Protocolized Post-Extubation Respiratory Support (PROPER) Study

Version 1.3

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1.0 Study Summary

Title:

Background:

Invasive mechanical ventilation is common in the ICU. Approximately 25% of patients in the Vanderbilt MICU require invasive ventilation at some point during their hospitalization. Protocols for low tidal volume ventilation, daily spontaneous awakening trials, and daily spontaneous breathing trials have significantly shortened the duration of mechanical ventilation and improved patient outcomes. Despite these improvements, the period of time following extubation remains high risk. Around 25% of patients develop recurrent respiratory failure after extubation and up to 15% require reintubation. Reintubation is an independent predictor of increased mortality.

Post-extubation respiratory support with non-invasive ventilation or high flow nasal cannula appears to reduce the reintubation rate, but utilization remains low. Whether implementation of a protocol identifying patients who may benefit from post-extubation respiratory support and coordinating with respiratory therapists to deliver respiratory support as part of routine protocolized care without a specific physician order decreases reintubation rates remain unknown. To determine the effect on reintubation rate of a protocol for post-extubation respiratory support, we propose a three phase study: an initial period of observation of current practices; an intervention period comparing protocolized post-extubation respiratory support with usual care; and (if protocolized post-extubation respiratory support decreases the rate of reintubation) a dissemination period during which the protocol will be extended to all patients and post-intervention practices and outcomes will be observed.

Primary Aim:

- To compare the effect of protocolized post-extubation respiratory support, versus usual care, on the rate of reintubation within 96 hours (4 days) of extubation.

Primary Hypotheses:

- Protocolized post-extubation respiratory support will decrease the reintubation rate experienced by adults undergoing extubation in the Vanderbilt MICU.

Inclusion Criteria:

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

Exclusion Criteria:

1. Patient is receiving ventilation via a tracheostomy
2. Patient is being extubated to comfort measures or has "Do Not Re-intubate" 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

Consent: Given that (1) all therapies in the protocolized post-extubation respiratory support group and usual care group are part of current routine medical care for patients undergoing extubation in the Vanderbilt MICU, (2) lack of established risk or benefit of a post-extubation respiratory support protocol, (3) provisions allowing treating clinicians to employ non-invasive ventilation, high-flow nasal cannula, or any other form of respiratory support (regardless of group assignment) when felt to be needed for the safe treatment of any specific patient, and (4) the impracticability of obtaining informed consent for the implementation of a protocol to all patients cared for by a single respiratory therapist, waiver of informed consent will be requested.

Group Assignment: Patients' treatment group will be determined by room number, with the MICU divided into two clusters, based on geography (front hall and back hall). Geographical group assignment is designed to align with the rooms covered by each of the two respiratory therapists who staff the unit. Based on MICU admitting protocols, patients are arbitrarily assigned to the first available room with no intentional movement/placement of patients by severity of illness, amount of nursing needs, or other clinical factors. To control for any potential bias created by geographic assignment of the study intervention, the groups will undergo five cross-overs so that each bed will spend half of the study in the protocolized post-extubation respiratory support group and half in the usual care group.

Study Interventions:

- **Protocolized post-extubation respiratory support** – At the time of extubation, all qualifying patients will be initiated on either non-invasive ventilation or high flow nasal cannula, which will be continued until the earlier of 5AM the following day or ICU transfer.
- **Usual Care** – The decision for post-extubation respiratory support will be left to the patient's clinical team.

Primary Endpoint:

- Reintubation within 96 hours (4 days)

Secondary Endpoints:

1. All cause in-hospital mortality
2. ICU-free days
3. Ventilator-free days
4. Time to reintubation
5. Indication for reintubation
6. Respiratory-caused reintubation
7. Laryngeal edema requiring reintubation
8. Delirium within 96 hours of extubation
9. Agitation within 96 hours of extubation
10. Lowest S/F ratio at 0-6, 6-12, and 12-24 hours post-extubation
11. Highest respiratory rate at 0-6, 6-12 and 12-24 hours
12. Use of HFNC or NIV beyond 24 hours post-extubation

