OhioHealth

Exploratory Trial to Improve Postextubation Management for Patients at Risk for Extubation Failure

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1 ABBREVIATIONS

AE	Adverse Event
ACV	Assist Control Ventilation
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
BiPAP	BiLevel Positive Airway Pressure
CCU	Coronary Care Unit
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
DSMB	Data Safety Monitoring Board
FiO2	Fraction of inspired oxygen
GMC	Grant Medical Center
HCO3	Bicarbonate
HFNC	Heated High Flow Nasal Cannula oxygen
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
LAR	Legally Authorized Representative
LOS	Length of Stay
MICU	Medical Intensive Care Unit
MRN	Medical Record Number
MV	Mechanical ventilation
NIV	Non-invasive ventilation
OHRI	OhioHealth Research Institute
OHSP	Office of Human Subjects Protections
PaO2	Partial pressure of oxygen
PaCO2	Partial pressure of carbon dioxide
PHI	Protected Health Information
PSV	Pressure Support Ventilation
REDCap	Research Electronic Data Capture
RSBI	Rapid Shallow Breathing Index
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SICU	Surgical Intensive Care Unit
SIMV	Synchronized Intermittent-Mandatory Ventilation
VAP	Ventilator-Associated Pneumonia

2 STUDY SUMMARY

2.1 Protocol Summary Table

Protocol Title & Number	Exploratory trial to improve postextubation management for patients at risk for extubation failure IRB# 1332767
Study Short Title	GMC – Devulapally – Postextubation Management Pilot
Research Method	Prospective Interventional
Therapeutic Area	Pulmonary/Critical Care
Department	Intensive Care Unit, Critical Care Unit, 4 East
Study Description	This is an exploratory study designed to gather baseline information to determine the effectiveness of a standardized postextubation management protocol in a subset of patients at risk for reintubation.
Primary Endpoints	• Proportion of patients that require reintubation within 72 hours • Association between reintubation rates and patient demographics or characteristics
Secondary Endpoints	• Length of stay (ICU and total) • Ventilator time • In-hospital mortality • In-hospital adverse event rate • 30-day readmission rate
Prospective Cohort Study Population[a]	This study will include up to 40 mechanically ventilated, adult patients considered at-risk for re-intubation. See Section 6.3. for detailed inclusion criteria.
Intervention(s)	• Early NIV via BiPAP • High Flow Nasal Cannula breaks from NIV • Wean after 24 hours
Duration	Intervention Duration – Approximately 24 hours Study Duration – 3 months Participant Duration- total hospital stay, estimated at 14.1 ± 16.9 days (American Association for the Surgery of Trauma, 2011).

[a] Data for this study will be compared to a historical control cohort, comprising mechanically ventilated, high-riskpatients who underwent standard of care postextubation management.

2.2 Study Diagram

3 INTRODUCTION

3.1 Study Rationale

It is clinically challenging to predict when patients can be successfully removed from mechanical ventilation (MV). Liberating high-risk patients such as the elderly and those with complex, chronic cardiac or pulmonary diseases from MV is particularly challenging.

Evidence from randomized trials and meta-analyses suggests that the type of postextubation supportive care provided, such as oxygen delivery via nose or mouth, may affect the risk of reintubation. However, it is unclear which of many possible postextubation management protocols results in the best patient outcomes, particularly for this subset of high-risk patients.

The purpose of this exploratory study is therefore to assess a standardized combined protocol of postextubation oxygen delivery consisting of early, alternating NIV with HFNC over 24 hours following extubation. NIV and HFNC are both currently provided to patients at Grant Medical Center as standard of care, based on clinician judgement; however, the timing and nature of the methods are variable.

The purpose of this exploratory study is therefore to obtain preliminary data that will be used to plan a larger, randomized control trial designed to explicitly compare a standardized postextubation management protocol to other standard of care protocols in patients that are traditionally at high risk for extubation failure.

3.2 Background

Intensive Care Unit (ICU) patients that are on mechanical ventilation (MV) are assessed regularly to determine whether they will be able to successfully breathe on their own if removed from the ventilator. This determination is important, as keeping patients on the ventilator longer than necessary can result in lung injury, infections, and increased length of stay (Zein et al., 2016; Karthika et al., 2016). Conversely, removing a patient from the ventilator too soon, when the patient cannot breathe unsupported, can result in multiple complications that require the patient to be placed back on the ventilator and may increase morbidity and mortality (Karthika et al., 2016).

