

PILOT TRIAL EVALUATING A MECHANICAL POWER TARGETED VENTILATION STRATEGY IN ADULT VV ECMO PATIENTS WITH SEVERE ARDS

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with applicable United States (US) Code of Federal Regulations (CFR) and the NIH Terms and Conditions of Award International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines will be incorporated consistent with institutional practice. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Principal Investigator		
_____	_____	_____
Name (print)	Signature	Date

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
UVA	University of Virginia

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	Pilot Trial Evaluating a Mechanical Power Targeted Ventilation Strategy in Adult VV ECMO Patients with Severe ARDS	
Study Description:	Acute respiratory distress syndrome (ARDS) is a common intensive care unit (ICU) admission diagnosis with high mortality. Traditional management focuses on lung protective ventilation consisting of low tidal volumes while limiting plateau and driving pressures. Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a guideline recommended intervention for patients with severe ARDS refractory to other interventions. The optimal lung protective ventilation strategy for patients supported by VV-ECMO is unknown.	
Objectives & Endpoints:	Objectives and Endpoints	
	Objectives	Endpoints
	Primary	
	Given the extensive observational data independently associating lower mechanical power with improved outcomes in severe respiratory failure, it is essential to assess the feasibility of a prospective, randomized mechanical power (MP)-based strategy to begin establishing a causal relationship between MP and clinical outcomes.	The primary outcome is to assess the feasibility of the intervention protocol, as assessed by the number of patients adhering to mechanical power (MP) protocol, with a target adherence of $\geq 90\%$ of the intervention time spent within the assigned mechanical power range."
	Secondary	
	To evaluate the safety and tolerability of a total lung protective ventilation strategy utilizing a mechanical power targeted strategy versus conventional ultra-low tidal volume ventilation, as well as to collect preliminary data on the impact on plasma biomarkers of ventilator induced lung injury (VILI) in patients with moderate to severe ARDS supported by VV-ECMO.	Secondary outcomes are twofold: safety and tolerability as measured by sedative requirements (as assessed by daily RASS score and use of continuous sedatives/analgesia and daily use of neuromuscular blockade) and impact on physiologic markers of VILI via serial measurements of plasma biomarkers.

	Exploratory Additional exploratory clinical outcomes will include the duration of ECMO support, successful weaning off ECMO, ventilator free days at day 60, survival to ICU discharge, survival to hospital discharge, 60-day mortality, and number of organ failure-free days by day 28 defined as: absence of vasopressor support (cardiovascular), absence of invasive or noninvasive (HFNC or NIPPV) respiratory support (pulmonary), and absence of renal replacement therapy (renal)."
Study Population:	Adult patients newly placed on VV ECMO for management of severe ARDS
Description of Sites/Facilities Enrolling Participants:	This study will take place solely at University of Virginia TCV-ICU. We will recruit a total of 24 subjects. Subjects will be allocated into two groups with a 1:1 allocation ratio with a total of 12 subjects assigned to each arm.
Description of Study Intervention:	Subjects will be randomized to either a low mechanical power target (2-4 J/min) or usual care. As a part of the protocol, patients in both arms will meet the current standard of care regarding individual parameters of ultra-lung protective ventilation and "lung rest" while on VV-ECMO as it is currently defined. The low mechanical power target arm will follow a well-defined mechanical ventilator management algorithm to meet the assigned target, as described below. Subjects in the usual care arm will be managed at the discretion of the treating intensivist with care, including mechanical ventilation settings, sedation, VV ECMO, and additional adjunct therapies, reflecting current best practice guidelines.
Study Duration:	24 Months
Participant Duration:	7 days of active study intervention followed by 21 days of data collection and review during hospitalization. There will be a final study visit 12 weeks post discharge.

1.2 Schema

Below is a summary of the proposed timeline for the 2-year project with major milestones listed.

Timeline with Target Milestones			
Q1	Q1-Q4	Q5-Q8	Q8
Protocol finalization	Enrollment target 3-5 patients per quarter	Enrollment target 3-5 patients per quarter	Data analysis, submission for publication, and study closure
IRB submission and approval	Interim analysis of protocol adherence rate for first 12 patients; adjustments to MP equation used if needed	Interim analysis of protocol adherence rate for second 12 patients	Preparation for definitive trial and future grant submission
Study team planning meetings	Interim analysis of sedative requirements for first 12 patients	Interim analysis of sedative requirements for second 12 patients	
Educate ICU, ECMO, and RT staff on protocol	Batch analysis of plasma biomarkers for first 12 patients	Batch analysis of plasma biomarkers for second 12 patients	
Distribute study abstract to referring ICUs			

Figure 1. Summary of the proposed timeline.

