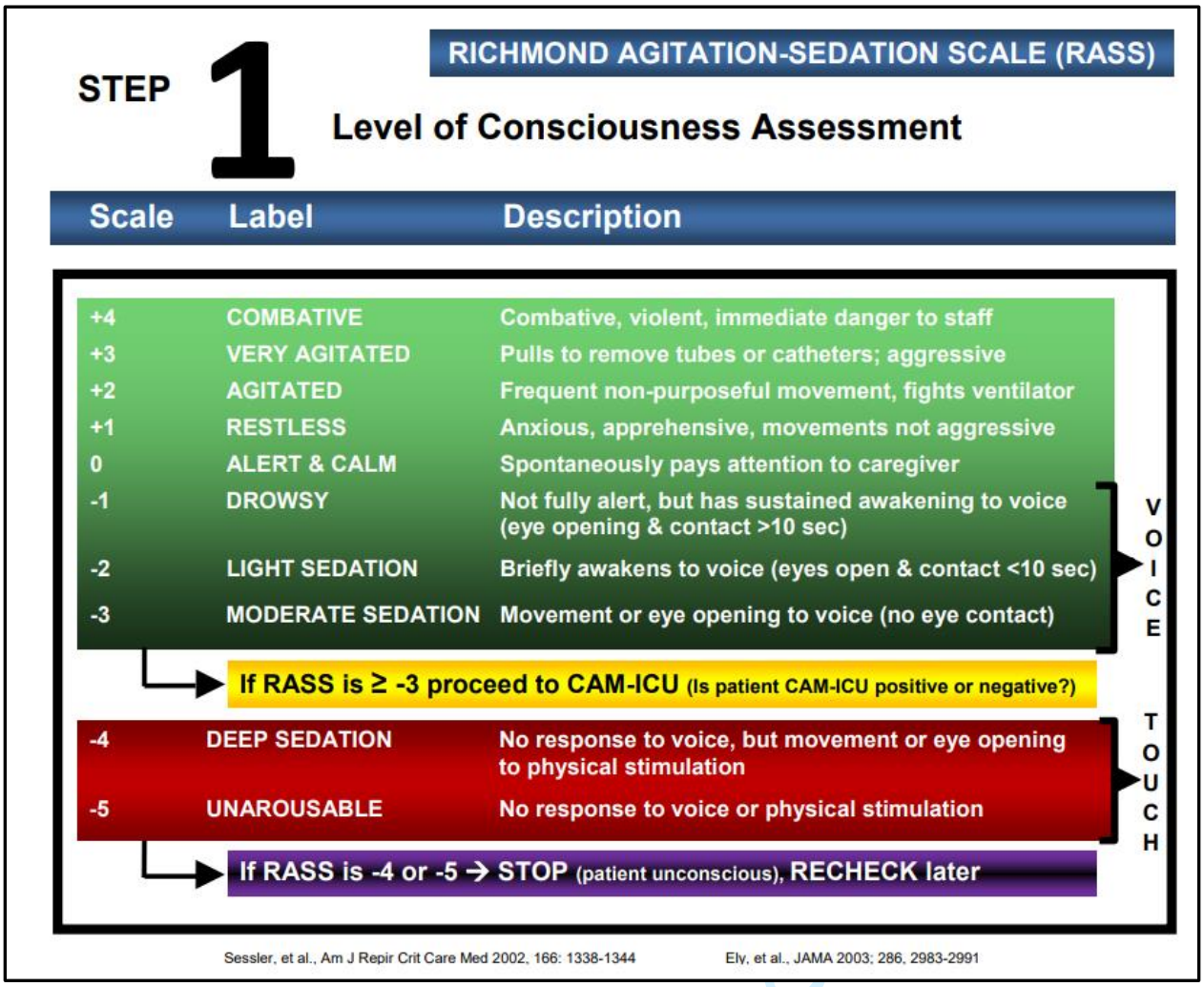
4. Protocol for Assessment of Agitation (RASS score)



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5. Protocol for Choice of Analgesia and Sedation in Mechanically Ventilated Patients

- Analgesia
    a. Intermittent Dosing
        i. Fentanyl 50 mcg IV push every 15 minutes to goal CPOT ≤3, then 50mcg IV push every 2 hours as needed to maintain a CPOT ≤ 3
        ii. Hydromorphone 0.2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 0.2 mg IV push every 4 hours as needed to maintain CPOT ≤ 3
        iii. Morphine 2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 2 mg IV push as needed to maintain CPOT ≤ 3
    b. Continuous Infusions
        i. None
        ii. Fentanyl infusion 50mcg/hr, titrate by 25 mcg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 400mcg/hr. NHO when CPOT target not met with maximum rate.
        iii. Morphine infusion 2mg/hr, titrate by 0.5mg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 20 mg/hr. NHO when CPOT target not met with maximum rate.
- Sedation
    a. None (if RASS at goal with analgesia-based regimen)
    b. Propofol Infusion 5mcg/kg/min, titrate by 5mcg/kg/min every 15 minutes to goal RASS. Max rate of 50mcg/kg/min. NHO when RASS target not met with maximum rate.
    c. Dexmedetomidine Infusion 0.2mcg/kg/hr, titrate by 0.1 mcg/kg/hr every 15 minutes to goal RASS. Max rate 1.5 mcg/kg/hr. NHO when RASS target not met with maximum rate.

    For propofol intolerance consider one of the following:

    d. Midazolam 1mg IV push every 2 hours as needed to meet goal RASS.
    e. Midazolam Infusion 0.5mg/hr, titrate by 0.5mg/hr every 15 minutes to achieve goal RASS. Max infusion rate 10mg/hr. NHO when RASS target not met with maximum rate.

(Propofol intolerance refers to propofol infusion syndrome, hemodynamic instability precluding propofol use, elevated creatinine phosphokinase (CPK) >5000 International units/L, triglycerides>500mg/dl, or propofol use >96 hours)

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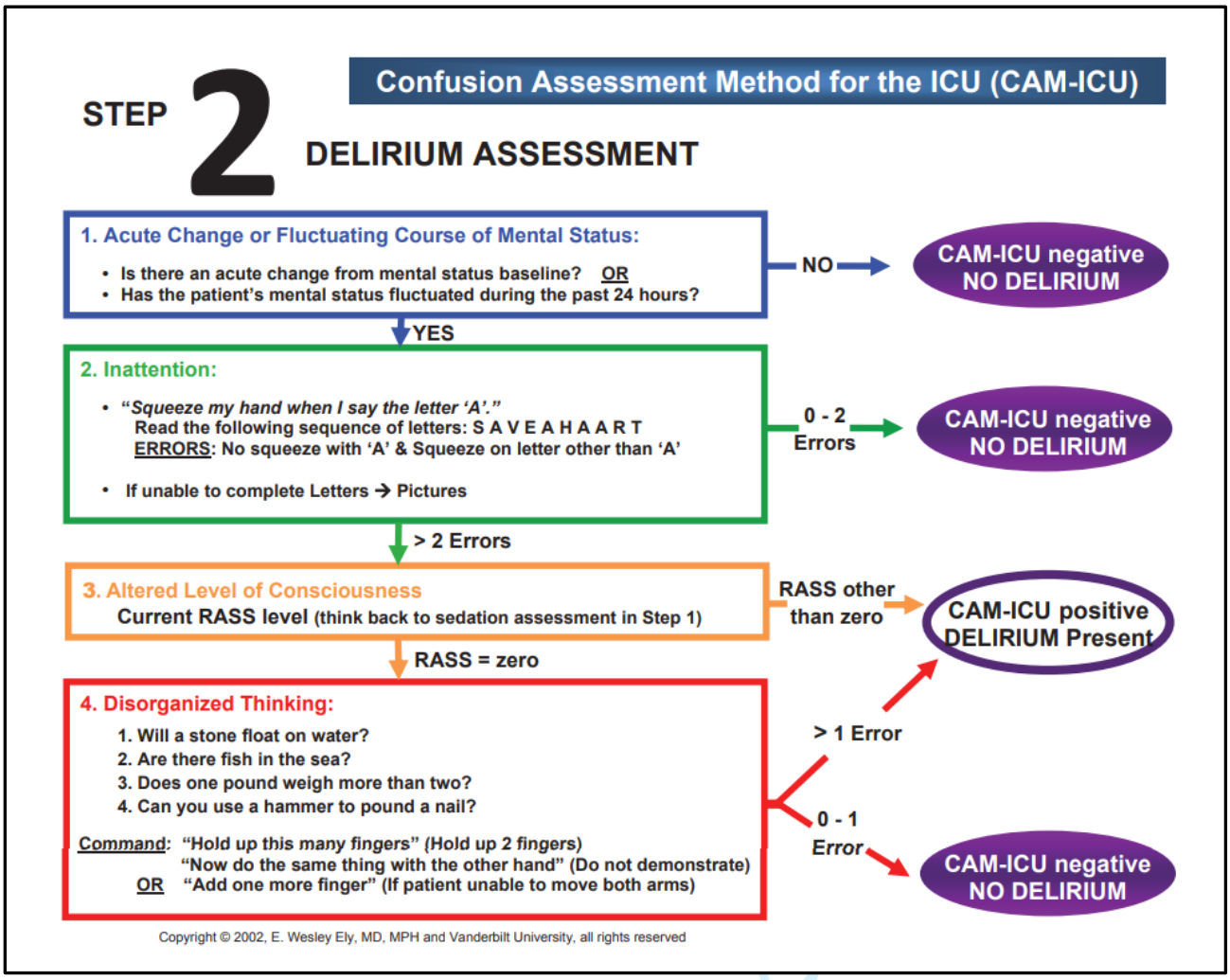
6. Protocol for Delirium Assessment (CAM-ICU)



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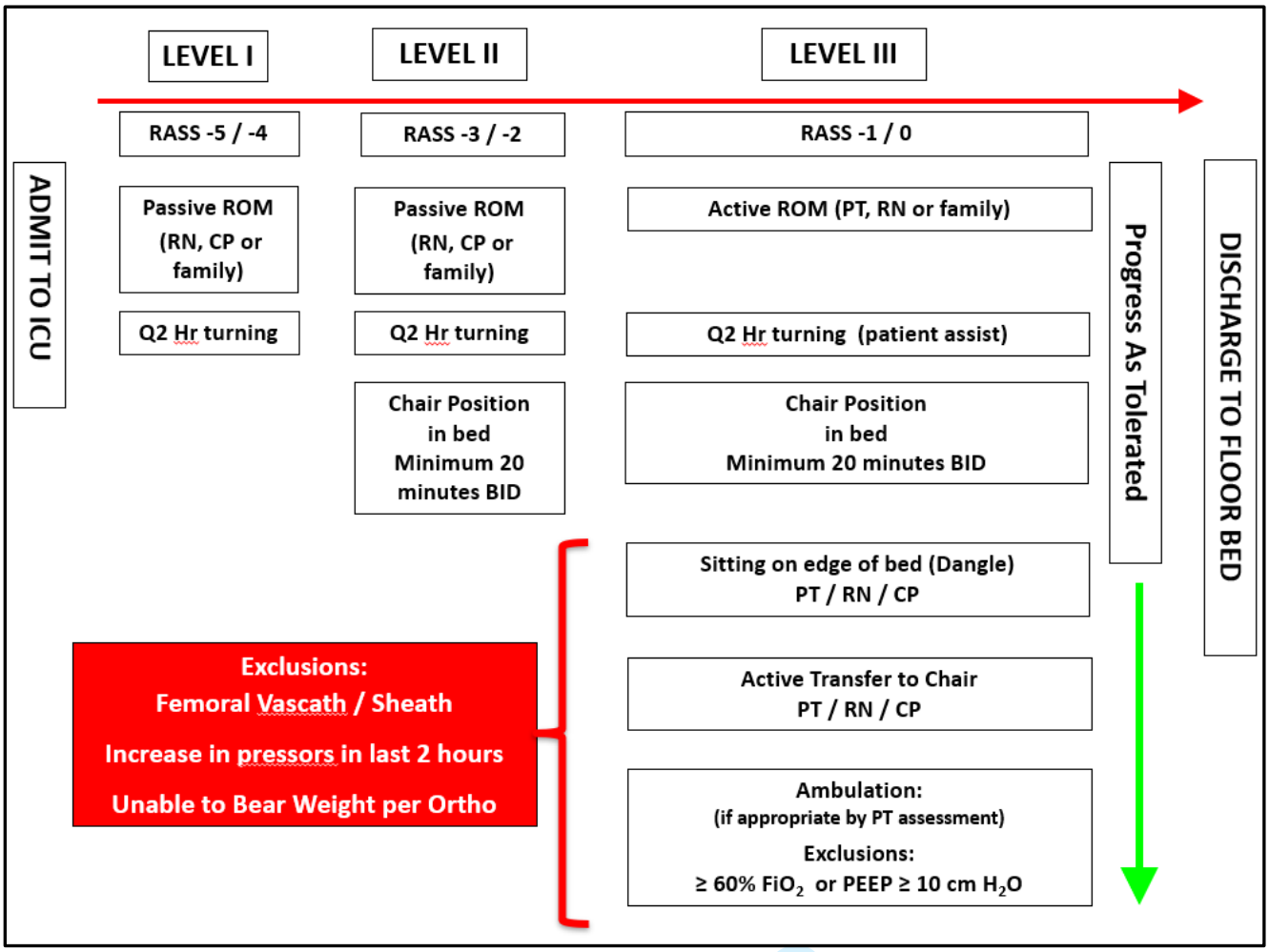
7. Protocol for Early Mobility



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8. Development of the Model for the Primary Analysis

In preparation for PROPER, we collected data on the provision of post-extubation respiratory support and the incidence of reintubation from 420 patients who met inclusion/exclusion criteria for PROPER in a 12-month period (6/1/2015 to 5/31/2016) prior to the trial. Using generalized linear mixed-effects modeling treating the two geographic regions of the unit as clusters and the four 3-month blocks as periods, we calculated the intra-cluster correlation coefficient to be <0.001, the intra-period correlation coefficient to be <0.001, and the intra-cluster intra-period correlation coefficient to be <0.001.