2.0 Background

Invasive mechanical ventilation is common in the ICU. Approximately, 25% of Vanderbilt MICU patients require invasive mechanical intubation at least once during their hospitalization. Protocols for low tidal volume ventilation, daily spontaneous awakening trials, and daily spontaneous breathing trials have significantly shortened the duration of mechanical ventilation and improved outcomes for these patients. Despite these improvements, the period of time following extubation remains high risk. Around 25% of patients experience post-extubation respiratory failure and 11 to 15% of patients require reintubation after their first extubation.[1–3] In patients identified to be at high risk, reintubation rates may be as high as 28%.[2,4] Reintubation is associated with increased rates of nosocomial infection[5] and is an independent predictor of mortality, with a relative risk ranging from 3.29-5.34 and an absolute mortality ranging from 19-50%.[3,6,7] Despite significant improvements in the management of patients receiving invasive mechanical ventilation, the rate of reintubation has not changed significantly in the last 20 years.[8–10]

Based on unadjusted, retrospective data from our ICU, reintubation is associated with a relative risk of in-hospital mortality of 4.5 (absolute rate of mortality of 28.8%, compared to 6.0%). The prevention of complications following extubation is a key focus of critical care research and quality improvement.[1–3,11,12] The only therapy to date shown to reduce the rate of reintubation is post-extubation respiratory support with either non-invasive ventilation or high flow nasal cannula. Use of these therapies in usual care, however, remains low.

2.1 Prophylactic non-invasive ventilation (NIV) following extubation

NIV prevents intubation and decreases mortality in patients with respiratory failure from COPD.[13,14] It also improves the safety of the intubation process.[15] In patients who experience recurrent respiratory failure after extubation, however, the data have been disappointing, with evidence that post-extubation “rescue” NIV (applied when a patient develops respiratory failure hours or days after extubation) delays the time to reintubation and is associated with an increase in ICU-mortality.[11,16] More recent trials have explored the use of prophylactic NIV (started at the time of extubation and continued for a predetermined period of time). Two trials of 97 and 162 patients at high risk of reintubation, showed that prophylactic NIV for a period of 24 to 48 hours after

extubation decreased the rate of post-extubation respiratory failure and the rate of reintubation.[4,17] A subsequent trial of patients who were hypercarbic on their pre-extubation spontaneous breathing trial showed that 24 hours of prophylactic NIV decreased 90 day mortality from 31% to 11%.[18] National guidelines for management following extubation were recently updated to include a recommendation for NIV in patients at high risk of reintubation.[19]

2.2 Prophylactic high flow nasal cannula (HFNC) following extubation

HFNC is an apparatus that delivers flow rates up to 60 liters per minute with a consistent percent of oxygen that can be finely titrated up to an FIO2 of 1.0. HFNC has been shown to provide patients with a low level of continuous positive airway pressure, with dead space washout, decreasing the work of breathing while also improving patient comfort and secretion management.[20–24] HFNC has been suggested to improve mortality in patients with hypoxemic respiratory failure.[13] Prophylactic HFNC for 24 to 48 hours after extubation in non-hypercapneic patients has been demonstrated to prevent reintubation in high risk patients, low risk patients, and a general population of ICU patients.[12,25,26]

2.3 Current Utilization of Post-extubation Respiratory Support at Vanderbilt MICU

Prophylactic NIV and HFNC have been shown to improve outcomes following extubation in numerous patient populations. When taken together, these studies suggest that all patients might benefit from some form of post-extubation respiratory support (NIV or HFNC) – and post-extubation respiratory support has been recommended in national guidelines[19]. Despite this, the utilization of any form of post-extubation respiratory support remains low in the Vanderbilt Medical Intensive Care Unit. Review of 12 months of data from the Vanderbilt MICU, obtained from a prospective trial enrolling a similar patient population, showed that post-extubation respiratory support is provided in only 8.3% of extubations. Several reasons may explain the low rate of post-extubation respiratory support provided in the Vanderbilt MICU.

First, the existing studies on post-extubation respiratory support were all performed in Europe, where practice patterns and patient populations differ dramatically from ICUs in the United States. These differences are highlighted by the reintubation rates, which in European ICUs have been reported to be 14.4% for "low risk" patients[25] and 19.1% for "high risk" patients,[26] compared to a reintubation rate of just 12.1% for all patients in the Vanderbilt MICU. Second, evidence-based recommendations may take as long as 17 years to translate into routine clinical practice[27]. The majority of trials examining NIV and HFNC after extubation have been published in the last 5 years, and these results may not yet have diffused into practice. Third, provision of post-extubation respiratory support requires coordination between the physicians, nurses, and respiratory therapists. The results of studies of spontaneous awakening and breathing trials suggest that this coordination may be inefficient or incomplete in routine care and can be aided by implementation of a structured protocol[28].