2 INTRODUCTION

2.1 Study Rationale

Acute respiratory distress syndrome (ARDS) is a common intensive care unit (ICU) admission diagnosis with high mortality. Recent estimates show that nearly one in every four patients requiring mechanical ventilation and more than 10% of patients admitted to the ICU meet ARDS criteria affecting approximately 200,000 patients each year.¹ This same data shows mortality rates track with disease severity, being approximately 34.9%, 40.3%, and 46.1% for patients with mild, moderate, and severe ARDS respectively, resulting in nearly 75,000 deaths in the U.S. each year. The utilization of veno-venous extracorporeal membrane oxygenation (VV ECMO) for refractory respiratory failure has grown significantly over the past decade, reaching over 20,000 cases in the past 3 years compared to less than 300 over a similar timeframe two decades ago. VV ECMO is now a guideline recommended intervention for patients with severe ARDS refractory to other interventions.² VV ECMO utilization for this specific indication has also grown substantially, from a mean of 13.8 annual runs between 2000 and 2004 to a mean of 1,203.6 annual runs over the past 5 years.³ While the absolute numbers are likely to be grossly underestimated due to differences in how primary diagnoses are reported, the relative increase over the past two decades is likely to be more accurately reflective of the increasing utilization of VV ECMO for respiratory support in the setting of severe ARDS. Given this trend, optimizing evidence-based care for patients supported by VV ECMO is important to help improve patient survival.

2.2 Background

Over the past few decades, significant effort in the form of multiple international, multicenter, randomized controlled trials have evaluated lung protective ventilation strategies in ARDS, highlighted by the ARMA trial which showed an 8.8% absolute mortality reduction with low tidal volume ventilation and limiting plateau pressure to <30 cmH₂O compared to standard of care at the time.^{4,5} These trials have helped define lung protective ventilation parameters over the past few decades, leading to significant improvements in mortality over that time.^{6,7} For patients with respiratory failure refractory enough to require VV ECMO support, avoiding further ventilator induced lung injury (VILI) is paramount to optimize the chances of lung recovery and avoid extrapulmonary organ dysfunction. However, despite the rapid increase in the utilization of VV ECMO for severe respiratory failure, very little prospective research has attempted to evaluate what constitutes lung protective ventilation in this patient population. In the absence of any current randomized trial evidence guidelines rely on expert opinion alone.^{8,9,10} These guidelines are extrapolated from lung protective ventilation studied in patients undergoing conventional mechanical ventilation despite significant differences introduced by the presence of the ECMO circuit, most notably the ability of the circuit to assume most if not all of the pulmonary support, and recommend ultra-low tidal volume “lung rest” ventilation with tidal volumes of 3-4 cc/kg predicted body weight (PBW), limiting plateau pressures to ≤ 24 cmH₂O but no greater than 30 cmH₂O, and maintaining a respiratory rate of 4-15 breaths/minute but no greater than 30.¹¹ Importantly, these same guidelines acknowledge “the optimal ventilatory strategy in patients with severe ARDS undergoing ECMO is not well defined.” Notably, the largest prospective observational trial of patients supported by VV ECMO for respiratory failure did not suggest an outcome benefit for any single traditionally targeted ventilator variable.¹² Given the increasing utilization of VV ECMO for ARDS, there is a need for prospective evaluation of a more comprehensive approach to ventilator management as a means to minimize VILI and improve outcomes in this critically ill patient population.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Although the individual parameters titrated to reach the overall low mechanical power target value will meet current standard of care consensus recommendations, there may still be associated with differences in ventilator induced lung injury risk, hemodynamic stability, levels of required ECMO support, or sedation requirements when compared to usual care. These risks are mitigated by the capped duration of intervention being 7 days, close clinical monitoring, and interim analysis. Breach of protected health information is a minimal risk as all data will be securely stored, with access restricted to the study team

2.3.2 Known Potential Benefits

There is no guaranteed direct therapeutic benefit to participants. However, the knowledge gained may improve ventilatory strategies for ECMO patients in future clinical trials and shape

care standards. ARDS patients on ECMO remain at high risk for ventilator associated complications, and optimal ventilator settings in this context remain undefined. This feasibility study will inform a larger randomized controlled trial with the potential to reduce ventilator induced lung injury, multiple organ failure, and improve outcomes. Understanding the feasibility and tolerability of mechanical power-targeted ventilation is essential to designing a larger trial that could transform supportive care for this critically ill population.