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9. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

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10. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

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11. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

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12. Data Sharing Plan

Upon reasonable request, a completely de-identified data set may be provided by the authors. Request to share data from the PROPER trial should be sent to the principal investigator, Jonathan Casey, MD at Jonathan.D.Casey@vumc.org. The data set will be provided to researchers whose proposed use of the data has been approved by the steering committee and an Institutional Review Board.

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SUPPLEMENTAL FIGURES

Figure S1. PROPER Consort Diagram Template

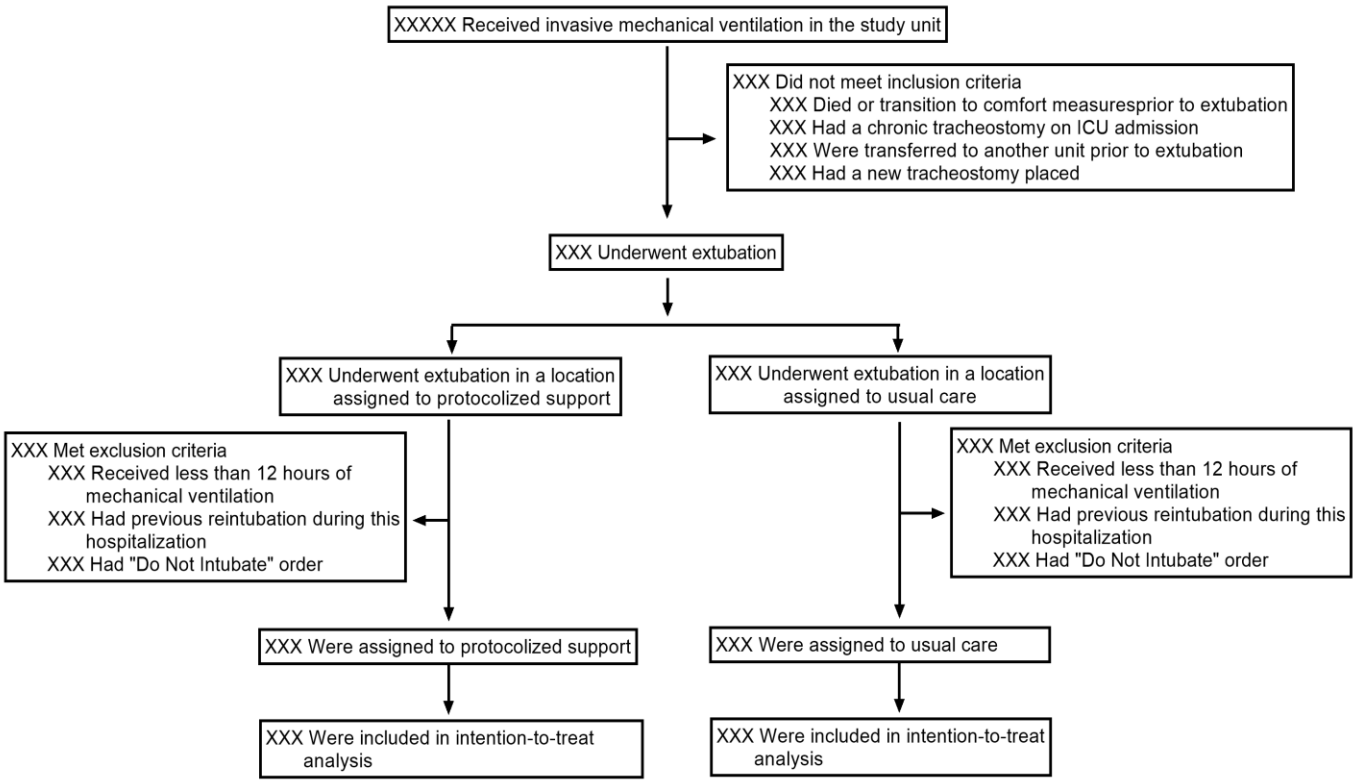

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Figure S2. Protocol for Initiation, Titration, and Weaning of Non-Invasive Ventilation

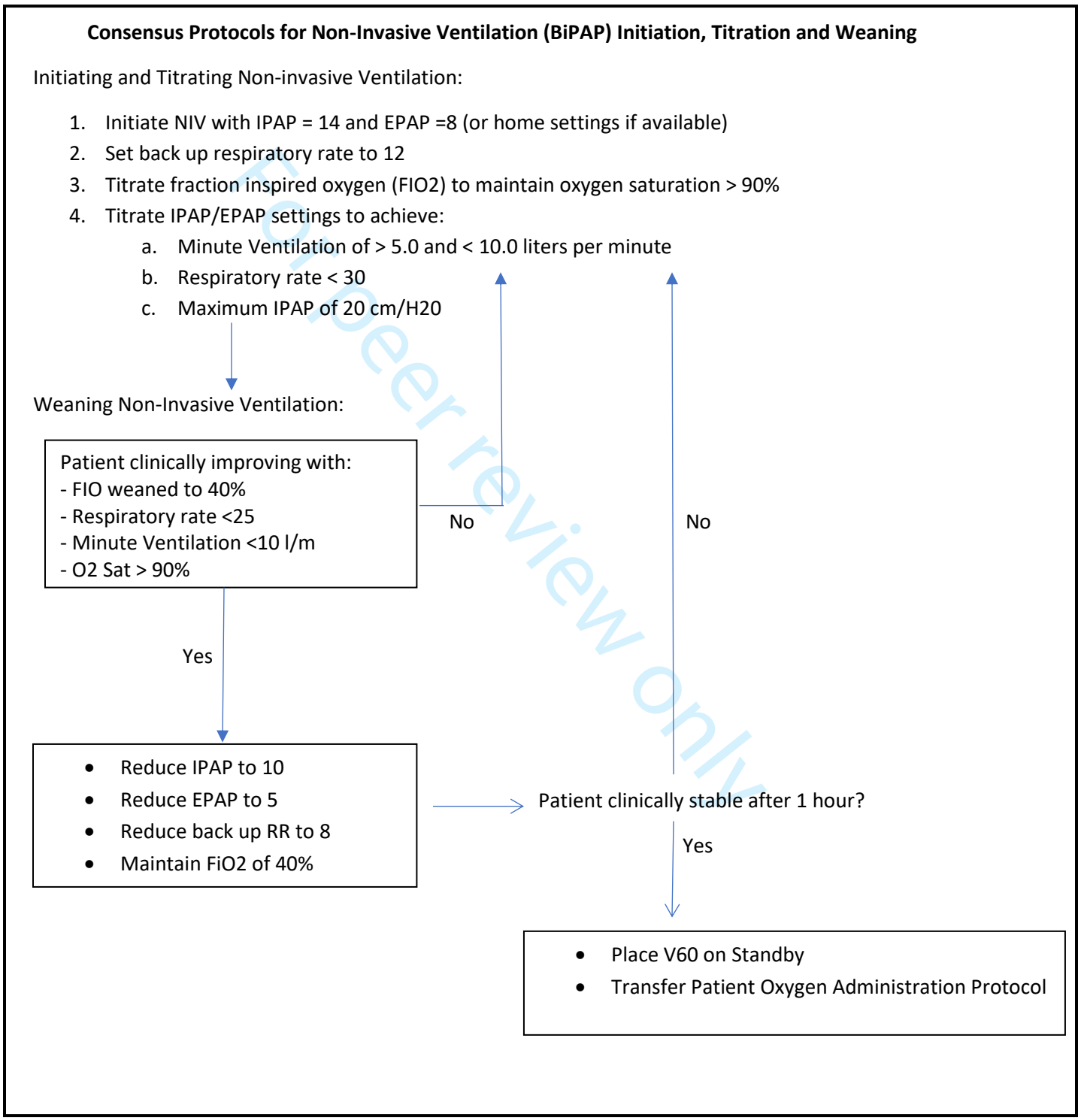

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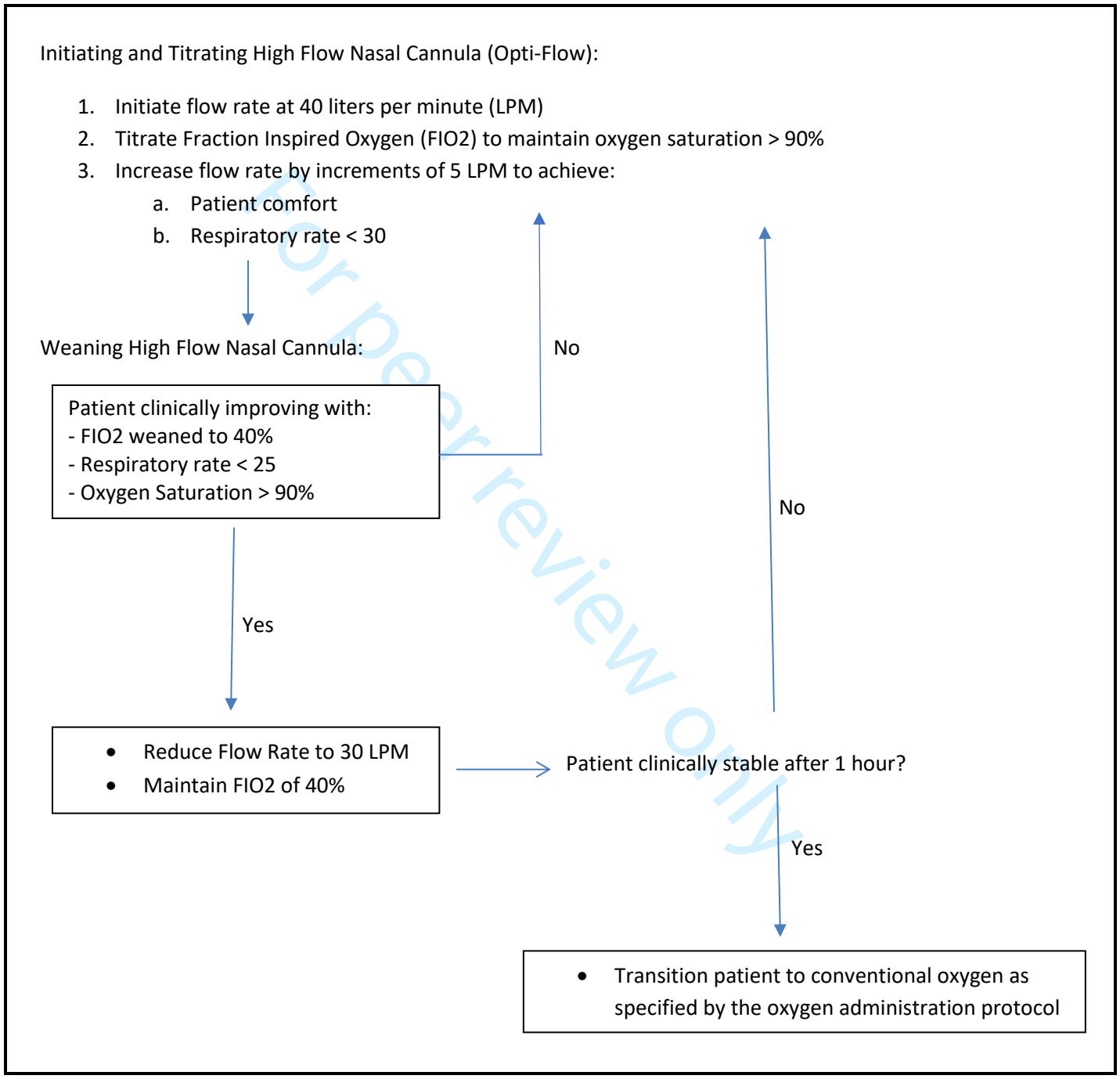
Figure S3. Protocol for Initiation, Titration, and Weaning of High Flow Nasal Cannula



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BMJ Open

Protocolized Post-Extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Clinical Trial

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Respiratory medicine
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Respiratory physiology < THORACIC MEDICINE

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Manuscripts

Protocolized Post-Extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Clinical Trial

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Authors contributions: Study concept and design: J.D.C., T.W.R., M.W.S.; Acquisition of data: J.D.C., E.M.V., B.D.L., P.A.B., E.J.H., A.H.T., K.G.B., R.M.B., R.K.R., J.C.R. M.W.S.; Analysis and interpretation of data: J.D.C, and M.W.S.; Drafting of the manuscript: J.D.C, M.W.S.; Critical revision of the manuscript for important intellectual content: J.D.C., C.J.L., E.W.E, W.H.S., G.R.B, T.W.R., M.W.S.; Statistical analysis: J.D.C., L.W., C.J.L., and M.W.S.; Study supervision: T.W.R.