Implementation of a respiratory therapist driven protocol to provide post-extubation respiratory support to all patients undergoing extubation in the ICU has the potential to improve utilization of recommended respiratory support and decrease the rate of reintubation, but currently (1) no validated protocols exist and (2) the effect of such a protocol on reintubation in our patient population is unknown.

We propose a three-phase study: an initial period of observation of current practices, an intervention period comparing a respiratory therapist driven protocol for post-extubation respiratory support with usual care, and (if protocolized post-extubation respiratory support decreases the rate of reintubation) a dissemination period during which the protocol will be extended to all patients and post-intervention practices and outcomes will be observed.

3.0 Rationale, Aims, and Hypotheses

To determine whether protocolized post-extubation respiratory support (high flow nasal cannula or non-invasive ventilation) prevents reintubation compared to usual care, a comparative-effectiveness study is needed.

Study Aims:

- **Primary**
  - To evaluate the effect of respiratory therapy driven protocolized post-extubation respiratory support, compared with usual care, on the rate of reintubation of critically ill adults.
- **Secondary**
  - To evaluate the effect of the same intervention in the same population on clinical outcomes (ventilator-free days, ICU-free days, and in-hospital mortality, physiologic outcomes (heart rate, respiratory rate, FIO_2, SaO_2:FIO_2 hours post-extubation, arterial pH, and $PaCO_2$) at 0-6, 6-12, and 12-24 hours post-extubation, procedural outcomes (e.g. indication for reintubation), and other ICU-related morbidity (e.g., delirium).

Study Hypotheses:

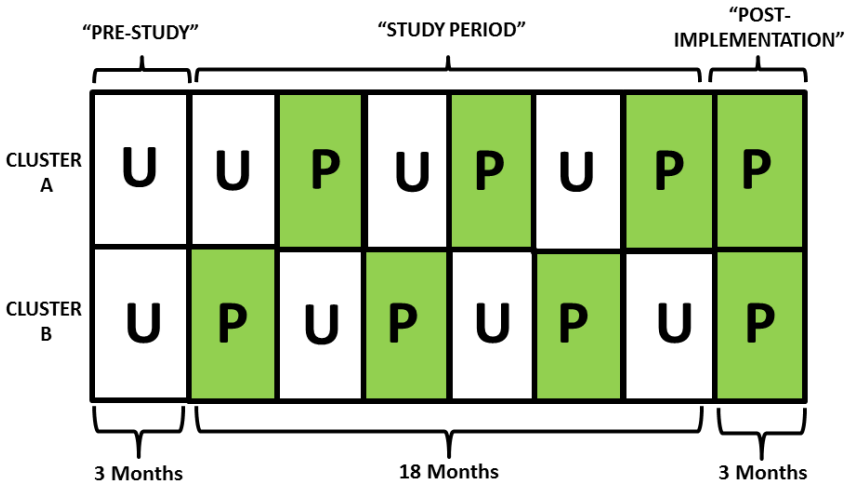
- **Primary:**
  - Respiratory therapy driven protocolized post-extubation respiratory support will decrease the incidence of reintubation among patients extubated in the medical intensive care unit, compared with usual care.

- **Secondary:**
  - Protocolized post-extubation respiratory support will increase the number of ventilator free days and ICU-free days without affecting in-hospital mortality.

4.0 Study Description

To address the aims outlined above, we propose a three-part quality improvement study, comprised of an initial observational period, an interventional period of cluster-randomized double-crossover design, and a dissemination period of post-implementation surveillance.

STUDY DESIGN



U= Usual Care
P = Protocolized Post-Extubation Respiratory Support

Period 1: During the first 3 months of the study, we will prospectively collect information on the baseline rates of post-extubation respiratory support and reintubation without any intervention.

Period 2: Over the subsequent 18 months, the intervention will be applied at the level of the respiratory therapist. Patients in the MICU are cared for by two respiratory therapists, each of whom covers half of the ICU beds, based on geography (front hall, back hall). A protocol for post-extubation respiratory support and education on the delivery of NIV and HFNC after extubation will be provided to one of the two respiratory therapists. The delivery of the intervention will include (1) provision of a written protocol detailing which patients qualify for post-extubation respiratory support and the manner in which post-extubation respiratory support may be delivered, (2) an initial 30 minute educational session for the respiratory therapist on the techniques and evidence surrounding post-extubation respiratory support, (3) bi-weekly five-minute debriefing on the experience with and barriers to post-extubation respiratory support, (4) a set of physical reminders in the location in which the intervention will be provided, and (5) 24/7 availability of the study team for questions concerning the provision of post-extubation respiratory support. One half of the MICU patients will receive protocolized post-extubation respiratory support (from the respiratory therapist using the protocol and receiving the educational interventions). The remaining half of MICU patients,

cared for by the respiratory therapist not using the protocol or receiving the educational interventions, will serve as a control and receive usual care. The 18-month interventional period will be divided into six blocks of 3 months, with a cross-over between the intervention and the usual care group occurring at the end of each block. Outcomes will be analyzed at the end of the 18-month intervention period.