2.3.3 Assessment of Potential Risks and Benefits

Risks to both study populations are anticipated to be minimal, as the research protocol is designed to merely measure and quantify more precisely the effects of a therapy customarily utilized in the study patient population as opposed to a new procedure or novel pharmacologic therapy, but nonetheless will be minimized through multiple means.

The biomarkers tested may be drawn no differently than routine laboratory studies and requiring no additional IV or invasive central line placement, nor excessive repeated additional needle sticks/exposures. Exceedingly minimal risk may be ascribed to the additional volume of blood sampling required in each study arm (approximately 12mL per sample).

In regard to the mechanical ventilation strategy, the same thresholds regarding the upper limits of allowed ultra-low tidal volume ventilation will be followed in each arm, as is currently standard of care. Sedation (as measured by daily RASS score) and the use of neuromuscular blockade might be expected to trend higher in the intervention arm due to the need to more strictly control spontaneous respiratory efforts as a means of reaching the targeted MP goal. However, optimization of the ECMO support will be employed first to control spontaneous breathing prior to increases in sedatives or neuromuscular blockade. The associated risks/harms normally ascribed to these interventions (neuromuscular weakness, ICU delirium, hemodynamic alterations, etc.) would not be expected to vary between the two arms of treatment.

In the intervention arm, ECMO support is expected to potentially be higher than that of the control arm due to the intentionally limited contribution of native pulmonary gas exchange. This may confer an increased risk of refractory hypoxemia and/or hypercarbia, hemolysis, recirculation, need for transfusion for refractory hypoxemia, and right ventricular (RV) failure due to need for increased ECMO flow, all known complications of ECMO. To mitigate some risk, the limit for what is considered refractory hypoxemia in the intervention arm will be a sustained PaO₂ of <50 mmHg or saturation <85% for >30 minutes and for hypercarbia will be sustained PaCO₂ >65 mmHg with associated respiratory acidosis noted by a pH < 7.20 for >30 minutes. As is already standard of care in patients supported by ECMO, patients in both arms will be monitored continuously for signs of the development of hemolysis through routine laboratory evaluations (LDH, haptoglobin, plasma free hemoglobin, bilirubin) and clinical evidence (hemoglobinuria, need for transfusion). Transfusion protocols utilizing extensive screening and close observation for adverse reactions will be followed as is standard of care in both arms.

There are no identified additional psychological, social, or financial harms associated with the study interventions extending beyond those ordinarily encountered by populations of similar critical illness requiring similar therapies (i.e., ECMO, invasive mechanical ventilation,

analgo-sedation, neuromuscular blockade, etc.). All patient-sensitive data will be stored in a password protected data bank (REDCap).

Significant benefits may result from the proposed research by studying how these modes of mechanical ventilation in patients on VV-ECMO influence biomarkers of acute lung injury, which may provide a physiologic basis for discovering the most beneficial mode of mechanical ventilation in these patients. This knowledge has the potential to significantly reduce morbidity and mortality in this critically ill patient population in the coming years.

3 OBJECTIVES AND ENDPOINTS

Objectives and Endpoints	
Objectives	Endpoints
Primary	
Given the extensive observational data independently associating lower mechanical power with improved outcomes in severe respiratory failure, it is essential to assess the feasibility of a prospective, randomized mechanical power (MP)-based strategy to begin establishing a causal relationship between MP and clinical outcomes.	The primary outcome is to assess the feasibility of the intervention protocol, as assessed by the number of patients adhering to the mechanical power (MP) protocol, with a target adherence of $\geq 90\%$ of the intervention time spent within the assigned mechanical power range.
Secondary	
To evaluate the safety and tolerability of a total lung protective ventilation strategy utilizing a mechanical power targeted strategy versus conventional ultra-low tidal volume ventilation, as well as to collect preliminary data on the impact on plasma biomarkers of ventilator induced lung injury (VILI) in patients with moderate to severe ARDS supported by VV-ECMO.	Secondary outcomes are twofold: to assess the safety and tolerability of a MP-targeted protocol as measured by sedative requirements (daily RASS score and requirement for continuous sedatives/analgesia and daily use of neuromuscular blockade) and impact on physiologic markers of VILI as serially measured by plasma biomarkers.
Exploratory	