Sources of Funding:

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The funding institutions had no role in (1) conception, design, or conduct of the study, (2) collection, management, analysis, interpretation, or presentation of the data, or (3) preparation, review, or approval of the manuscript.

Conflicts of Interest: All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declared no potential conflicts of interest with the current work. Todd. W. Rice reported serving as a consultant for Avisa Pharma, LLC, and as the Director of Medical Affairs for Cumberland Pharmaceuticals, Inc.

Key words for indexing: Mechanical ventilation, Reintubation, Post-extubation, High flow nasal cannula, Non-invasive ventilation

Subject Descriptor Number: 4.4 Clinical Trials in Critical Care Medicine

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ABSTRACT:

Introduction: Following extubation from invasive mechanical ventilation, nearly 1 in 7 critically ill adults requires reintubation. Reintubation is independently associated with increased mortality. Post-extubation respiratory support (non-invasive ventilation or high flow nasal cannula applied at the time of extubation) has been reported in small-to-moderate sized trials to reduce reintubation rates among hypercapnic patients, high-risk patients without hypercapnia, and low-risk patients without hypercapnia. It is unknown whether protocolized provision of post-extubation respiratory support to every patient undergoing extubation would reduce the overall reintubation rate, compared to usual care.

Methods and Analysis: The Protocolized Post-Extubation Respiratory Support (PROPER) trial is a pragmatic, cluster-crossover trial being conducted between October 1, 2017 and March 31, 2019 in the medical intensive care unit of Vanderbilt University Medical Center. PROPER compares usual care versus protocolized post-extubation respiratory support (a respiratory therapist-driven protocol that advises the provision of non-invasive ventilation or high flow nasal cannula based on patient characteristics). For the duration of the trial, the unit is divided into two clusters. One cluster receives protocolized support and the other receives usual care. Each cluster crosses over between treatment group assignments every three months. All adults undergoing extubation from invasive mechanical ventilation are enrolled except those who received less than 12 hours of mechanical ventilation, have “Do Not Intubate” orders, or have been previously reintubated during the hospitalization. The anticipated enrollment is approximately 630 patients. The primary outcome is reintubation within 96 hours of extubation.

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Ethics and dissemination: The trial was approved by the Vanderbilt Institutional Review Board. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences. The trial was registered with ClinicalTrials.gov (NCT03288311) on September 20, 2017, prior to the enrollment of the first patient on October 1, 2017.

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ARTICLE SUMMARY

Strengths and limitations of this study

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes between protocolized post-extubation respiratory support and usual care following extubation of critically ill adults
- The broad inclusion criteria will increase generalizability and the moderately large size will provide the opportunity to examine subgroups of interest
- The trial is being conducted at a single center
- The nature of the study intervention does not allow blinding
- Decisions regarding management of post-extubation respiratory failure and reintubation are deferred to the clinical team

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INTRODUCTION

Up to 40% of patients admitted to an intensive care unit require invasive mechanical ventilation [1]. Protocols for low tidal volume ventilation, daily spontaneous awakening trials, and daily spontaneous breathing trials have considerably shortened the duration of invasive mechanical ventilation and improved outcomes for these patients [2,3]. Despite these improvements, the period of time following extubation remains high risk, with rates of reintubation between 10 and 15% in the first 96 hours after extubation [4–8]. Reintubation is associated with increased rates of nosocomial infection [9] and is independently associated with an increased risk of death [7,10,11]. Despite significant improvements in the management of patients receiving invasive mechanical ventilation, the rate of reintubation has not changed meaningfully over the last 20 years [12–14]. One of the few therapies suggested to reduce the rate of reintubation is post-extubation respiratory support with either non-invasive ventilation (NIV) or high flow nasal cannula (HFNC).

For patients with respiratory failure from an acute exacerbation of chronic obstructive pulmonary disease (COPD) [15] and cardiogenic pulmonary edema [16], NIV can prevent the need for the initial intubation, improve the safety for those progressing to intubation [17], allow earlier extubation [18–20], and decrease mortality. Among patients who experience respiratory failure after extubation, however, the data have been disappointing. “Rescue” NIV, applied when a patient develops respiratory failure hours or days after extubation, delays the time to reintubation and may be associated with an increase in ICU mortality [21,22]. Post-extubation respiratory support with NIV,

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started at the time of extubation as prevention, not as treatment for recurrent respiratory failure after extubation, has had more promising initial results.

In unselected ICU populations, several trials failed to demonstrate significant benefit of post-extubation respiratory support with NIV [23,24], but success has been observed in targeted sub-populations, specifically those presumed to be at high risk. These trials have defined risk of re-intubation using various criteria, including duration of ventilation, age greater than 65, Acute Physiology and Chronic Health Evaluation (APACHE) II score exceeding 12 on the day of extubation, congestive heart failure, hypercapnia, weak cough, upper airway stridor, and co-morbidities. For these high-risk patients, post-extubation support with NIV may decrease the rate of reintubation [5,25]. For patients who are hypercapnic during a spontaneous breathing trial, post-extubation support with NIV appears to reduce reintubation and improve 90-day mortality [26]. Recent national guidelines for management following extubation recommend post-extubation respiratory support with NIV for patients at high risk of reintubation [3]. While “high-risk” was not defined in these guidelines, it was suggested that the criteria may include hypercapnia, COPD, congestive heart failure, or other serious comorbidities.

HFNC, a device capable of providing 100% oxygen at flow rates that exceed peak inspiratory flow rates, decreases work of breathing, provides a low level of continuous positive airway pressure, washes out dead space, and improves patient comfort and secretion management [27–33]. HFNC may decrease mortality in non-intubated patients with hypoxemic respiratory failure [34]. In non-hypercapnic patients undergoing extubation in a medical ICU, post-extubation respiratory support with HFNC, started at the time of extubation and continued for 24 to 48 hours, has been reported to reduce

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the rate of reintubation in high risk patients, low risk patients, and a general population of ICU patients [35–37].

In combination, these studies raise the hypothesis that all critically ill adults undergoing extubation from invasive mechanical ventilation might benefit from some form of post-extubation respiratory support, either NIV or HFNC. Concerns remain, however, that results of recent studies may not generalize to the broader population of patients extubated in intensive care units outside of the settings in which the studies were conducted. Rates of reintubation in reported trials range from 14.4% in "low risk" patients [36] to 19.1% for "high-risk" patients [37], considerably higher than the 10% reintubation rate cited by large national registries [8]. Use of any form of post-extubation respiratory support during routine clinical practice remains uncommon at many centers.

Given the potential benefits for post-extubation respiratory support for multiple patient populations, the low uptake in current usual care in many settings, and concerns about generalizability from prior explanatory trials, an effectiveness trial among critically ill adults undergoing extubation from mechanical ventilation is warranted. We designed the Protocolized Post-Extubation Respiratory Support (PROPER) Trial to determine the overall effect of a protocolized approach to post-extubation support (protocolized support) on the primary outcome of reintubation within the 96 hours of extubation, among a broad population of critically ill adults receiving invasive mechanical ventilation.

METHODS AND ANALYSIS

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This manuscript was prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Fig. 1; SPIRIT checklist in online supplement, section 1). [38]

Study Design

The Protocolized Post-Extubation Respiratory Support (PROPER) Trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted between October 1, 2017 and March 31, 2019 in the medical intensive care unit of Vanderbilt University Medical Center in Nashville, TN, USA. PROPER compares the rate of reintubation within 96 hours of extubation between patients provided protocolized support (a respiratory therapist-driven protocol that advises the provision of non-invasive ventilation or high flow nasal cannula based on patient characteristics), to usual care (where post-extubation management is at the discretion of treating clinicians). Consistent with the concept of a pragmatic clinical trial [39], the eligibility criteria are broad and the study procedures are embedded into routine care and executed by clinical personnel. The goal is to evaluate the effectiveness of protocolized support when applied to “real-world” practice. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB 170650). The trial is investigator-initiated with funding provided by the Vanderbilt Institute for Clinical and Translational Research through a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences (UL1 TR000445). The trial protocol was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifier: NCT03288311).

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Patient and Public Involvement

Patients and the public were not involved in identifying the research question or the design of the study. The results of the study will be disseminated to the public at the completion of the trial.

Study Site and Population

The trial is being conducted in the 35-bed medical intensive care unit at Vanderbilt University Medical Center.

The inclusion criteria are:

1. Patient is located in a participating unit
2. Patient undergoing extubation from mechanical ventilation
3. Patient has been receiving mechanical ventilation for at least 12 hours
4. Age ≥ 18 years old

The exclusion criteria for the trial are:

1. Patient is receiving ventilation via a tracheostomy
2. Patient is being extubated to comfort measures or has "Do Not Reintubate" order in place at the time of extubation
3. Patient has required reintubation after a prior attempt at extubation during this hospitalization
4. Unplanned or self-extubation, where immediate reintubation is deemed necessary by the clinical team

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The time of enrollment is considered to be the time of extubation. A patient flow diagram describing the number of patients screened for the trial (all patients who received invasive mechanical ventilation in the study unit), the number who did not meet inclusion criteria (e.g. died before extubation), and the number who were excluded, will be provided in the manuscript reporting the results of the trial (template of flow diagram is provided as supplementary Figure S1).

Randomization and Treatment Allocation

The medical intensive care unit is divided into two geographic clusters (the front hallway and the back hallway), each of which is staffed by a respiratory therapist. During each three-month block of the study, patients extubated in one cluster receive protocolized support delivered by one respiratory therapist while patients extubated in the other cluster receive usual care delivered by another respiratory therapist. All beds in the study unit care of patients of the same acuity, and patients are assigned to bed location based on availability without selection by patient characteristics. Patients admitted to the ICU remain in the same bed until death or ICU discharge. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, there was no difference in the incidence of reintubation in patients admitted to the beds in each of the two clusters. The assigned treatment group alternates every three months over the course of the trial so that each cluster will experience an equal number of months of protocolized support and usual care. A single randomization was performed which determined that the cluster associated with back hallway would

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receive protocolized support during the first block. The front hallway received usual care during the first block, and the blocks have alternated every three months (Fig. 2).

The rationale for dividing the study unit into two clusters by geographic location of the beds was so that all patients assigned to a given respiratory therapist's cluster will receive the same treatment. A respiratory therapist caring for patients in the cluster assigned to protocolized support receives education on post-extubation respiratory support and structured feedback on his or her performance at the practice level. Assigning some patients cared for by a respiratory therapist protocolized support and some patients to usual care was expected to introduce contamination because the respiratory therapist would be more likely to deliver post-extubation respiratory support to patients in their care assigned to the usual care arm. Given the nature of the intervention, patients, treating clinicians, and investigators are not blinded to group assignment.