Period 3: If protocolized post-extubation respiratory support decreases the reintubation rate, the protocol will be provided to all MICU respiratory therapists and applied to all MICU patients. For 3 months post-implementation, we will monitor the compliance with the protocol and reintubation rate, in the absence of ongoing education and feedback to capture use of and performance of the protocol during routine care.

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

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

5.2 Exclusion Criteria:

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

6.0 Enrollment

6.1 Study Sites:

- Medical Intensive Care Unit at Vanderbilt University Medical Center

6.2 Study Population:

All adults located in the Vanderbilt MICU who have been receiving mechanical ventilation for more than 12 hours via an endotracheal tube and who undergo extubation. Patients will be excluded if they are being extubated to comfort measures or have a "Do Not Reintubate" order in place at the time of extubation or if they are immediately re-intubated after a self- or unplanned extubation.

If the clinical team feels that respiratory support is contraindicated, it will be withheld, regardless of group assignment, but the patient's data will be collected and included in the intention-to-treat analysis. Patients will be included regardless of gender, race, weight, body mass index, history of underlying lung disease, oxygen requirement, or other clinical factors.

6.3 Enrollment: Patients will be enrolled at the time of extubation if the patient meets inclusion but not exclusion criteria.

6.4 Consent:

Extubation without protocolized respiratory support and a respiratory therapist driven protocol guiding respiratory support after extubation are both within the spectrum of current routine care in MICUs like Vanderbilt. All of the interventions examined are interventions to which the patient might be exposed to undergoing extubation in the MICU outside of the context of a study. There are no established benefits or risks to a post-extubation respiratory support protocol. In our study, treating clinicians will always be allowed to use post-extubation respiratory support in the usual care group or no respiratory support in the intervention group, if they feel it is necessary for the safe treatment of that individual patient. For these reasons, we feel that this study of a post-extubation respiratory support protocol poses minimal risk.

The intervention in this study is applied at the level of the respiratory therapist who will receive education on post-extubation respiratory support, a protocol for applying post-extubation respiratory support, and structured feedback on their performance. The intervention occurs at a practice level and is applied to every patient under that respiratory therapist's care. All patients assigned to a respiratory therapist in the intervention group will receive protocolized post-extubation respiratory care. All patients in the control arm will be provided usual care by a respiratory therapist who will not be using a protocol for post-extubation respiratory support. Patient-level informed consent would cause unacceptable contamination of the study intervention as therapists using the protocol on some patients are likely to apply it to other patients for whom no protocols are in place. In such a cluster-level design, enrolling every patient

cared for by two respiratory therapists who will be using two different approaches to extubation in the ICU, obtaining informed consent from all intubated MICU patients would be impracticable.

Given the minimal risk and impracticability of informed consent, we will request waiver of informed consent. The use of the secure, online database REDCap for the collection of any Protected Health Information required for the study minimizes the risk to the privacy rights of the individual and the protection of privacy will be not be affected by the presence or absence of a waiver of consent.

6.5 Group Assignment

This is a pragmatic, quality improvement study comparing protocolized post-extubation respiratory support to usual care using a cluster-crossover design. Patients' treatment group will be determined by their ICU room number. In the VUMC MICU, patients are assigned to rooms based on bed availability with no selection preference for severity of illness or other clinical criteria. To control for any potential bias created by geographic assignment of the study intervention, the groups will undergo five cross-overs so that each ICU bed will spend half of the study in the protocolized post-extubation respiratory support group and half in the usual care group. The initial group assignment will be generated by simple, computerized randomization. Each cluster will then alternate group assignment for each block for the remainder of the study. Blinding of treating providers and nursing staff will not be possible in this study.