Additional exploratory clinical outcomes will include the duration of ECMO support, successful weaning off ECMO, ventilator free days at day 60, survival to ICU discharge, survival to hospital discharge, 60-day mortality, and number of organ failure-free days by day 28 defined as: absence of vasopressor support (cardiovascular), absence of invasive or noninvasive (HFNC or NIPPV) respiratory support (pulmonary), and absence of renal replacement therapy (renal).

4 STUDY DESIGN

4.1 Overall Design

For patients meeting inclusion and no exclusion criteria, we will obtain written informed consent from the patient or their legally authorized representative (LAR). After obtaining consent, subjects will be randomized to either a low mechanical power targeted strategy or usual care. Participants in the proposed study will be randomized with the minimization method based on three baseline covariates: age (> 45 or ≤ 45 years), gender (male or female), and baseline compliance (> 25 or ≤ 25 mL/cmH₂O). Patients will be allocated into two groups with a 1:1 allocation ratio, with a total of 12 patients assigned to each arm. Data from each arm will be collected daily from cannulation onto ECMO until Day 28 of hospitalization post cannulation or discharge, whichever is reached first. Patients will be followed until their 12 week follow up appointment with their Pulmonary team post hospital discharge.

4.2 End of Study Definition

Primary completion date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes defined as the final date for the collection of data for the primary endpoint. For the purposes of this study, the End of Study date will be the follow up visit of the last patient randomized into a study arm.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. On VV ECMO for less than 24 hours at time of study consent
2. Severe ARDS as the primary etiology of respiratory failure defined by:

- Acute onset: Within 1 week of known clinical insult
 - Bilateral infiltrates: Evidence of fluid/inflammation in both lungs on X-ray, CT, or US, not fully explained by cardiac failure or fluid overload
 - Origin of Edema: Respiratory failure not fully explained by cardiac failure or fluid overload
 - Oxygenation impairment (Severe): $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm HG (Partial pressure of arterial oxygen/Fraction of inspired oxygen)
3. Age 18 or greater

5.2 Exclusion Criteria

1. Have received ECMO for >24 hours
2. Are on VV ECMO but are not mechanically ventilated, or are planned not to have/not require invasive mechanical ventilation for >24 hours
3. Patient is pregnant
4. Patient is a prisoner
5. Receiving VV ECMO as a bridge to transplant or history of lung transplant
6. History of pneumectomy or lobectomy
7. Age < 18
8. Are on any hybrid configuration of ECMO including an arterial limb (i.e., VAV, VVA, VA, etc.)

5.3 Justification for Study Population

Our study population will include only adult VV ECMO patients (18 years or older) with evidence of ARDS. Pediatric and neonatal ECMO patients will be excluded, as ECMO practices and the reasons for ECMO are different in children compared to adults.

We will recruit VV ECMO patients of all races and ethnicities, as well as men and women. We will not exclude patients of any racial or ethnic background. We will consider all VV ECMO patients in our center who meet study inclusion criteria for recruitment into the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 Strategies for Recruitment and Retention

We will screen for adult patients who are on VV ECMO each morning using our hospital's daily ECMO census list. Study investigators who round in the cardiothoracic surgical ICU, where all adult VV ECMO patients are cared for, may also identify eligible patients as they round on them in the ICU, or receive consults for VV ECMO elsewhere in the medical center. Further, study investigators who round in the medical ICU may also identify patients with ARDS who are at risk of requiring VV ECMO support, allowing for earlier recognition of potentially eligible patients. If potentially eligible patients at UVA who are at risk of needing VV ECMO support are identified, they may be approached prior to cannulation for trial consent and participation should they ultimately require VV ECMO. If these patients do not require VV ECMO after consenting, they will be considered a Screen Failure. The study investigators will work to distribute awareness of the ongoing study and enrollment criteria to surrounding referring medical centers to enhance recruitment efforts.