Study Interventions

Protocolized Support

Patients in the protocolized support group are assigned to receive post-extubation respiratory support starting at the time of extubation. The choice between non-invasive ventilation and high-flow nasal cannula is made using a standardized protocol for post-extubation respiratory support and is implemented by the patient's respiratory therapist (Fig. 3).

Based on the results of previous trials, the protocol for post-extubation respiratory support recommends NIV immediately upon extubation via a full facemask

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for all patients in the protocolized support group who have suspected hypercapnia [25,26] or are intubated for an acute exacerbation of COPD [40]. Because arterial blood gases are not routinely performed during spontaneous breathing trials in the study unit, suspected hypercapnia is defined as known chronic hypercapnic respiratory failure, known obesity hypoventilation syndrome, or an arterial blood gas with a partial pressure of arterial carbon dioxide (PaCO2) >45 mmHg on a spontaneous breathing trial. Recommended initial settings for NIV include initiation with an initial inspiratory positive airway pressure of 14 cmH_2O, an expiratory positive airway pressure of 8 cmH_2O, and a backup respiratory rate of 12 breaths per minute. Settings are titrated to maintain a minute ventilation between 5.0 and 10.0 liters per minute and a respiratory rate below 30 breaths per minute, with a maximum inspiratory positive airway pressure of 20 cmH_2O. Inspired fraction of oxygen is titrated to maintain an oxygen saturation > 90% (Fig. S2). Removal of NIV for up to one hour at a time for patient comfort and to allow patients to eat or drink is encouraged and administration of sedatives to increase patient tolerance of NIV is discouraged (Figure 3). Device settings may be altered at the discretion of the respiratory therapist or the clinical team.

Given previous data suggesting that post-extubation support with HFNC may be superior to conventional oxygen in low-risk patients [36] and equivalent to NIV in non-hypercapnic high-risk patients [37], the protocol for post-extubation respiratory support recommends HFNC for all patients in the protocolized support group who were not intubated for an acute exacerbation of COPD and who do not have suspected hypercapnia. Additionally, HFNC is recommended for patients who have a contraindication to NIV (facial or cranial trauma or surgery, recent gastric or esophageal

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surgery, inability to protect the airway, active emesis or upper gastrointestinal bleeding, excessive amount of respiratory secretions, or lack of cooperation). Patients who are extubated to NIV but are unable to tolerate it may be transitioned to HFNC.

For patients in the protocolized support group without suspected hypercapnia or a COPD exacerbation, HFNC is initiated immediately upon extubation. Recommended initial settings for HFNC and titration and weaning parameters include initial flow rates of at least 40 liters per minute, adjustment of flow rates in increments of 5 liters per minute, titration to patient comfort and a respiratory rate less than 30, a maximum flow rate of 60 liters per minute, and titration of the fraction of inspired oxygen to maintain an arterial oxygen saturation > 90% (Fig. S3).

Post-extubation respiratory support is provided from the time of extubation until 5AM on the day following extubation. At 5AM on the day following extubation, a respiratory therapist assesses for readiness for weaning from post-extubation respiratory support. This timing was designed to allow patients to transfer out of the ICU on the day following extubation if clinically appropriate. Based on timing of extubation during the year preceding this trial, patients are expected to receive a median of 17 hours of respiratory support, and no less than five hours of respiratory support prior to being evaluated for weaning.

If the patient meets weaning criteria (Fig S2, S3) at the time of their assessment, the device is removed and the patient may be initiated on conventional oxygen therapy through a nasal cannula or face mask if needed. Post-extubation respiratory support with NIV or HFNC may be continued at the discretion of the treating clinicians, in which case subsequent titration and weaning is determined by the treating clinicians. Post-

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extubation respiratory support may be discontinued prior to 5AM on the day following extubation if the patient is transferred out of the ICU, the patient declines further post-extubation respiratory support, or the treating clinicians determine that discontinuation is needed for the optimal care of the patient.

The decision to use HFNC or NIV as rescue treatment for post-extubation respiratory failure is made by treating clinicians and is prospectively recorded but is not encouraged. For patients in the protocolized support group, treating clinicians may decide to use invasive mechanical ventilation, NIV, HFNC, or conventional oxygen therapy at any time, regardless of group assignment, if felt to be needed for the safe care of the patient.

Usual Care

All aspects of post-extubation management for patients in the usual care arm are determined by treating clinicians. Treating clinicians may elect to use NIV or HFNC as post-extubation respiratory support for those patients they believe will benefit from these therapies. No guidance is provided by the study regarding patient selection, device selection, titration or weaning parameters, or timing of removal of support. In the study ICU in the year prior to the trial, 8.3% of patients received post-extubation respiratory support during routine clinical care; 7.1% received NIV and 1.2% received HFNC.

For patients in the usual care group, treating clinicians may decide to use invasive mechanical ventilation, NIV, HFNC, or conventional oxygen therapy at any time, regardless of group assignment, if felt to be needed for the optimal care of the patient.

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Co-interventions

Study group assignment determines only the approach to post-extubation respiratory support. Treating clinicians determine all management prior to extubation, including the approach to sedation, timing of spontaneous breathing and awakening trials, and readiness for extubation. The study ICU has established clinical protocols for the care of patients receiving invasive mechanical ventilation including:

1. Critical Care Pain Observation Tool (CPOT score) [41]
2. Daily spontaneous awakening trial (SAT) safety screen, SAT performance, spontaneous breathing trial (SBT) safety screen, and SBT performance [2]
3. Richmond Agitation and Sedation Scale (RASS score) [42,43]
4. Choice of analgesia and sedation
5. Confusion Assessment Method for the ICU (CAM-ICU) [44,45]
6. Early Mobility [46]

The clinical protocols used in the study unit can be found in the supplementary appendix.

Following extubation, all clinical care decisions, other than use of NIV and HFNC for post-extubation respiratory support until 5AM the day following extubation, are made by treating clinicians, including use of diuretics, intravenous fluids, antibiotics, corticosteroids, airway clearance measures, and breathing treatments.

Training

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The protocols for initiation, titration, and weaning of NIV and HFNC were developed by consensus with local respiratory therapy leaders using best-practice recommendations from professional societies [3], protocols from prior randomized trials, and local protocols regarding the provision of non-invasive respiratory support. In addition to these materials, all respiratory therapists received a 30-minute lecture on the delivery of post-extubation respiratory support prior to caring for patients assigned to the protocolized support group. Ongoing education on post-extubation respiratory support is provided by study staff throughout the trial. Additional education was provided to the critical care fellows and attendings who cared for patients in the study units, in the form of a structured 60-minute lecture reviewing existing literature on post-extubation respiratory support and describing the rationale and protocol for the trial.

Data Collection

Data are prospectively collected from the electronic health record by trained study personnel. Data are stored in a secure, online database [47]. Collected data include:

Characteristics: Age; gender; height; weight; body mass index; race; chronic comorbidities; indication for intubation; APACHE II score at ICU admission

Baseline (i.e. time of extubation): APACHE II score; length of mechanical ventilation; last known left ventricular ejection fraction; active medical problems; failure of more than one spontaneous breathing trial; last known Glasgow Coma Score [48]; last known Richmond Agitation and Sedation Score [42]; last known CAM-ICU score [44]; highest FiO2 delivered in the 6 hours prior to extubation;

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lowest oxygen saturation during a spontaneous breathing trial; highest respiratory rate in the 6 hours prior to extubation; highest respiratory rate during a spontaneous breathing trial; highest heart rate in the 6 hours prior to extubation; highest heart rate during a spontaneous breathing trial; use of vasopressors in the 6 hours prior to extubation; results of any arterial blood gas obtained during a spontaneous breathing trial.

Data from 0 to 96 hours: The need for reintubation within 96 hours; time to reintubation; indication for reintubation; presence of laryngeal edema requiring reintubation; amount of time spent receiving HFNC and NIV in the first 24 hours post-extubation; the amount of time spent receiving prophylactic post-extubation respiratory support from 0-96 hours post-extubation; the highest and lowest levels of respiratory support (flow rate; FiO2; IPAP; EPAP) at three time points (0-6, 6-12, and 12-24 hours post-extubation); the highest and lowest respiratory rate, heart rate, SaO2; and FiO2 at three timepoints (0-6, 6-12, and 12-24 hours post-extubation); the presence of delirium at any timepoint from 0-96 hours post-extubation (as determined by CAM-ICU score).

Clinical Outcomes: Reintubation between baseline and the first of either hospital discharge or 28-days; in-hospital mortality; time to death; ICU-free days and ventilator-free days in the 28 days after enrollment.

Primary Outcome

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The primary outcome is reintubation in the 96 hours following enrollment. Reintubation is defined as placement of an endotracheal tube or tracheostomy tube in the trachea for any reason.

Death may be a competing event for the outcome of reintubation. Among the patients who would have met criteria for enrollment in the year prior to the trial, every patient who died within 96 hours of extubation experienced reintubation prior to death. In the event that any patient in the trial dies in the 96 hours following enrollment without experiencing reintubation, they will be classified in the primary analysis as having met the primary outcome. Patients who are discharged from the hospital before 96 hours following enrollment without having experienced reintubation will be classified as not meeting the primary outcome.

Any decision to reintubate will be made by the clinical team. Prior studies have attempted to protocolize the decision to reintubate [34,36,37]. Because the goal of the PROPER study is to evaluate the performance of protocolized support when applied to a broad population of critically ill adults in "real-world" practice, we deliberately deferred all decisions regarding management of post-extubation respiratory failure and reintubation to the clinical team with no involvement or guidance from the research team.

Secondary Outcome

The single, pre-specified, secondary outcome is the number of ICU-free days in the 28 days following enrollment. This is defined as the number of whole calendar days alive and not admitted to an intensive care unit beginning at midnight on the day of

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extubation to 28 days following enrollment. Patients who are never discharged from the intensive care unit will receive a value of 0. Patients who die before day 28 will receive a value of 0. For patients who return to an ICU and are subsequently discharged prior to day 28, ICU-free days will be counted as the number of whole calendar days from midnight on the day following the final ICU discharge to 28 days following enrollment. All data collection will be censored at the first of hospital discharge or 28 days.

Exploratory Outcomes

- All-cause in-hospital mortality
- Ventilator-free days in the 28 days following enrollment (defined in the online supplement)
- Time from enrollment to reintubation
- Indication for reintubation (respiratory indication, laryngeal edema, other)
- Delirium in the 96 hours following enrollment
- Lowest SpO2/FiO2 ratio in the 24 hours following enrollment
- Highest respiratory rate in the 0-6 hours, 6-12 hours, and 12-24 hours following enrollment

Statistical Analysis and Reporting

Sample Size Estimation

Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment [49], the incidence of reintubation within 96 hours after extubation was 12.1%. Similar rates have been reported in previous observational studies of

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extubation in the ICU [6,7]. Prior randomized trials have reported that prophylactic post-extubation respiratory support with NIV may reduce the relative risk of reintubation by 49% to 66% in high risk patients [5,25], while post-extubation respiratory support with HFNC may reduce the relative risk of reintubation by 81% in high risk patients and 60% in low risk patients [35–37]. Based on the results of these prior randomized trials, we estimated that protocolized support would reduce the relative risk of reintubation by at least 55%. This is equivalent to an absolute risk reduction of 6.7%, from 12.1% in the usual care group to 5.4% in the protocolized support group.

Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, the intra-cluster correlation, intra-period correlation, and intra-cluster intra-period correlation for the primary outcome were all <0.001 assuming a cluster-crossover design with two clusters and three-month periods. Using PS version 3.1.2 with the above assumptions and a chi-squared test of the primary hypothesis with an alpha level of 0.05, we calculated that enrolling 566 patients (283 per group) would achieve at least 80% statistical power. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, 8.3% received post-extubation respiratory support during usual care. In order to account for loss of statistical power due to use of post-extubation respiratory support in the usual care group during the trial, we increased our sample size estimate by 10% to 623 patients. Based on data from the study ICU in the year prior to the trial, we anticipated that enrollment of at least 630 patients would require a study duration of 18 months.

Data and Safety Monitoring Board and Interim Analysis

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For this 18-month, single-center study comparing a minimal risk intervention with usual care, a data and safety monitoring board was not appointed and an interim analysis is not planned.