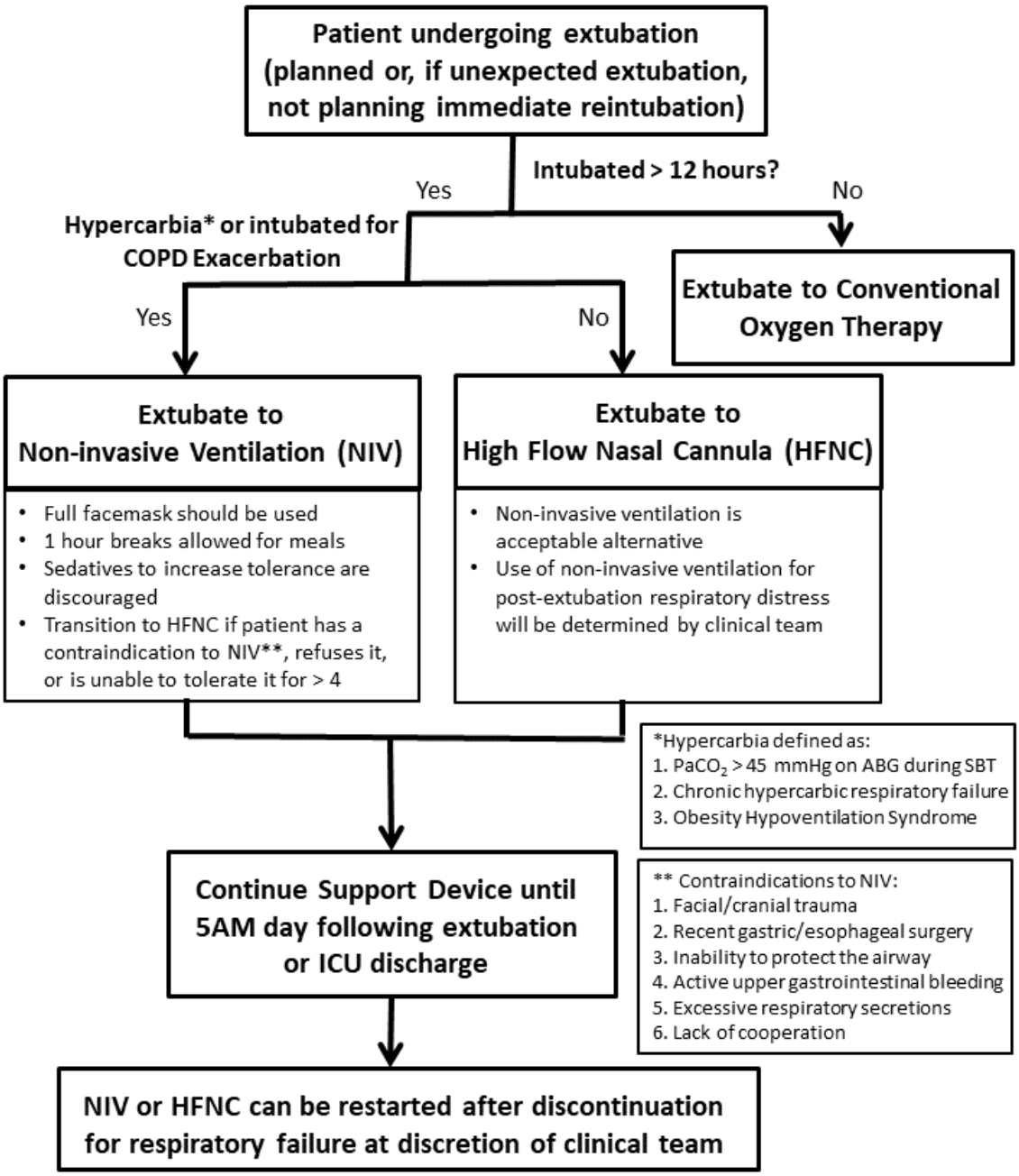
7.0 Study Procedures

7.1 Treatment Arms

Protocolized Post-extubation Respiratory Support (Intervention)

All respiratory therapists will be given a 30-minute educational lecture on the techniques and evidence base surrounding post-extubation respiratory support before the start of the period assigned to implementing the protocol. During the study period, respiratory therapists in the intervention group will be provided with the protocol below, which identifies patients who are eligible for post-extubation respiratory support group, provides criteria for selection of non-invasive ventilation (NIV) or high flow nasal cannula, and provides instructions for the implementation of these interventions:

Post-Extubation Respiratory Support Protocol (PROPER Trial)