Predicting whether or not a patient can be successfully liberated from mechanical ventilation is challenging, and approximately 12-14% of patients who undergo planned extubation require reintubation within 48-72 hours (Thille et al., 2013). Several risk factors have been associated with reintubation, including a weak cough and frequent suctioning (Esteban et al., 2002), rapid shallow breathing index >58 breaths/min/L, positive fluid balance during the 24 hours preceding extubation, and pneumonia as the reason for initial intubation (Frutos-Vivar et al., 2006). Patients who are ≥65 years of age with severe chronic cardiac or respiratory disease appear to be at particularly high risk for extubation failure, with reintubation rates ranging from 35% to 67% (Thille et al., 2013; Robriquet et al., 2006). Given the subsequent extubation failure in a high percentage of patients deemed appropriate for extubation, a number of studies have been conducted to determine whether postextubation management can be optimized in order to reduce the likelihood that a patient will need to be reintubated.

Postextubation management typically includes oxygenation via facemasks or nasal cannula, and airway clearance using suctioning, bronchodilator therapy, and/or diuresis. Alternative approaches include the use of noninvasive ventilation (NIV) such as bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) and/or high flow nasal cannula oxygenation (HFNC). At OhioHealth Grant Medical Center, postextubation oxygen therapy is based solely on clinician discretion and there is limited data to support whether one approach is better than another. Published literature for trials designed to determine the clinical benefit of varying postextubation management protocols are difficult to interpret due to a lack of standardized approach to oxygenation and ventilator support following extubation, heterogeneity in the populations studied, and variable duration of therapy. Specifically, there is some evidence that NIV may prevent postextubation respiratory failure (Nava et al., 2005; Ferrer et al., 2006; El-Solh et al., 2006; Ferrer et al., 2009; Burns et al., 2014; Khilnani et al., 2011). However, results from other trials indicate that NIV may be ineffective or even potentially harmful if it is not initiated until after the onset of postextubation respiratory failure (Esteban et al., 2004; Keenan et al., 2002). Similarly, trials exploring the effect of HFNC on reintubation indicate that outcomes are highly dependent on patient population of interest, as HFNC has been shown to be equivalent to NIV in preventing reintubation in post-cardiac surgery patients (Stéphan et al., 2015) but inferior to NIV in patients intubated following abdominal surgery (Jaber et al., 2016).

Few studies explicitly compare HFNC to NIV in the high-risk patient population of interest and no trials have evaluated a combined postextubation management protocol. In the largest randomized control of HFNC vs. NIV to-date, Hernández et al. (2016) compared HFNC with NIV immediately after planned extubation in patients considered at high risk for reintubation and found that HFNC administered for 24 hours after extubation resulted in similar rates of reintubation compared to NIV (23% vs. 19%, respectively). This trial suggests that HFNC and NIV are equivalent in high-risk patients, in terms of safety and efficacy.

The purpose of this study is to evaluate a standardized postextubation management protocol consisting of intermittent BiPAP during the day (2 hours on, 2 hours off), BiPAP throughout the night, and HFNC administered during BiPAP breaks. The study investigator hypothesizes that patients who are placed on a combined protocol of intermittent NIV and HFNC following extubation may be at lower risk for reintubation.

4 SPECIFIC AIMS

The purpose of this study is to establish baseline data regarding the institutional reintubation rate in a specific, high-risk patient population of interest and to determine the preliminary effectiveness of a standardized intermittent NIV/HFNC protocol in patients considered high risk for reintubation. This is a prospective, non-randomized exploratory trial with the following specific aim(s):

Aim 1. Compare reintubation rates (within 72 hours) between patients that undergo a standardized, intermittent NIV/HFNC protocol and a historical control cohort.

Aim 2. Determine whether reintubation rates differ as a function of age, gender, co-morbidity, reason for intubation, service line/operative status, or modified RSBI.

Secondary aims include calculating length of stay (ICU and total hospital), total ventilator time, in-hospital mortality rate, adverse event rates, and 30-day readmission rate. The overall demographics of the interventional group will also be compared to the historical control cohort.

5 STUDY POPULATION AND SAMPLE SIZE

There are approximately 3-4 patients per business day (Monday through Friday) that require mechanical ventilation at OhioHealth Grant Medical Center, resulting in approximately 80 patients per month. An estimated 30% of these patients are high risk, resulting in an estimated 24 high-risk patients per month.