Statistical Analysis Principles

All analyses will be conducted at the level of the individual patient during an individual hospitalization on an intent-to-treat fashion, unless otherwise specified. Continuous variables will be reported as median and IQR; categorical variables will be reported as frequencies and proportions. Given the cluster cross-over design, all comparisons between the protocolized post-extubation respiratory support group and the usual care group will take into account the cluster and period level correlations. With only one primary outcome and one secondary outcome, a two-sided p-value of 0.05 will be considered statistically significant.

Comparison of primary outcome between groups

We will compare the binary primary outcome of reintubation within 96 hours between the protocolized support group and the usual care group. It is possible to estimate a marginal effect, which is interpreted as the population effect of implementing a general policy of post intubation ventilatory support, or a conditional effect, which is interpreted as the effect on an individual patient given the values of the covariates for that patient [50]. Since our intervention may be applied at both the unit level as a general policy, or at the patient level as an individual intervention, both may be of interest. We will use a generalized estimating equation (GEE) approach to estimate the

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marginal effect, and we will use a generalized linear mixed model with logit link function to estimate the conditional effect. Group assignment will be a fixed effect, and cluster and period will be included as random effects [51,52]. We will report both adjusted and unadjusted comparisons; for the purposes of declaring success on the primary endpoint, we will consider the unadjusted marginal effect.

Adjusted comparisons will include age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, chronic pulmonary disease, and respiratory rate on a spontaneous breathing trial. To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous covariates and the outcome.

Comparison of secondary outcome between groups

The secondary outcome is the number of ICU-free days in the 28 days following enrollment. We will use a proportional odds model to compare this outcome between groups. As with analysis of the primary outcome, a generalized estimating equation approach will be used to estimate marginal effects and generalized linear model approach will be used to estimate conditional effects, and both unadjusted and adjusted comparisons will be reported. Adjustment will include age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, chronic pulmonary disease, and respiratory rate on a spontaneous breathing trial.

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Sensitivity analyses

To assess the impact of design considerations on the outcomes, we will conduct several sensitivity analyses. First, we assumed all patients who died within 96 hours to have required reintubation. We will repeat the analysis of the primary and secondary outcome classifying patients who died within 96 hours without experiencing reintubation as not meeting the primary outcome. Second, we have included all patients who are extubated, regardless of reason. We will repeat the analysis of the primary and secondary outcome excluding patients with an unexpected extubation, such as self-extubation. Finally, it is possible that some patients received less than 5 hours of post-extubation respiratory support due to, for example, a protocol error or patient intolerance. We will conduct a modified intent to treat analysis of the primary and secondary outcomes that excludes these patients.

Exploratory Analyses

Time to reintubation. In our design, we selected a 96-hour window as being appropriate for capturing re-intubation that might reasonably be associated with the post-extubation respiratory support. Different rates may have been observed if different time windows had been used. To evaluate the relative risk of reintubation over time, we will construct a proportional hazards model. This will also allow us to account for the competing risk of death.

Effect Modification (Subgroup Analyses). We will test for effect modification on the primary outcome by evaluating the interaction between group assignment and

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pre-specified subgroups. Any interaction term with a p-value less than 0.1 will putatively identify an effect modifier. Subgroup analyses may proceed within levels of a modifying variable. Pre-specified subgroups include:

1. Number of risk factors for reintubation, as defined by Hernandez et al. [37]:
    - Age > 65 years
    - Heart failure as the primary indication for mechanical ventilation
    - Moderate to severe COPD
    - APACHE II score at extubation > 12
    - Body mass index > 30 kg/m^2
    - Failure of one or more spontaneous breathing trials
    - Duration of invasive mechanical ventilation greater than 7 days
2. Chronic hypercapnia or mechanical ventilation for COPD exacerbation
3. Time of extubation (the effect of “dose” of therapy received will be evaluated using this baseline variable anticipated to correlate with the duration of post-extubation support, as patients are evaluated for removal from protocolized support at 5AM on the day following extubation)
4. Primary indication for mechanical ventilation:
    - Hypoxemic respiratory failure

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- Hypercapnic respiratory failure
- Altered mental status
- To facilitate a procedure
- Other

5. Duration of invasive mechanical ventilation prior to enrollment
6. Chronic pulmonary disease, defined as any of:
   - COPD, interstitial lung disease, asthma, cystic fibrosis, non-cystic fibrosis bronchiectasis, recurrent aspiration, pulmonary sarcoidosis, obstructive sleep apnea, obesity hypoventilation syndrome, pulmonary malignancy, pulmonary hypertension, chronic respiratory infection, or restrictive lung disease due to neuromuscular weakness
7. APACHE II score at extubation
8. Respiratory rate during a spontaneous breathing trial prior to extubation
9. Failure of more than one spontaneous breathing trial
10. Body mass index

Corrections for multiple testing

We have pre-specified a single primary outcome and a single secondary outcome. Consistent with recommendations of the Food and Drug Administration [53] and the European Medicines Association [54], each will be tested using a two-sided p-value with a significance level of 0.05. For all other analyses, emphasis will be placed

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on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors* [55], and no corrections for multiple comparisons will be performed.

Handling of missing data

The primary outcome, reintubation within 96 hours, is not anticipated to be missing for any patients. If ventilator status throughout the 96 hours is unavailable, which may occur if the patient is discharged home or transferred to a skilled nursing facility, we will use last known status carried forward. Missing data will not be imputed for the primary outcome, or any of the analyses of secondary or exploratory outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations. We expect that age, APACHE II score, duration of invasive mechanical ventilation, indication for intubation, chronic hypercapnia, and chronic pulmonary disease will not be missing in any patients. Respiratory rate during the spontaneous breathing trial may not be available in all patients, particularly those who undergo unexpected extubations.

Trial Status

PROPER is an ongoing pragmatic trial comparing protocolized respiratory support to usual care following the extubation of critically ill adults. Patient enrollment began on October 1, 2017 and will complete on March 31, 2019.

Ethics and dissemination

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IRB Approval

The trial was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center with a waiver of informed consent (IRB# 170650).

Consent

There are no known randomized trials or evidence-based guidelines that advocate for or against the use of protocolized support for all critically ill adults undergoing extubation in a medical intensive care unit. This study was submitted to the IRB as meeting the criteria for minimal risk because:

(1) Respiratory support was used *ad hoc* in the clinical care of patients undergoing extubation in the participating ICU prior to initiating the research.

(2) There are no data asserting the superiority or inferiority of protocolized respiratory support for all patients compared with usual care.

(3) If needed for the optimal care of a patient, treating clinicians can administer NIV, HFNC, or conventional oxygen therapy to any patient, at any time, regardless of group assignment.

(4) All other activities of the research are limited to collection of data from the medical record with no other participant interaction.

In addition to the criteria for minimal risk, the conduct of the study was thought to be impracticable without an alteration or waiver of informed consent. Obtaining prospective, informed consent from all patients being extubated by each respiratory therapist in each cluster would not be feasible, and would risk systematically excluding

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patients experiencing urgent or unplanned extubation. Excluding such patients would introduce bias and limit generalizability by neglecting a group at high risk of reintubation.

Publication

The results of the trial will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

DISCUSSION

Upon completion, PROPER will provide the most comprehensive data to date on the effect of protocolized post-extubation respiratory support on reintubation in an unselected medical ICU population. Previous trials have suggested that patients with hypercapnia [24,25], non-hypercapnic patients at high risk of reintubation [3,5,24], and non-hypercapnic patients at low risk of reintubation [36] could all potentially benefit from post-extubation respiratory support. The protocolized provision of respiratory support to a broad population of ICU patients encompassing each of these previously-examined subgroups in a randomized, controlled trial has yet to be reported.

If our results demonstrate that protocolized respiratory support reduces the rate of reintubation, this would provide compelling evidence that nearly all patients undergoing extubation in a medical intensive care unit should receive respiratory support in the form of either NIV or HFNC at the time of extubation. Conversely, if we demonstrate that protocolized respiratory support does not reduce the rate of reintubation overall, this would allow providers to avoid unnecessarily expending the resources required to provide post-extubation respiratory support to nearly all patients undergoing extubation. Instead, resources might be targeted to those patient subgroups for whom benefit has

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been previously noted, or for whom benefit is noted in our subgroup analyses. The results may also guide future research toward identifying patients at highest risk of reintubation and those most likely to benefit from respiratory support.

Previous trials have provided 24 to 48 hours of support [5,25,26,36,37]. We elected a lower minimum duration because this support can only be provided in an ICU setting at many centers, and in a population with a low baseline reintubation rate the intervention could potentially lead to longer ICU lengths of stay than necessary. The design of the PROPER trial specifies the provision of post-extubation respiratory support from extubation until at least 5AM the following day, at which point the patient's readiness to wean from post-extubation respiratory support is assessed. This strategy involves a minimum of 5 hours of respiratory support, and our preliminary data suggest a median of 17 hours of support. While shorter than other studies, our approach allows removal of support and transfer from the ICU on the day following extubation, if clinically appropriate, or continuation of respiratory support when clinically indicated.

The primary outcome is reintubation, defined as placement of an endotracheal tube or tracheostomy tube in the trachea for any reason, in the 96 hours following enrollment. Previous studies have evaluated reintubation over a broad range of time intervals, from 48 hours [36,37,56] to 7 days [57] and longer [5]. Longer time intervals capture more events but increase the risk that the reintubation is unrelated to the original illness and respiratory function in the immediate post-extubation period. Intubation within 96 hours of extubation was chosen as the primary outcome based on a large observational study assessing time to reintubation in 96,367 adults who received ventilation in an intensive care unit in the United States. That study proposed 96 hours

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as the optimal time point at which to assess reintubation [8]. While justifiable, selection of a binary endpoint occurring within a defined time window might miss evidence for benefit, and so we have prespecified a survival analysis that considers time to reintubation.

In our design, we have made choices to bias towards the null. This means there are several threats to observing a difference between study groups. Foremost, the anticipated median duration of post-extubation respiratory support of 17 hours is shorter than the 24-48 hours delivered in some prior trials. Some patients may be intolerant of post-extubation respiratory support, which may further limit the average exposure to the study interventions. It is also possible that the use of post-extubation respiratory support in the usual care group may be higher during the study period than prior to the trial due to increasing provider familiarity with post-extubation respiratory support, contamination from the unblinded intervention being delivered in the same study location, or both. The provision of post-extubation support provided in the usual care group of this single center trial may not match the experience at other centers so we will provide data on the use of NIV and HFNC in the usual care arm of PROPER to assist in the interpretation of the results. Another potential possibility is that use of one therapy will be similar between the intervention and usual care groups (e.g., use of NIV) with substantial separation between groups in the other therapy (e.g., use of HFNC). This would require a more nuanced interpretation of the study findings. Treating clinicians are aware of study group assignment and so clinicians may alter the timing of extubation or management of post-extubation respiratory failure based on group assignment. To assess for such bias, we will present characteristics of the two study

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groups at extubation, including duration of mechanical ventilation prior to extubation, and information about use of rescue respiratory support in the two groups. We will also perform analyses that adjust for these factors or conduct prespecified sensitivity analyses. Finally, group assignment at the level of the cluster with multiple cluster-level crossovers introduces the possibility for intracluster correlation, intraperiod correlation, and intracluster intraperiod correlation, which may confound the relationship between group assignment and outcome. In the PROPER trial, the two clusters are anticipated to be extremely similar, as they are two halves of a single ICU. The periods are relatively short and each cluster alternates between group assignment relatively frequently. Among patients in the study ICU in the year prior to the trial who would have met criteria for enrollment, we measured these correlations and found the effect of intracluster correlation, intraperiod correlation, and intracluster intraperiod correlation to be negligible (see Supplemental methods).

CONCLUSION

We describe, before the conclusion of enrollment or data un-blinding, our trial design and our approach to analyzing the data from a large, pragmatic, cluster-crossover trial comparing the rate of reintubation between patients receiving protocolized post-extubation respiratory support and those patients receiving usual care. Disseminating this pre-specified framework enhances the rigor and reproducibility of our final report, and will allow readers to better judge the impact of our findings.

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FIGURES

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, Interventions, and Assessments.

Figure 2. Group assignment during the trial. During each three-month period of the study, one cluster is assigned to protocolized support (P), and the other to usual care (U).

Figure 3. Post-extubation respiratory support protocol. Visual summary of study protocol used at the bedside by a respiratory therapist caring for patients assigned to the protocolized support group.