NIV will be recommended for all patients intubated for a COPD exacerbation and for all hypercarbic patients. Hypercarbia will be defined as a partial pressure of arterial carbon dioxide (PaCO2) >45 mm Hg on an ABG if one is obtained during a spontaneous breathing trial, known chronic hypercarbic respiratory failure, or obesity hypoventilation syndrome. Any patient meeting one of these criteria will be placed on NIV immediately following extubation. Patients with any of the following conditions are felt to have a contraindication to non-invasive ventilation, and it will not be provided:

1. Facial or cranial trauma or surgery,
2. Recent gastric or esophageal surgery
3. Inability to protect the airway
4. Active upper gastrointestinal bleeding
5. Excessive amount of respiratory secretions
6. Lack of cooperation

NIV may be discontinued at any point if felt by the clinical team to be impeding patient safety. Patients may take breaks of one hour to eat or drink or for comfort. Patients who have one of the contraindications listed above or are unable to tolerate NIV for more than 4 hours should be placed on high flow nasal cannula. Sedatives to increase tolerance to NIV will be discouraged. NIV will be continued until 5AM the day following extubation (the time at which spontaneous breathing trials are initiated on mechanically ventilated patients in our intensive care unit). If a patient is felt to be stable for transfer out of the ICU prior to 5AM the day following extubation, NIV can be discontinued at the time of ICU transfer. Patients who develop respiratory failure following the discontinuation of respiratory support can be restarted on NIV or HFNC at the discretion of their clinical teams.

NIV is a routinely employed intervention familiar to clinicians and respiratory therapists in the intensive care unit. In keeping with the pragmatic focus of the study, non-invasive ventilation will be delivered by the same clinicians who would perform the intervention outside of the research setting. NIV will be delivered using a full facemask. Inspiratory pressure support will be titrated according to standard respiratory protocols with a suggestion range of (12–20 cm H2O) and suggested goal respiratory rate less than 25 breaths per min. Expiratory pressure and FIO2 will be adjusted to maintain SPO2 of greater than 90%.

HFNC will be recommended for all patients who are not hypercarbic and were not intubated for a COPD exacerbation. HFNC will be started immediately following extubation and will be continued until 5AM the following day at which time it will be weaned according to a pre-existing protocol developed by respiratory therapy. If a patient is felt to be stable for transfer out of the ICU prior to 5AM the day following extubation, NIV can be discontinued at the time of ICU transfer. NIV is an acceptable alternative for patients in whom this approach is preferred by the clinical team. The decision to use NIV as a rescue treatment for patients with post-extubation respiratory

failure on HFNC will be made by the clinical team but will not be encouraged and will be recorded.

Decisions regarding all other respiratory treatments (diuretics, intravenous fluids, antibiotics, corticosteroids, breathing treatments) will be made by the clinical team. The diagnosis of post-extubation respiratory failure and the decision to use rescue NIV or reintubate will be made by the treating clinicians. If any healthcare provider participating in the patient's care believes that the study intervention cannot be safely provided, the study intervention will be halted and the patient will be provided whatever post-extubation respiratory support is felt to be appropriate by the clinical team.

Usual Care (Control)

The respiratory therapist will not be provided with a protocol for post-extubation respiratory support. Decisions regarding post-extubation respiratory support will be made by the patient's clinical team. NIV and HFNC may be used at the discretion of the clinical team as post-extubation respiratory support or as rescue therapy for post-extubation respiratory therapy. The use of NIV for the treatment of post-extubation respiratory failure will not be encouraged but will be allowed at the discretion of the clinical team. Decisions regarding all other respiratory treatments (diuretics, intravenous fluids, antibiotics, corticosteroids, breathing treatments) will be made by the treating clinicians as will the diagnosis of post-extubation respiratory failure and the decision to use rescue NIV or reintubate. If NIV or HFNC are given as post-extubation respiratory support to a patient in the control arm, we will request that the ordering physician and that patient's respiratory therapist complete a brief data collection sheet explaining the type of device planned, home NIV use, the indication for the device, and the initial device settings.

7.2 Blinding

Given the nature of the study intervention, patients, clinicians, and investigators will not be blinded to group assignment.

7.3 Data Collection

Baseline: Age, gender, height, weight, body mass index, race, APACHE II score, length of mechanical ventilation (prior to first extubation), active medical problems at the time of extubation, mean arterial pressure and vasopressor use prior to extubation, highest FiO_2 delivered in prior 24 hours, lowest oxygen saturation in prior 24 hours, pH, PaO_2, $PaCO_2$, SaO_2:FIO_2, indication for intubation, reason for ICU admission. Date of first spontaneous breathing trial.