A historical control cohort will consist of up to 80 randomly selected high-risk patients that underwent planned extubation in an OhioHealth Grant Medical Center Intensive Care Unit prior to initiation of the prospective cohort.

For the prospective, interventional cohort we plan to consent all adult mechanically ventilated patients that meet pre-screening criteria in order to obtain a final sample size of 40 enrolled patients who meet all criteria on the day of extubation. We anticipate this will result in up to 240 patients consented and 40 patients enrolled over approximately 12 weeks; however, this time period can be extended if needed to obtain 40 patients in the final data set.

See Section 6.3 for detailed inclusion/exclusion criteria.

6 STUDY DESIGN

6.1 Overall Design

We propose a prospective, non-randomized exploratory study to obtain baseline data on reintubation rates for patients enrolled into a standardized postextubation management protocol compared to a historical control cohort consisting of mechanically ventilated high-risk patients that received clinician-directed, non-standardized postextubation management. We do not have current data demonstrating the specific type(s) of postextubation oxygen delivery but estimate that few patients receive combined BiPAP and HFNC. We will, however, record the types of postextubation oxygen management for the historical control cohort so that any subsequent statistical analyses can account for this potential confound.

6.2 Study Groups

Historical Control Group (Group 1): The historical control group will consist of up to 80 mechanically ventilated patients with documented presence of one or more chronic cardiac or pulmonary conditions that underwent planned extubation during the study period and meet all inclusion criteria outlined below.

Interventional Group (Group 2): The interventional group will consist of up to 40 patients for whom the LAR provides informed consent and who meet all study eligibility criteria.

6.3 Participant Identification Procedures and Eligibility Criteria

6.3.1 Historical Control Group:

Reintubation rates are tracked at the institutional level as part of quality assessments; a delegated member of the study team will utilize this patient list to generate a study-specific subset of high-risk patients who were mechanically ventilated between February and October 2019. This list will be screened for the inclusion/exclusion criteria below by a delegated member of the study team. The study statistician or designee will then use a random number generator to generate a final group of 80 patients that meet inclusion criteria.

Inclusion Criteria

1. Age ≥18 years
2. Chronic cardiac or pulmonary condition
    - COPD, history of based on any documentation notes
    - CHF, history of based on any documentation notes
    - Positive fluid balance, defined as a positive number when calculating fluid input minus fluid output over the approximate 24-hour-period prior to extubation
3. Documented modified RSBI between 58-105 on the day of extubation

Exclusion Criteria

1. Patients receiving comfort care or terminal extubation
2. Home ventilator, based on any documentation notes
3. Only primary extubations will be included (i.e., if the patient list query identifies multiple mechanical ventilations, only the primary encounter/event will be included)

6.3.2 Prospective Group:

An EMR-based report of all patients that have been on mechanical ventilation (MV) at Grant Medical Center for at least 24 hours will be generated daily (Monday through Friday), per standard procedure. Eligibility determination for this cohort will be conducted by a delegated member of the study team across two time points: pre-screening to determine eligibility to approach for consent, and eligibility on the day of extubation to determine enrollment eligibility (Appendix A). Only patients meeting all required eligibility criteria above will be enrolled to the study; any PHI collected for patients that are not subsequently enrolled will be destroyed after non-eligibility determination.

Pre-Screening Criteria:

1. No home ventilator, based on any documentation notes
2. Not scheduled for terminal extubation/comfort care
3. Has not had a failed extubation during the current hospital stay
4. Has not previously participated in the current trial
5. Any other reason, at the discretion of the study team/clinical care staff, that should preclude the LARs being approached. These include, but are not limited to, facial trauma or other severe injuries that make extubation unlikely or that would make BiPAP contraindicated. Because patients will be screened daily, it is possible that a patient that fails pre-screening earlier in the stay may be eligible for enrollment later in their stay. This is okay.