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	STUDY PERIOD				
	Allocation	**Enrollment**	**On-Study**		**On-Study**
TIMEPOINT	**Admission**	**Extubation**	***0-24 hrs post-extubation***	**24-96 hours post-extubation**	***Discharge or 30 days after enrollment***
ENROLLMENT:		X			
Eligibility screen	X	X			
Allocation		X			
INTERVENTIONS:					
Protocolized Support			X		
Screening for contraindications	X	X	X		
Usual Care			X		
Screening for contraindications	X	X	X		
ASSESSMENTS:					
Baseline Variables	X	X			
Peri-procedural variables		X	X	X	
Clinical Outcomes			X	X	X

Baseline variables are obtained from electronic medical record and include: indication for intubation, duration of invasive mechanical ventilation, risk factors for reintubation, respiratory rate at extubation, APACHE II score at ICU admission and at extubation, chronic hypercapnia, history of pulmonary disease, history of congestive heart failure, failure of previous spontaneous breathing trial, age, BMI, and other demographic details. Post-extubation variables include: the amount of time spent receiving prophylactic post-extubation respiratory support from 0-96 hours postintubation, the level of support provided with these devices, and the need for rescue treatment with NIV or HFNC to prevent reintubation within 96 hours of extubation. Clinical outcomes include: the need for reintubation within 96 hours (the primary outcome), time to reintubation, indication for reintubation, vital status, number of ventilator-free days to 28 days, and number of ICU-free days to 28 days.

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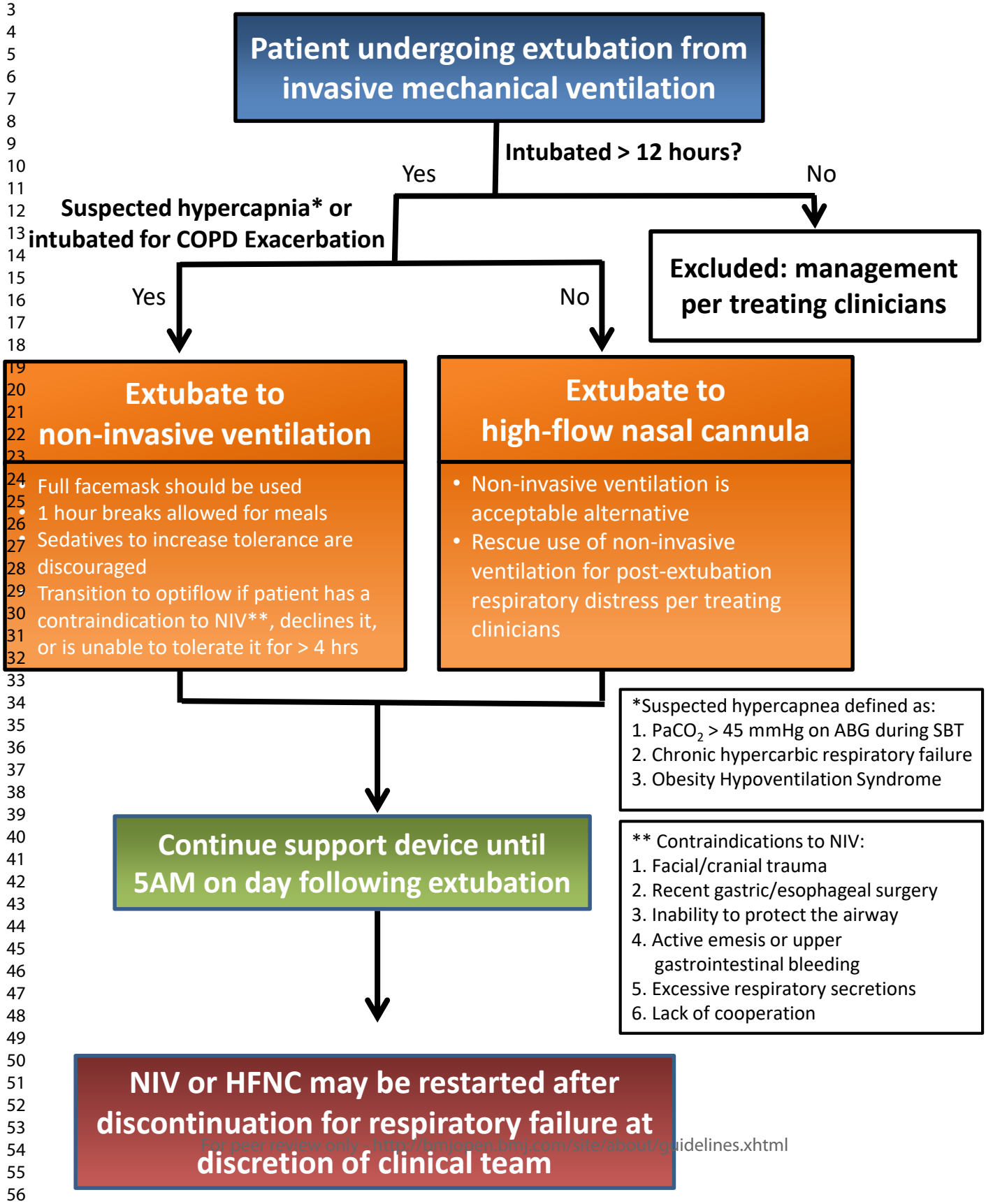
	Oct '17	Nov '17	Dec '17	Jan '18	Feb '18	Mar '18	Apr '18	May '18	Jun '18	Jul '18	Aug '18	Sep '18	Oct '18	Nov '18	Dec '18	Jan '19	Feb '19	Mar '19
Cluster A	U	U	U	P	P	P	U	U	U	P	P	P	U	U	U	P	P	P
Cluster B	P	P	P	U	U	U	P	P	P	U	U	U	P	P	P	U	U	U

Post-Extubation Support Protocol



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ONLINE SUPPLEMENT TO:

Protocolized Post-extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Randomized Trial

Jonathan D. Casey, Erin M. Vaughn, Bradley D. Lloyd, Peter A. Bilas, Eric J. Hall, Alexandra H. Toporek, Kevin G. Buell, Ryan M. Brown, Roger K. Richardson, J. Craig Rooks, Li Wang, Chris J. Lindsell, E. Wesley Ely, Wesley H. Self, Gordon R. Bernard, Todd W. Rice, Matthew W. Semler for the Pragmatic Critical Care Research Group.

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Supplemental Methods

1. Definitions

Study Intervention

Post-extubation respiratory support: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started immediately following extubation to prevent subsequent respiratory failure

Rescue therapy: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started minutes, hours, or days after extubation as treatment for respiratory failure

Hours to discontinuation of post-extubation respiratory support: number of hours from extubation to the permanent discontinuation of post-extubation respiratory support. Use of NIV or HFNC as rescue therapy will not be included.

Duration of respiratory support within the first 24 hours: number of hours spent receiving either NIV or HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

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Duration of HFNC within the first 24 hours: number of hours spent receiving HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

Duration of NIV within the first 24 hours: number of hours spent receiving NIV as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

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Outcomes:

Ventilator Free Days (VFD): Ventilator-free days are defined as the number of days alive and breathing without assistance from the patient's final receipt of assisted breathing to 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. If a patient survives to discharge and is never reintubated after enrollment, VFD is 28. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

In-hospital mortality: In-hospital mortality will be defined as death from any cause prior to hospital discharge.

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2. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Standard Protocol Items: Recommendations for Interventional Trials

Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3, 8
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 9
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
	5a	Names, affiliations, and roles of protocol contributors	1

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Roles and responsibilities	5b	Name and contact information for the trial sponsor	1, 2, 9
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 2
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	6-8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9

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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18, 19

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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19-20
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	19-20

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10, 11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, 11
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	10, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	2
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-26
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	26, 27
Methods: Monitoring			

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20, 21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16, 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9, 28
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	S19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	27, 28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27, 28
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	S20

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2, 9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	29
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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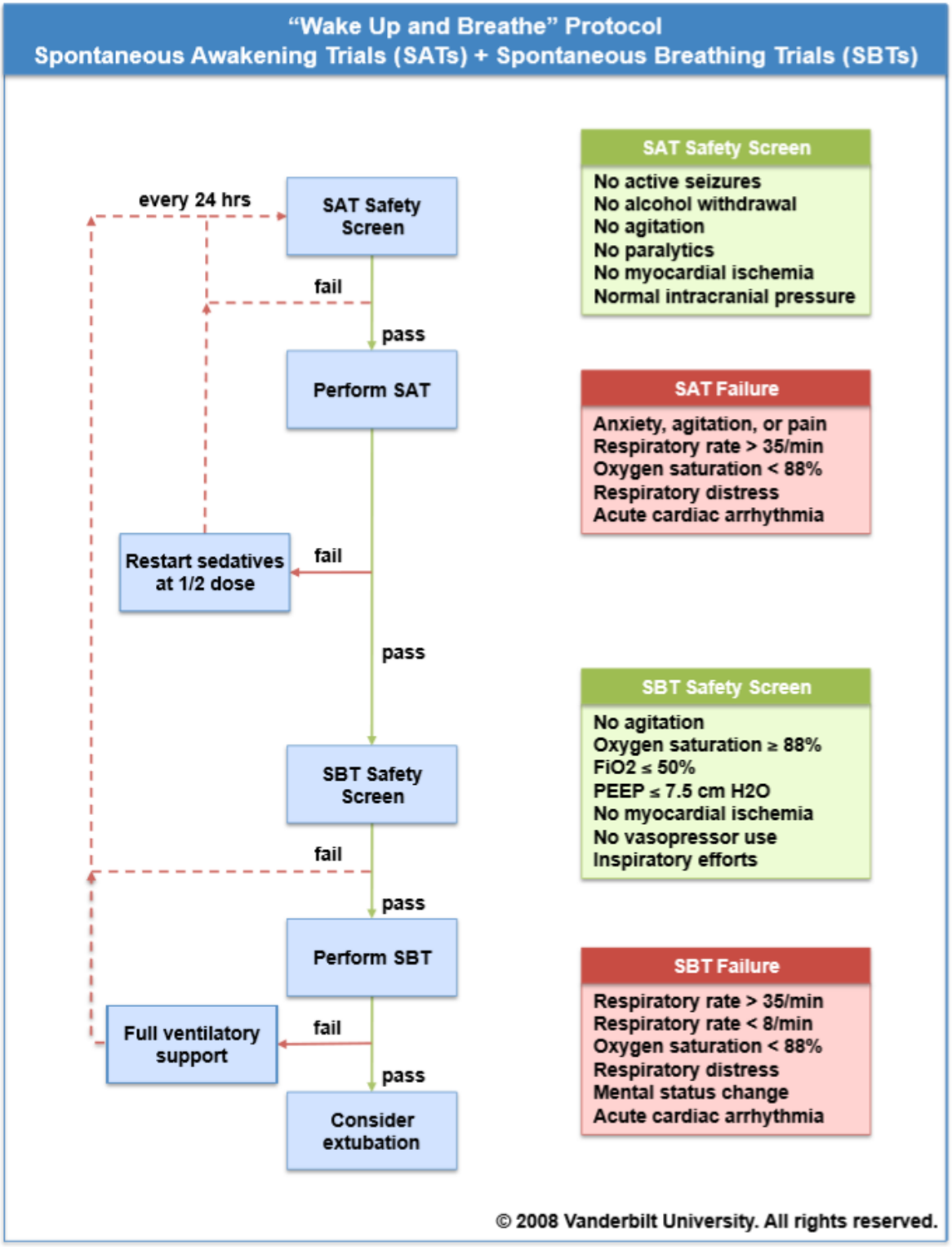
3. Protocol for Daily Spontaneous Awakening Trial (SAT) Safety Screen, SAT Performance, Spontaneous Breathing Trial (SBT) Safety Screen, and SBT Performance