0-96 hours: The need for reintubation within 96 hours (the primary outcome), time to reintubation. Indication for reintubation. Laryngeal edema requiring reintubation. The amount of time spent receiving HFNC and NIV. Levels of respiratory support provided with these devices (flow rate, FIO2, IPAP, EPAP). Respiratory rate, heart rate, pH, $PaCO_2$, SaO_2, FiO_2, at 0-6, 6-12, and 12-24 hours post-extubation. CAM-ICU score from 0-96 hours post-extubation. RAS score from 0 to 96 hours post-intubation.

In-Hospital Outcomes: Rate of reintubation, date of ICU discharge (for ICU-free days), date of death, ventilator-free days

7.4 Outcome Measures

Primary Endpoint:

- Reintubation within 96 hours of extubation

Secondary Endpoints:

1. All-cause in-hospital death
2. ICU-free days
3. Ventilator-free days
4. Time to reintubation
5. Indication for reintubation
6. Respiratory-caused reintubation
7. Laryngeal edema requiring reintubation
8. Delirium with 96 hours of extubation
9. Agitation with 96 hours of extubation
10. Lowest S/F ratio in the first 24 hours
11. Highest respiratory rate at 0-6, 6-12 and 12-24 hours
12. Use of HFNC or NIV beyond 24 hours post-extubation

ICU-free days to 28 days after enrollment will be defined as the number of days alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit in that hospitalization before 28 days. 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 from the date of final ICU discharge. All data collection will be censored at the first of hospital discharge or 28 days.

Ventilator-free days to day 28 will be defined as the number of days alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves

unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0. If a patient is discharged while receiving assisted ventilation, VFD will be 0. All data collection will be censored at the first of hospital discharge or 28 days.

8.0 Risks and Benefits:

For mechanically ventilated patients who are undergoing extubation in the MICU, there are currently no established risks or benefits to protocolized post-extubation respiratory support. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients undergoing extubation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective patient care for patients following extubation.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

This study will take place in the environment of the intensive care unit in which each participant will have access to invasive or noninvasive monitoring, and a bed-side nurse with high-acuity nurse-to-patient staffing ratio. During the study, the patient will be cared for by a respiratory therapist, a critical care nurse, and usually a pulmonary and critical care fellow or attending, in addition to continuous invasive or non-invasive monitoring.

Additionally, study personnel will be readily available to answer questions at any time during the study course. If any healthcare provider participating in the patient's care believes that the study interventions cannot be safely performed, the study

intervention will be halted and the patient will be provided whatever post-extubation respiratory support is felt to be appropriate by the clinical team.

9.2 Adverse Events

An adverse event is defined as any unexpected and untoward medical occurrence in a clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) will be defined for this trial as any unexpected and untoward medical occurrence that meets any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the clinical team or bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events. Serious and unexpected adverse events associated with study interventions will be recorded in a case report form in the study record and reported to the IRB within 7 calendar days in accordance with IRB policy. Patients who have required mechanical ventilation in the critical care setting are known to be at risk for numerous adverse events following extubation including hypoxemia, hypercarbia, aspiration, reintubation, hypotension, severe bradycardia, cardiac arrest, and death. These events will be recorded as study outcomes and monitored by the study personnel. However, in the absence of an imbalance of the above events between study groups, these events are expected in the routine performance of critical

care medicine and will not be individually recorded and reported to the IRB as serious and unexpected adverse events, unless the investigators or clinical team believe the event was related to the study intervention.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

SAMPLE SIZE CALCULATION (9/12/17):

Review of 12 months of data obtained during a previous prospective trial enrolling a similar population of patients in the same ICU demonstrated a reintubation rate of 12.1% within 96 hours, similar to that reported in previous observational studies of post-extubation outcomes.[1,3] Trials of prophylactic post-extubation NIV have suggested that it may reduce the relative risk of reintubation by 49 to 66% in high risk patients.[4,17] Trials of prophylactic post-extubation HFNC have suggested that it may reduce the rate of reintubation by 81% in high risk patients and 60% in low risk patients and is non-inferior to NIV in high risk patients[12,25,29]. We estimate that the initiation of a protocol for post-extubation respiratory support will reduce the relative risk of reintubation by 55% (equivalent to an absolute risk reduction of 6.655%).

Based on our analysis of retrospective data, we suspect that intra-cluster correlation, intra-period correlation, and intra-cluster-intra-period correlation will be negligible and will not affect our sample size calculations.