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Day of Extubation Criteria

1. Patient/LAR provided informed consent
2. Documented high-risk factors of interest (CHF, COPD, and/or positive fluid balance) as defined for the historical control cohort
3. The modified RSBI must be between 58-105
4. Patient must successfully complete spontaneous breathing trial and be determined eligible for extubation
5. Patient must not have extubated themselves
6. The patient must have no other contraindication that would preclude the postextubation protocol (e.g., facial trauma, tracheotomy, or any other reason that would preclude use of BiPAP or HFNC)
7. The patient must not be undergoing terminal extubation or placed on comfort care

6.4 Recruitment and Informed Consent (Prospective Group Only)

Patients are typically on mechanical ventilation for approximately 3-5 days, allowing several days from the time of identification for recruitment and consent. Because patients will be sedated and intubated, informed consent will be obtained from the patients' legally authorized representatives (LAR). Specifically, a member of the patient's care team will give each family of mechanically ventilated patients a recruitment card (Appendix B) and explain that a member of the research team will be approaching them to discuss the study. This ensures that the LARs are introduced to the study by the patients' care team.

The LAR will sign the informed consent document prior to any procedures being done specifically for the study only (i.e. above routine care). A copy of the signed informed consent document will be given to the LAR for their records, with a copy placed in the patient's medical record. Because patients may remain sedated following extubation, it may be not practicable to re-consent all patients following extubation. Patients in the Intensive Care Unit are assessed for confusion/delirium as standard of care using the Confusion Assessment Method for the ICU (CAM-ICU). Therefore, each patient's routine CAM-ICU score will be reviewed daily by a member of the study team. Those with negative CAM-ICU scores will be informed by a member of the study team that they were enrolled in a research study by their LAR, and the patient will be provided the opportunity determine whether they wish to remain enrolled in the study using the regained capacity portion of the consent form (Appendix C). Patients with positive CAM-ICU scores or who are transferred outside of the ICU (where CAM-ICU is not conducted) will not be re-consented. It is important to note that at this time all study interventions would have been completed; patient consent can only be obtained for continued data collection. Patients who do not wish to continue will be treated as outlined in Section 6.6.

All informed consent procedures (initial and in the event of regained capacity) will be obtained and documented on an IRB-approved informed consent form (Appendix C) in accordance with the OhioHealth Research Institute (OHRI) policy for obtaining and documented informed consent.

6.5 Study Treatment/Interventions (Prospective Group Only)

6.5.1 Standard of Care Extubation Readiness Assessments

As standard of care, mechanically ventilated patients are reviewed daily for extubation readiness. Extubation readiness is indicated if all of the following are true: 1. The cause of respiratory failure has improved; 2. The patient can protect his or her airway; 3. Mental status is awake and alert or easily aroused; 4. Cough/secretions are appropriately managed. This standard of care extubation readiness process will occur for all patients, regardless of whether or not they are enrolled in the research study.

Once the above criteria are met, patients undergo daily spontaneous breathing trials (SBT), where the patients are observed for approximately 30-120 minutes with reduced sedation and ventilator support.

Patients that do well with minimal ventilator support during this time can generally be scheduled for extubation. All SBTs will be conducted as outlined in Appendix D.

6.5.2 Postextubation Management

6.5.2.1 Standard of Care

Patients that **do not** meet the study eligibility criteria will **not** be enrolled in the study, and will undergo postextubation management according to their physician's orders. Please note, physician orders **may** include BiPAP/HFNC, as these postextubation management strategies are routine. However, only patients that meet the all study criteria per Section 6.3.2 will be included in the study.

6.5.2.2 Study Standardized, Intermittent NIV/HFNC Protocol

Patients that **do** meet all study eligibility criteria will be placed in the standardized, intermittent NIV/HFNC protocol as outlined below. For NIV, OhioHealth Grant Medical Center routinely utilizes BiPAP, a non-invasive ventilator. For HFNC, OhioHealth Grant Medical Center utilizes a heated high flow generator, an oxygen blender, and a humidifier. Please see Appendix D for BiPAP/HFNC setup, monitoring, and clinical decision making guide and Appendix E for device specification sheets.

Briefly, over the 24-hour-period following extubation, enrolled patients will receive BiPAP for 2-hour intervals (e.g., 2 hours on, 2 hours off) during the day and continuously at night. During BiPAP breaks, patients will receive heated high flow nasal cannula (HFNC) oxygen. As such, the intervention portion of this study is limited to approximately 24 hours (the 24-hour-period following extubation).