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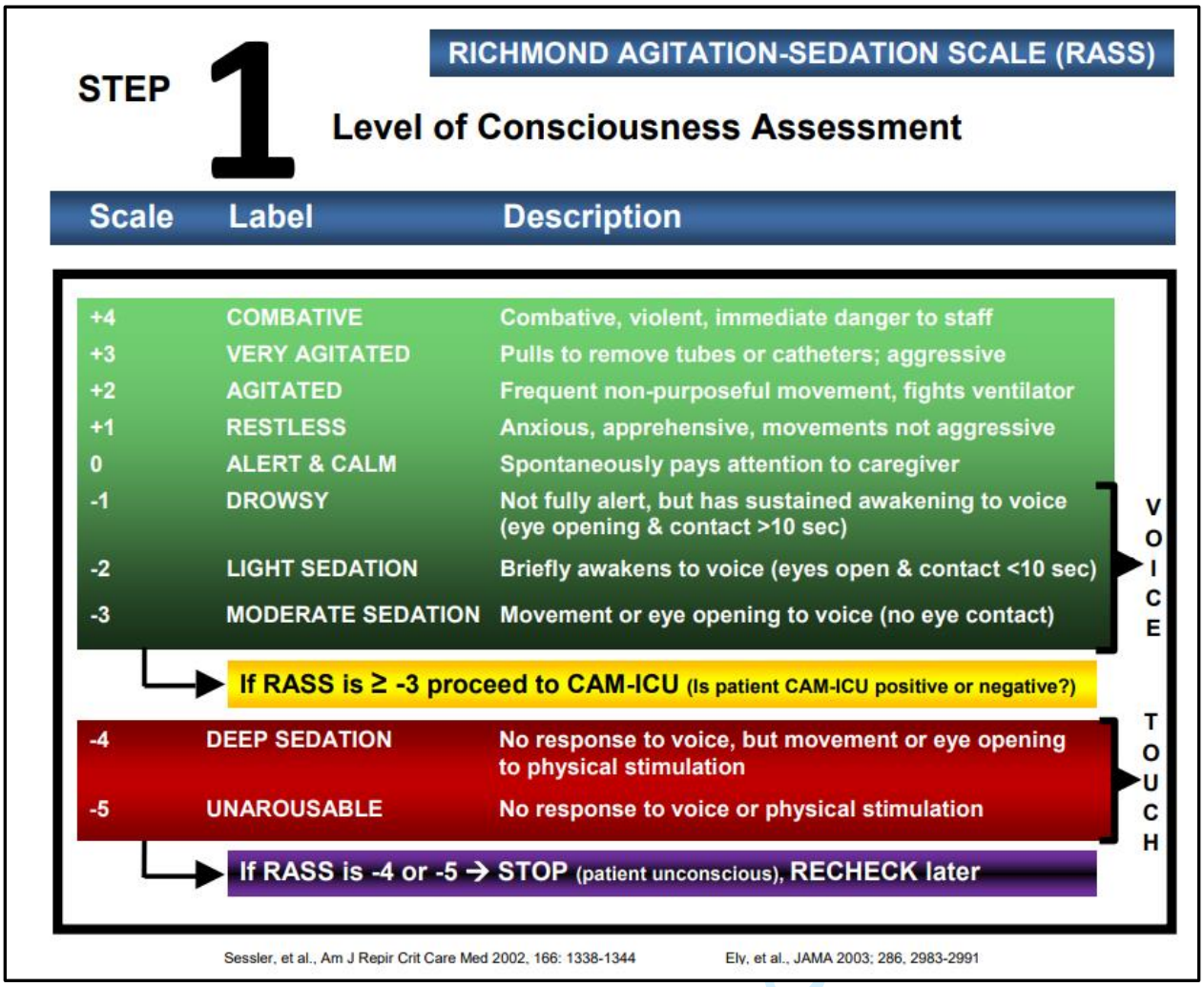
4. Protocol for Assessment of Agitation (RASS score)



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5. Protocol for Choice of Analgesia and Sedation in Mechanically Ventilated Patients

- Analgesia
    a. Intermittent Dosing
        i. Fentanyl 50 mcg IV push every 15 minutes to goal CPOT ≤3, then 50mcg IV push every 2 hours as needed to maintain a CPOT ≤ 3
        ii. Hydromorphone 0.2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 0.2 mg IV push every 4 hours as needed to maintain CPOT ≤ 3
        iii. Morphine 2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 2 mg IV push as needed to maintain CPOT ≤ 3
    b. Continuous Infusions
        i. None
        ii. Fentanyl infusion 50mcg/hr, titrate by 25 mcg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 400mcg/hr. NHO when CPOT target not met with maximum rate.
        iii. Morphine infusion 2mg/hr, titrate by 0.5mg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 20 mg/hr. NHO when CPOT target not met with maximum rate.
- Sedation
    a. None (if RASS at goal with analgesia-based regimen)
    b. Propofol Infusion 5mcg/kg/min, titrate by 5mcg/kg/min every 15 minutes to goal RASS. Max rate of 50mcg/kg/min. NHO when RASS target not met with maximum rate.
    c. Dexmedetomidine Infusion 0.2mcg/kg/hr, titrate by 0.1 mcg/kg/hr every 15 minutes to goal RASS. Max rate 1.5 mcg/kg/hr. NHO when RASS target not met with maximum rate.

    For propofol intolerance consider one of the following:

    d. Midazolam 1mg IV push every 2 hours as needed to meet goal RASS.
    e. Midazolam Infusion 0.5mg/hr, titrate by 0.5mg/hr every 15 minutes to achieve goal RASS. Max infusion rate 10mg/hr. NHO when RASS target not met with maximum rate.

(Propofol intolerance refers to propofol infusion syndrome, hemodynamic instability precluding propofol use, elevated creatinine phosphokinase (CPK) >5000 International units/L, triglycerides>500mg/dl, or propofol use >96 hours)

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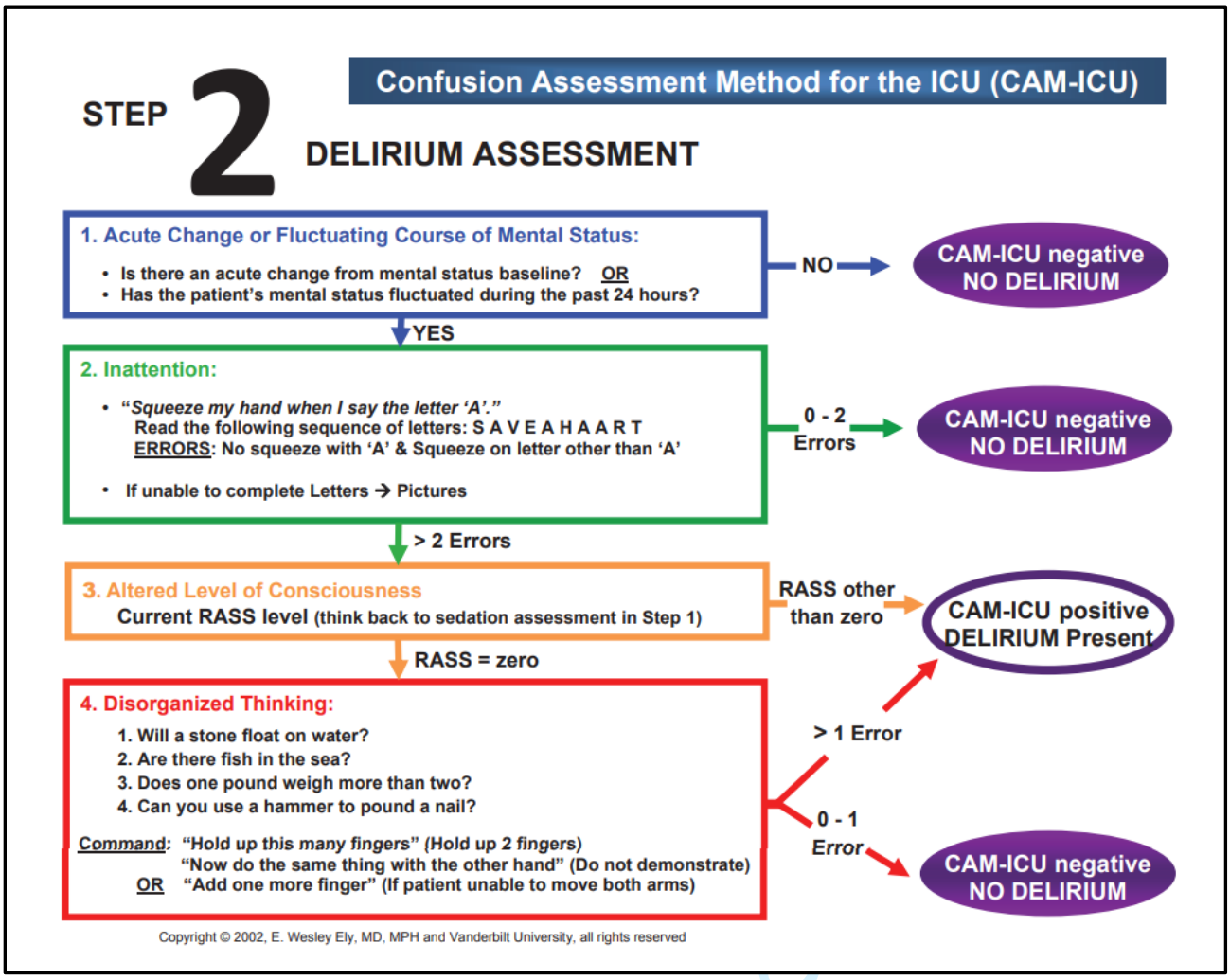
6. Protocol for Delirium Assessment (CAM-ICU)



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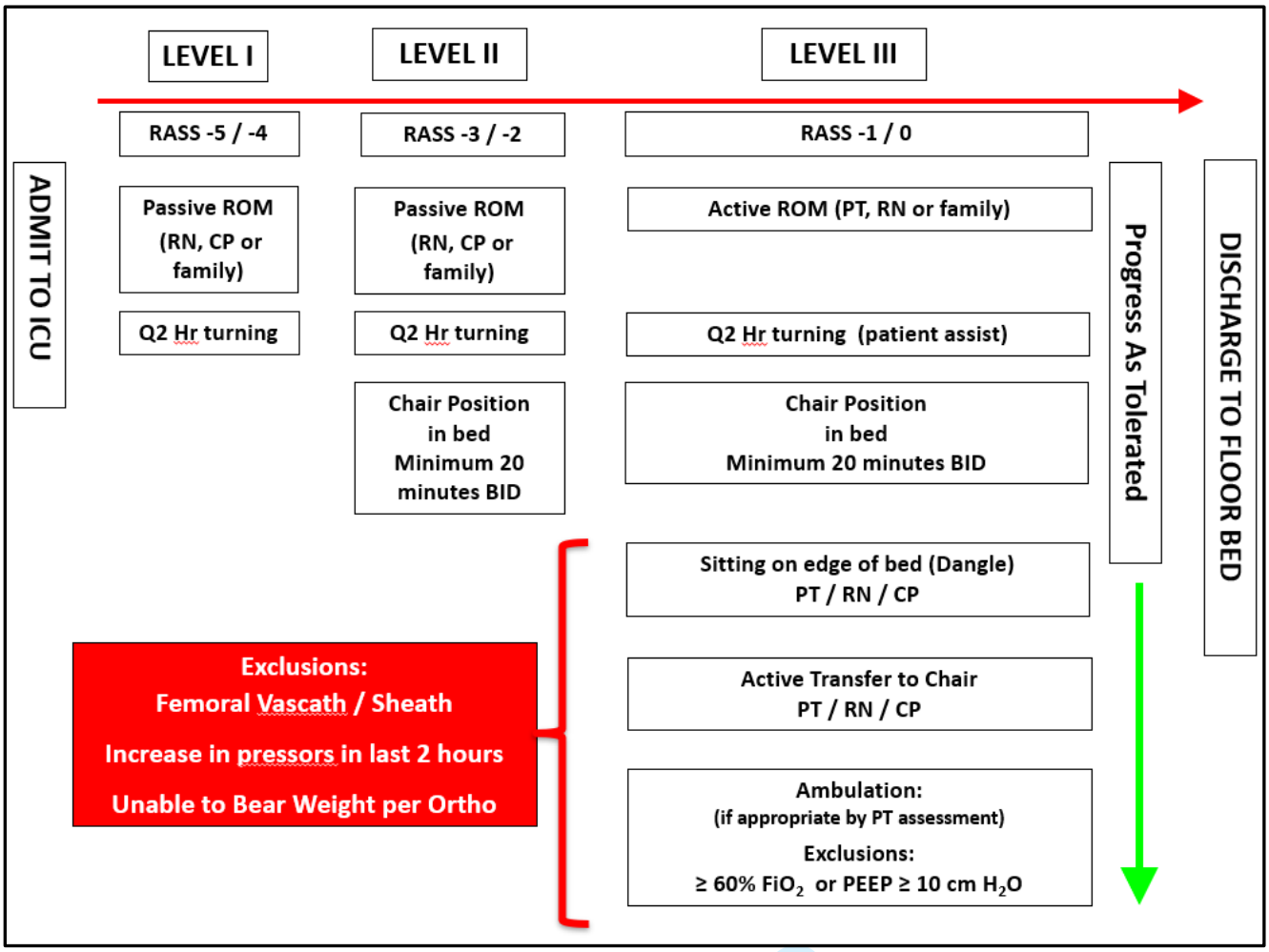
7. Protocol for Early Mobility



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8. Development of the Model for the Primary Analysis

In preparation for PROPER, we collected data on the provision of post-extubation respiratory support and the incidence of reintubation from 420 patients who met inclusion/exclusion criteria for PROPER in a 12-month period (6/1/2015 to 5/31/2016) prior to the trial. Using generalized linear mixed-effects modeling treating the two geographic regions of the unit as clusters and the four 3-month blocks as periods, we calculated the intra-cluster correlation coefficient to be <0.001, the intra-period correlation coefficient to be <0.001, and the intra-cluster intra-period correlation coefficient to be <0.001.