Using PS version 3.1.2 with the above assumptions and a chi-squared analysis with an alpha level of 0.05, we calculated that achieving a statistical power of 0.8 would require enrollment of 566 patients. To account for the low, baseline utilization of post-extubation respiratory support in the usual care group (8.3% of patients in retrospective cohort), which we expect to continue, we estimate that our sample size should be increased by 10% to 623 patients. Based on retrospective data suggesting 35 eligible patients are extubated each month, we have planned an 18-month intervention period during which we anticipate enrolling 630. We anticipate observing approximately 105 extubations during each of the initial observational and the dissemination periods.

At the end of the third cluster cross-over (12 months), we will examine the enrollment rate, the reintubation rate in the usual care arm, and the rate of utilization of post-extubation respiratory support in the intervention and control arms. Using these statistics, we will re-calculate the sample size needed for a power of 0.8 and an alpha level of 0.5. If appropriate, the principal investigator will have the ability to extend the trial by up to 6 months (two additional intervention periods with cross-overs at month 18 and 21).

SAMPLE SIZE UPDATE (1/4/19):

As a cluster-randomized, multiple-crossover trial, the intervention portion of PROPER has been designed to enroll for a fixed duration to ensure that each cluster spends an equal amount of time receiving each treatment group. The trial has been approved to enroll for 18 months, from 10/1/2017 to 3/31/2019. The total number of patients enrolled will depend on the rates of mechanical ventilation in the MICU during the fixed time period of the trial. Based on retrospective data, we estimated that approximately 630 patients would be enrolled under the planned study duration. The number of patients receiving mechanical ventilation in the MICU has increased over the duration of the trial, however, and we now anticipate between 720 and 740 patients will be enrolled during the planned study period.

Statistical Analysis:

Trial profile:

We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:

To assess for baseline differences between the groups, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities), indication for intubation, active illnesses at the time of extubation, severity of Illness (APACHE II score), ICU length of stay, hospital length of stay, and duration of mechanical ventilation (prior to first extubation)

Analyses:

We will develop and make publicly available prior to the conclusion of enrollment a complete statistical analysis plan. This will detail an approach to the primary analysis which adequately accounts for the intra-cluster, intra-period, and intra-cluster-intra-period correlation observed in the study environment (if applicable). We will analyze the effect of group assignment on all secondary. We will evaluate for heterogeneity of treatment effect between pre-specified baseline variables, group assignment, and outcome using formal tests of interaction. We will perform “per-protocol” and “as-treated” analyses assessing the impact of contamination.

Presentation of Statistics

Continuous variables will be described as mean and standard deviation or median and 25th percentile – 75th percentile or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as number and percentage. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests; categorical variables will be compared with chi-square testing or Fisher's exact test as appropriate.

12.0 Privacy/Confidentiality Issues

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 will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until death or hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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PROTOCOL CHANGES BY VERSION

1. Protocol 1.1 9/12/17
    a. This version of the protocol changes the definition of the primary outcome to reintubation within 96 hours, based on newly released research proposing this as a new, universal standard
        i. Miltiades A, et al. Cumulative Probability and Time to Reintubation in U.S. ICUs. Crit Care Med. 2017 May;45(5):835-842
    b. This version also updates the sample size calculation based on the new estimate of the event rate (which changed from 12.4 to 12.1 with the change in definition of the primary outcome). After adjusting sample size to account for

contamination in the control arm, the duration of the study remains the same (18 months). We have added plans to recalculate the power/sample size at 12 months, with the option of extending the trial by up to 6 months if the trial is found to be underpowered.

c. This version describes a new data collection sheet that will be used to collect information on patients receiving post-extubation respiratory support in the usual care arm. This data collection sheet will be submitted, along with this protocol for IRB approval.

d. Finally, this form includes additional patient variables to be collected: date of first spontaneous breathing trial and RAS score from 0-96 hours post-intubation

2. Protocol 1.2 12/22/17
    a. This update to the protocol addresses patients who are felt to be stable for transfer out of the ICU prior to 5AM the day following extubation (the time at which device removal was recommended in the initial protocol). Neither HFNC or NIV are permitted outside of the ICU at VUMC. The protocol will be updated to allow the removal of protocolized post-extubation respiratory support at the time of ICU transfer.
3. Protocol 1.3 1/4/2019
    a. This version reflects an updated estimate of the expected sample size of the trial, which as a cluster-randomized multiple crossover trial is designed to enroll for a fixed time period (18 months).