- The treating physician or advanced practice provider will order the BIPAP settings and care according to current standard methods.
- The Respiratory Therapy Team will set up, turn on and take off the BIPAP. They will also discuss the patient's care on BIPAP at the start of each shift with the RN and monitor the BIPAP approximately every 3 hours.
- The registered nurse (RN)/respiratory therapist (RT) team is responsible for the routine care they provide these patients, including assessing and monitoring the patient while they are on BIPAP for the study. They will identify, document and inform the physician and RT if problems and/or escalation of patient care occur.

6.6 End of Study Definition/Withdrawal Criteria

Patients that meet all required study eligibility criteria and for whom informed consent is obtained from the LAR will be considered enrolled into the study. A participant is considered to have completed the study after 30-day readmission data are abstracted from the medical records.

- Patients for whom informed consent is obtained but do not meet all eligibility criteria on the day of extubation will be deemed consented, not enrolled. These patients may be replaced.

- Patients who receive the study intervention but are subsequently withdrawn from the study because either they or their LAR elect to withdraw them from the study will not be replaced. Data for these patients will be included for an intention-to-treat analysis.
- Patients who receive the study intervention but for whom the intervention is discontinued or altered (due to tolerance, aversion to the BiPAP mask, or other clinical concerns) will not be replaced. Data will be included for an intention-to-treat analysis.
- It is possible that, despite a standardized order set, the intermittent treatment protocol may not be exactly 2 hours on/2 hours off during the day and that the nighttime BiPAP may not start and end at exactly the same time. Patients will be deemed to have received the protocol as directed if they receive BiPAP for at least 6 hours over a 24 hour period. All patients for whom the standardized protocol is ordered and initiated, regardless of whether or not the protocol was finished/followed, will be included in the analysis.

6.7 Study Calendar

	Pre-Enrollment Period	Study Day 0 (Day of Extubation)	Study Day 1	Study Day 2	End of Study
Patient Identification and pre-screening	X				
Recruitment/informed consent	X				
Spontaneous Breathing Trial	X	X			
Eligibility Verification		X			
Enrollment		X			
NIV/HFNC Protocol		X	X		
Postextubation Management Worksheet		X	X	X	
30-Days following Discharge					X

6.8 Study Limitations

A potential limitation of this study is that participants for whom informed consent is obtained may not be representative of the population as a whole, which would limit the generalizability of the data. The extent to which demographics of those enrolled differ from the population as a whole will be assessed as outlined in Section 7.1.

7 Data Collection, Handling & Record Keeping

With the exception of source data recorded using the Postextubation Management Worksheet (Appendix G), all study data will be recorded directly from electronic medical records into the study-specific REDCap database (Appendix A for prospective cohort data and Appendix F for historical control cohort). Research Electronic Data Capture (REDCap) is a secure web application for building and managing online surveys and databases. The REDCap program and the resulting data are maintained on internal servers and backed up regularly. REDCap has the technical capabilities to be HIPAA and 21 CFR 11 compliant.

The Postextubation Management Worksheet will be maintained at the patient's bedside until completed, at which point the data will be entered into REDCap and the paper files will be given to OhioHealth Research Institute.

The data collection and storage processes will follow HIPAA guidelines and OhioHealth policy to protect both confidentiality and privacy of each participant. Paper files will be stored in a secure facility with limited access (e.g., the offices of the OhioHealth Research Institute) and electronic files will be stored within the OhioHealth network, under password protection and encryption. All PHI data will be destroyed at the end of the study and only de-identified data will be maintained.

Per Health and Human Services Federal Regulations, research-related documents will be maintained for at least three years after completion of the research. All research-related documents (e.g., informed consent forms, data collection forms, electronic spreadsheets) will be provided to OHRI for retention.

7.1 Statistical Analysis Plan

In general, categorical variables will be summarized with counts and percentages; and continuous variables will be summarized with means, standard deviations, medians and ranges. The two groups will be compared on categorical variables using chi-square tests, or Fisher's exact tests if the data in the contingency table have cells with expected frequency of $n<5$. The two groups will be compared on the continuous variables using a t-test if the variable is approximately normally distributed or using a Wilcoxon rank sum test if the variable is markedly non-normally distributed. These general statistical methods will be used to compare groups on all the demographics and baseline characteristics, for the intention to treat (ITT) and per protocol (PP) populations.

Results will be considered statistically significant if the p-value is less than or equal to 0.05. SAS V9.3 or higher will be used for all summary statistics and statistical analyses.