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9. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

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10. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

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11. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

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12. Data Sharing Plan

Upon reasonable request, a completely de-identified data set may be provided by the authors. Request to share data from the PROPER trial should be sent to the principal investigator, Jonathan Casey, MD at Jonathan.D.Casey@vumc.org. The data set will be provided to researchers whose proposed use of the data has been approved by the steering committee and an Institutional Review Board.

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SUPPLEMENTAL FIGURES

Figure S1. PROPER Consort Diagram Template

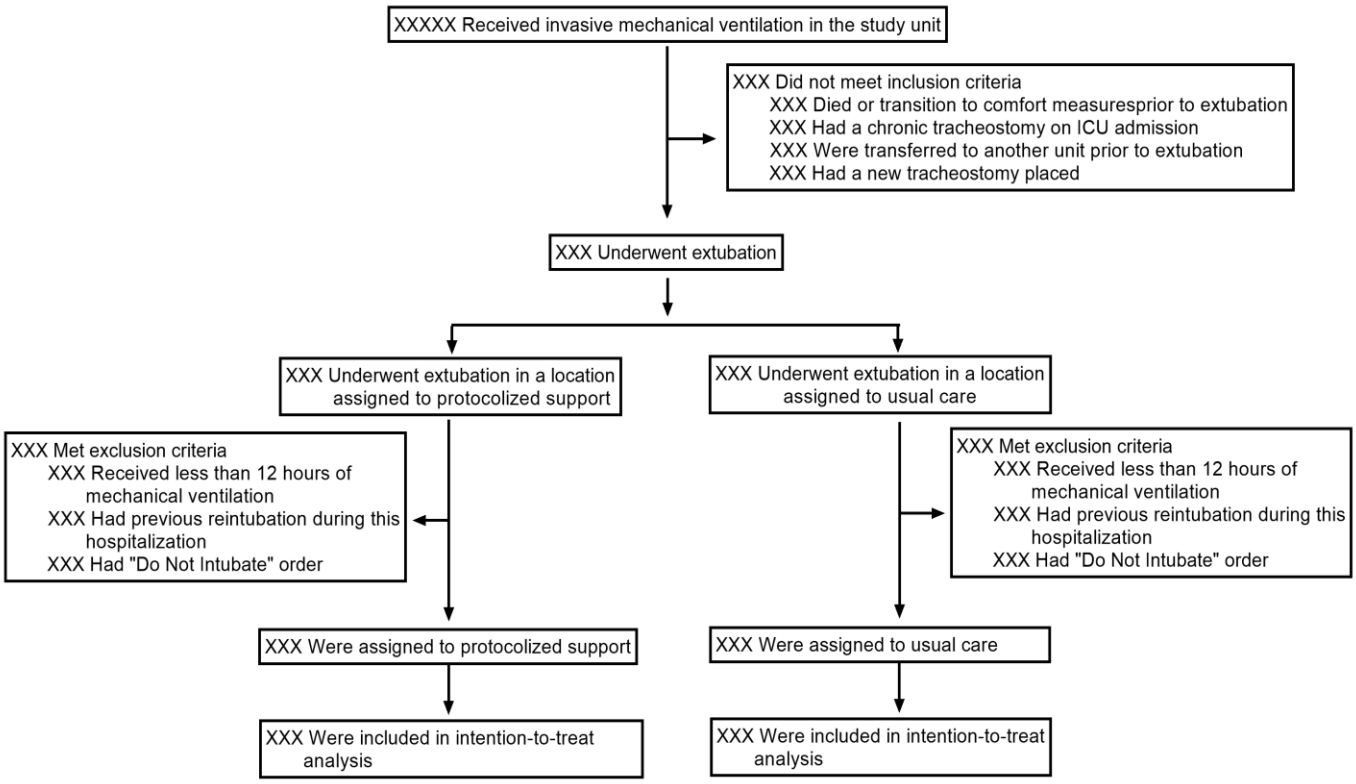

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Figure S2. Protocol for Initiation, Titration, and Weaning of Non-Invasive Ventilation

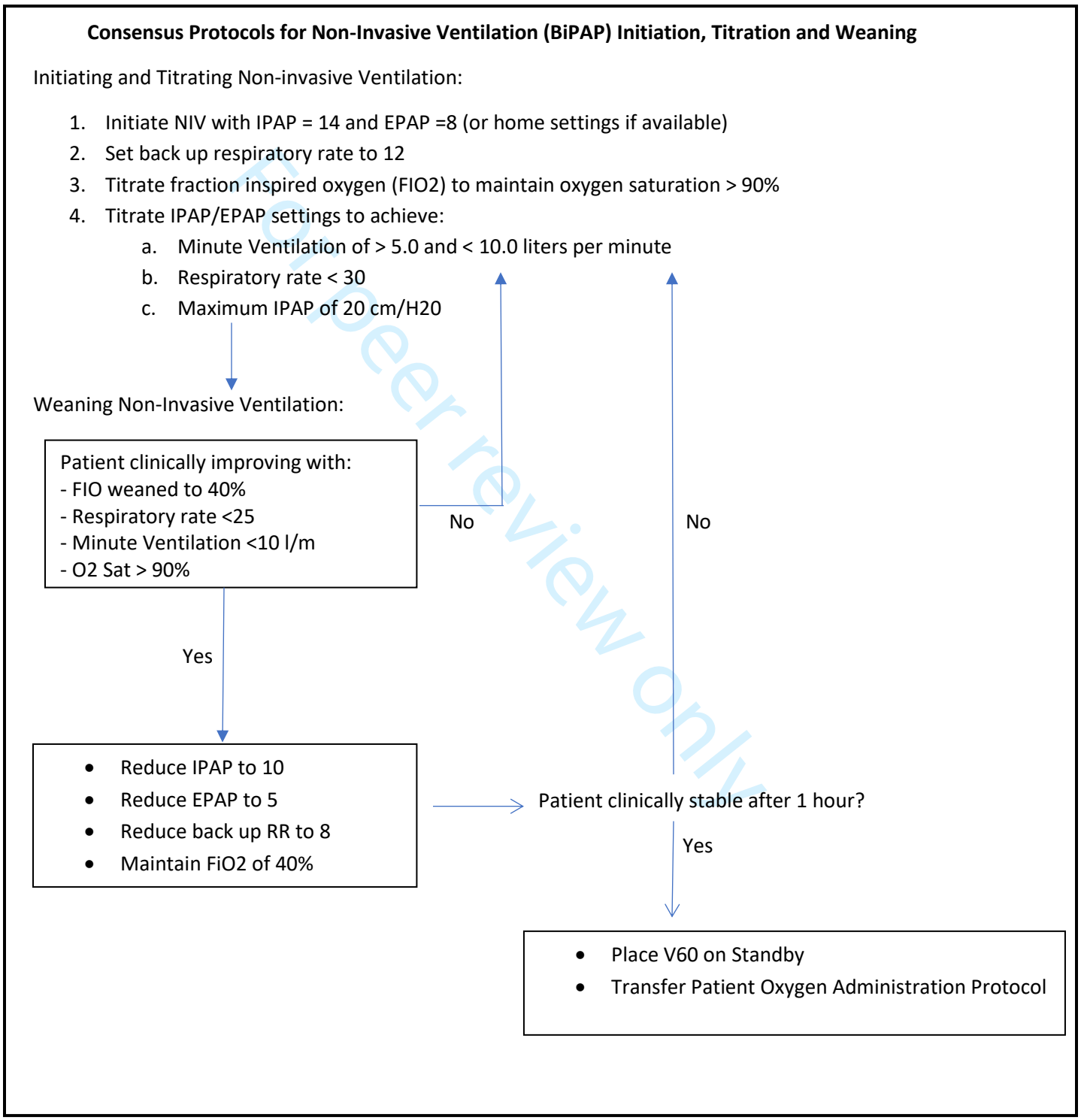

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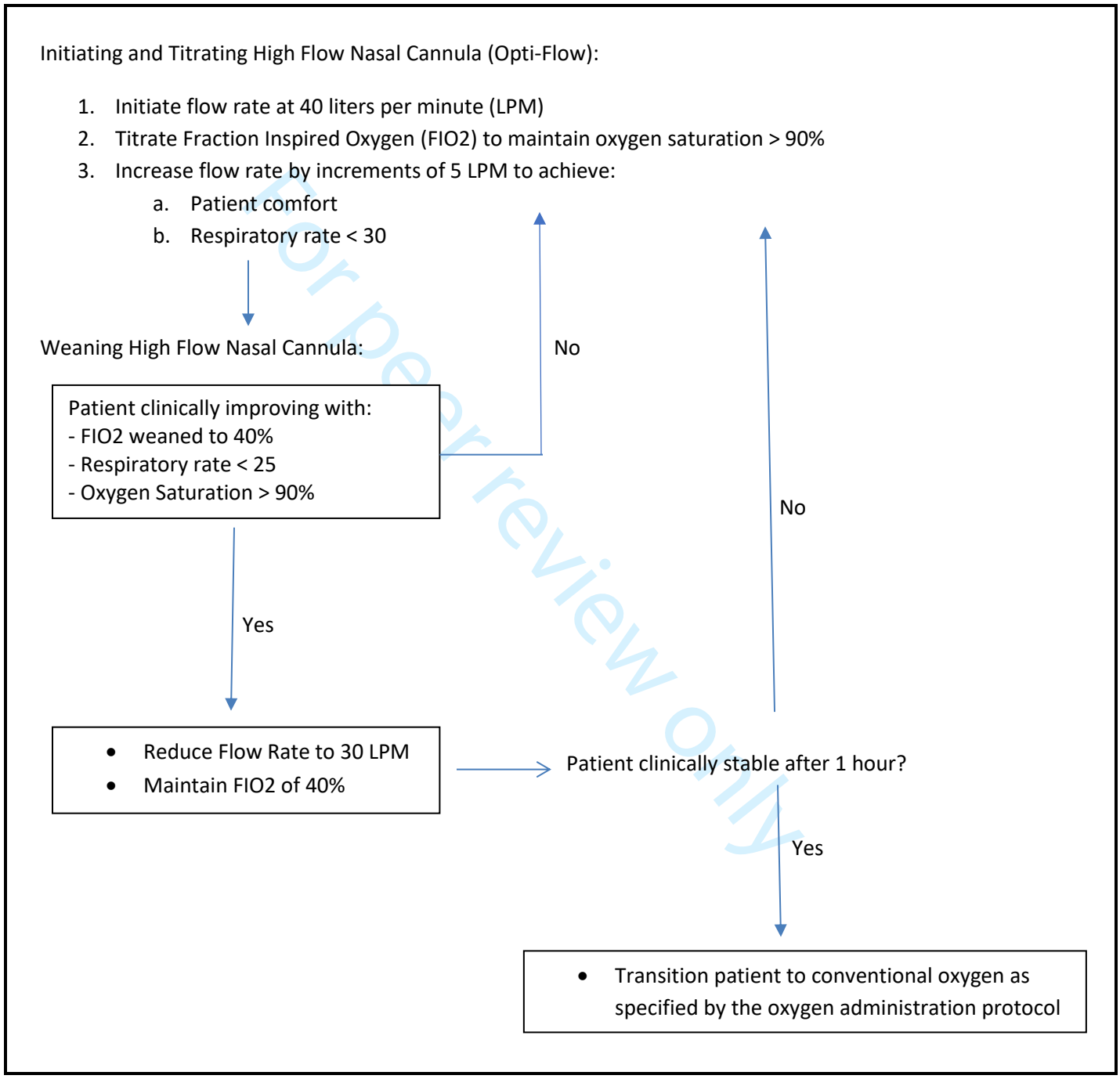
Figure S3. Protocol for Initiation, Titration, and Weaning of High Flow Nasal Cannula



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