7.1.1 Primary Statistical Analysis Methods

Because this is a non-randomized study, it is assumed that there will be some differences between groups on the demographics and/or baseline characteristics. Therefore logistic regression modeling

techniques will be used for the primary statistical analyses. This will allow for comparison of the groups on reintubation rate while adjusting out baseline differences.

The primary analysis is comparison of the groups on reintubation rates within 72 hours on the ITT population. Potential differences between groups on demographic and baseline characteristics will be adjusted for in the model by including any statistically significant demographic and baseline characteristics as covariates in the logistic regression model.

Additional primary analyses include:

Re-intubation required (no/yes)

a. Within 24 hours

b. From 24-48 hours

c. From 48-72 hours

d. >72 hours but ≤7 days

The same methods used for the primary analyses will be repeated for these additional primary outcomes (within 24, 24-48, 48-72, and >72hrs) for the ITT population; and these analyses will also be repeated for the PP population (within 24, 24-48, 48-72, and >72hrs).

7.1.2 Secondary Statistical Analysis Methods

Total hospital length of stay, ICU length of stay, ventilator time, in hours, will be compared between groups using Wilcoxon rank sum tests, as the durations are expected to be markedly non-normally distributed and skewed.

In-hospital mortality and 30-day readmission rates will be compared between the groups using a chi-square test, or Fisher's exact test if the data in the 2x2 contingency table have cells with expected frequency of n<5.

All secondary analyses will be completed on the ITT population.

7.1.3 Safety Analysis Methods

Details on adverse events will be collected. No formal statistical analyses are planned for the safety data, but summary statistics (counts and percentages) within each group will be tabulated based on ITT.

8 SAFETY INFORMATION AND EXPECTED RISKS

This exploratory study is designed to obtain baseline information to support the potential effectiveness of a standardized postextubation management protocol, utilizing BiPAP and Heated High-Flow Nasal Cannula oxygen (HFNC). BiPAP and HFNC are routinely used at OhioHealth Grant Medical Center; the

research study proposed evaluates these therapies in combination, according to a standardized (2 hours on/2 hours off) protocol.

There are multiple potential physical risks associated with being hospitalized and on mechanical ventilation (Table 1). These risks are present regardless of postextubation management strategies, i.e., assignment to the standardized postextubation management protocol of interest is not considered to add additional risk beyond that associated with routine care. In order to monitor and minimize any potential risks, a Data Safety Monitoring Board (DSMB) will be utilized for this study as outlined in Section 8.2.

Table 1 ***Potential Adverse Events (AEs) or Serious Adverse Events (SAEs).***

Frequency	**Mechanical Ventilation[a]**	**BiPAP/HFNC**
Common	Acute lung injury (ALI) Acute respiratory distress syndrome (ARDS) Barotrauma Mortality Organ impairment (hepatic, renal, gastrointestinal, CNS) Sepsis Side-effects of medications (delirium, confusion, agitation) Ventilator-acquired pneumonia (VAP)	Aerophagia (aerophagy) Agitation or delirium Claustrophobia Congestion Dry mouth, nose, and/or throat Other (describe)
Uncommon	Decreased cardiac output Endotracheal tube complications Infection	Breathing difficulty Delayed reintubation
Rare	Damage to trachea, lips, tongue, teeth, vocal cords Tracheostomy	

[a] Mechanical ventilation for all patients will be conducted per standard procedures. There are no changes to mechanical ventilation as a result of this research study. All risks associated with mechanical ventilation are present for all patients, regardless of whether or not they are enrolled into the study.

8.1 Risk/Benefit Assessment

While there are common risks associated with being on mechanical ventilation, these risks are independent of the research study. That is, this study is not expected to increase physical risk above that which would be encountered during routine treatment. The only research-related physical risks are

those associated with use of BiPAP or heated high-flow nasal cannula oxygen. These risks are common but are generally mild and reversible (Table 2). Risks will be minimized by ensuring appropriate patient monitoring, including oversight by a Data Safety Monitoring Board (Section 8.2 below).

The only other anticipated research risk is possible loss of confidentiality, which will be minimized by limiting access to study data, storing research-specific data in REDCap, providing only a de-identified data set to the statisticians, and removing identifiers at the earliest possible time point (following non-eligibility determination or at study closure, as applicable).

The information from this study will be used to identify opportunities to standardize processes and identify best practices for mechanically ventilated patients at high risk for reintubation. As such, the potential benefits from the study in the form of knowledge gained are considered to outweigh the risk associated with participation in the study.

Table 2. ***Risk Assessment***

Category	Risk	Likelihood	Seriousness
Physical	Minimal	Likely	Mild
Psychological	None	Not likely	N/A
Social	None	Not likely	N/A
Legal	None	Not likely	N/A
Financial	None	Not likely	N/A
Confidentiality	Minimal	Not likely	Mild

8.2 Data Safety Monitoring Board

Safety oversight will be under the direction of a Data Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including management of mechanically ventilated patients, trauma patients, and patients with complex co-morbidities. The DSMB will meet approximately monthly, unless other terms are agreed upon by the DSMB, to assess safety and efficacy data for prospectively enrolled patients. The DMSB will operate under the rules of an approved charter (Appendix H) that will be written and reviewed at the organizational meeting of the DSMB. Reporting of DSMB findings will occur in accordance with OhioHealth IRB policy for event reporting as outlined in Section 9 below. Briefly, in the absence of reportable unanticipated events, DSMB reports will be included for IRB review in the continuing review, while any event resulting in temporary or permanent interruption of study activities to avoid potential harm to subjects will be reported within 48 hours. Any other reportable event will be communicated to the IRB within 10 working days.

9 EVENT REPORTING

9.1 Unanticipated Problems

All events that meet OhioHealth's definition of an unanticipated problem must be reported to the OhioHealth IRB within 10 working days of notification of the event, with the following exception. Any event resulting in temporary or permanent interruption of study activities by the investigator, or DSMB to avoid potential harm to subjects should be reported within 48 hours.

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected, related or possibly related to participation in the research.

9.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research. As outlined above (Section 9.1), AEs that that are unexpected, related or possibly related to the research *and* suggest increased risk will be reported to the OhioHealth IRB.

It is possible that research participants may experience adverse events that do not meet OhioHealth's mandatory reporting requirements (e.g., they are not unexpected, they are not possibly related to participation in the research, they do not place the subjects or others at greater risk of harm). Adverse events that do not meet reporting requirements will be reported to the Data Safety Monitoring Board (DSMB) for review during standing DSMB meetings and summarized for the IRB during the continuing review.

Importantly, for the current study, adverse events associated with mechanical ventilation cannot be related to the study intervention, as study-specific interventions do not occur until the patient is extubated. As such, mechanical ventilation-related adverse events that occur prior to the day of planned extubation will not be reported to the OhioHealth IRB.

9.3 Definition of a Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity or disruption of the ability to conduct normal life functions;

- May (based upon appropriate medical judgement) jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

SAEs must be reported to the OhioHealth IRB if they meet the reporting criteria outlined in Section 9.1. All SAEs must be reported to the DSMB within ten business days.

9.4 Clinical Trial of an FDA-Regulated Device

This study meets the FDAAA 801 definition of an "Applicable Clinical Trial" of devices regulated by the United States Food and Drug Administration (FDA) and must therefore be registered on ClinicalTrials.gov. The Principal Investigator or designee will register and activate the study account prior to enrollment, the informed consent form will be posted within 60 days of the last patient enrollment, and all results will be entered within 12 months of the Primary Completion Date (PCD), which is the date of final data collection for the primary outcome measure (e.g., after the last enrolled patient is first extubated, regardless of whether or not they need to be reintubated).

The medical devices used in this study are lawfully marketed in the United States and are being used in accordance with current, FDA-approved labeling for the population of interest (Appendix E). The designed trial is not intended to support a new indication of the devices or to support a change in the labeling. The investigators will obtain IRB approval as well as informed consent before enrolling each prospective patient in the trial.

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11 APPENDICES

Appendix A: REDCap Screening Log and Data Collection Tool – Prospective Cohort

Appendix B: Recruitment Card

Appendix C: Informed Consent Form

Appendix D: BiPAP/HFNC Set-Up, Monitoring, and Clinical Decision Making

Appendix E: BiPAP and HFNC Product Specifications

Appendix F: REDCap Data Collection Tool - Historical control

Appendix G: Postextubation Management Worksheet

Appendix H: Data Safety Monitoring Board Charter

Appendix H1: DSMB Agreement

Appendix H2: DSMB Status Report

Appendix H3: DSMB Meeting Report