Patients who meet study eligibility criteria will be approached about participation if they have capacity to provide written informed consent. In most cases, this population of VV ECMO patients will not have capacity to provide written informed consent due to severity of illness, including required stabilizing medical intervention such as deep sedation and potentially paralysis. In such cases, the patient's legally authorized representative (LAR) will be contacted about the study. Risks, benefits, alternatives to participation, right to withdrawal at any time without penalty, and other study details will be described by the study team to the patient or LAR. If the patient or LAR express interest in participating, they will be asked to sign a written informed consent form before participating in the study.

We do not anticipate patient retention to be a significant issue in this study, as all VV ECMO patients are hospitalized. Our research coordinator will keep the patients or their LAR updated about study procedures during the course of their participation in the research.

6 STUDY INTERVENTION

6.1 Description of Study Intervention(s)

Mechanical Ventilation

After randomization, patients will subsequently be assigned to either a low mechanical power target (2-4 J/min) or usual care. This range was chosen as it closely mirrors the power of normal breathing in healthy subjects and falls on the lower range of that reported in retrospective and observational trials, indicating feasibility. As a part of the protocol, patients in both arms will meet the current standard of care regarding the individual parameters of ultra-lung protective ventilation and "lung rest" while on VV-ECMO as it is currently defined. The low mechanical power target arm will follow a well-defined mechanical ventilator management algorithm to meet the assigned target, as described below. Patients in the usual care arm will be managed at the discretion of the treating intensivist with care, including mechanical ventilation settings, sedation, VV ECMO, and additional adjunct therapies, reflecting current best practice guidelines.

For patients assigned to the intervention arm, the patient will be placed on volume control (VC) or pressure control (PC) ventilation with either an initial tidal volume of 3-4cc/kg predicted body weight (PBW) (for VC) or inspiratory pressure required to reach the same tidal volume goal (for PC), F_{iO_2} set between 0.30-0.50, and a PEEP of at least 10. This tidal volume or inspiratory pressure, for VC and PC ventilation respectively, will then be titrated down to meet a goal plateau pressure of ≤ 24 cmH₂O, but no greater than 30, and a target driving pressure no greater than 14 cmH₂O. Finally, the respiratory rate will then be titrated between 1 and 15 to meet the specified mechanical power goal range. Once the respiratory rate has been lowered to 8, tidal volumes (or inspiratory pressure required to meet this goal) will be lowered to 3cc/kg PBW prior to further reductions in respiratory rate. MP will be calculated every two hours and adjusted as needed to stay within the goal MP range until prespecified weaning criteria (detailed below) are met.

Mechanical Power Equations		
Volume Control	Pressure Control	Dynamic
$MP = VT \times (PIP - [\Delta P \times 0.5]) \times RR \times 0.098$	$MP = VT \times (\Delta P_{insp} + PEEP) \times RR \times 0.098$	$MP = VT \times (P_{peak} - (\Delta P_{dyn})/2) \times RR \times 0.098$
Where PIP is the peak inspiratory pressure, ΔP is the driving pressure defined by $P_{plateau} - PEEP$, ΔP_{insp} is the amount of set inspiratory pressure above PEEP, ΔP_{dyn} is equal to the change in airway pressure during inspiration ($P_{peak} - PEEP$), and 0.098 represents a conversion factor from liters*cmH ₂ O to joules		

Figure 2: Definitions of mechanical power equations.

Mode specific equations will be prioritized and utilized for patients for whom the required static measurements can be obtained. This offers the benefit of using equations which offer the most robust validation and accuracy. For patients whose static measurements cannot be obtained the dynamic equation will be substituted. This equation will be utilized as it has the advantage of being applied regardless of the mode of ventilation and can be calculated on a breath-to-breath basis without the need to obtain static respiratory parameters, such as inspiratory and expiratory holds, required for mode specific equations. Target adherence is $\geq 90\%$ of the intervention time spent within the assigned mechanical power range. If at any time the patients' mechanical power is noted to be outside the assigned range, note will be made as to why this is the case (spontaneous breathing, unable to meet oxygenation/ventilation goals despite optimization as outlined below, miscalculation of MP, etc.) and what steps were made to bring the patient back into the assigned range.

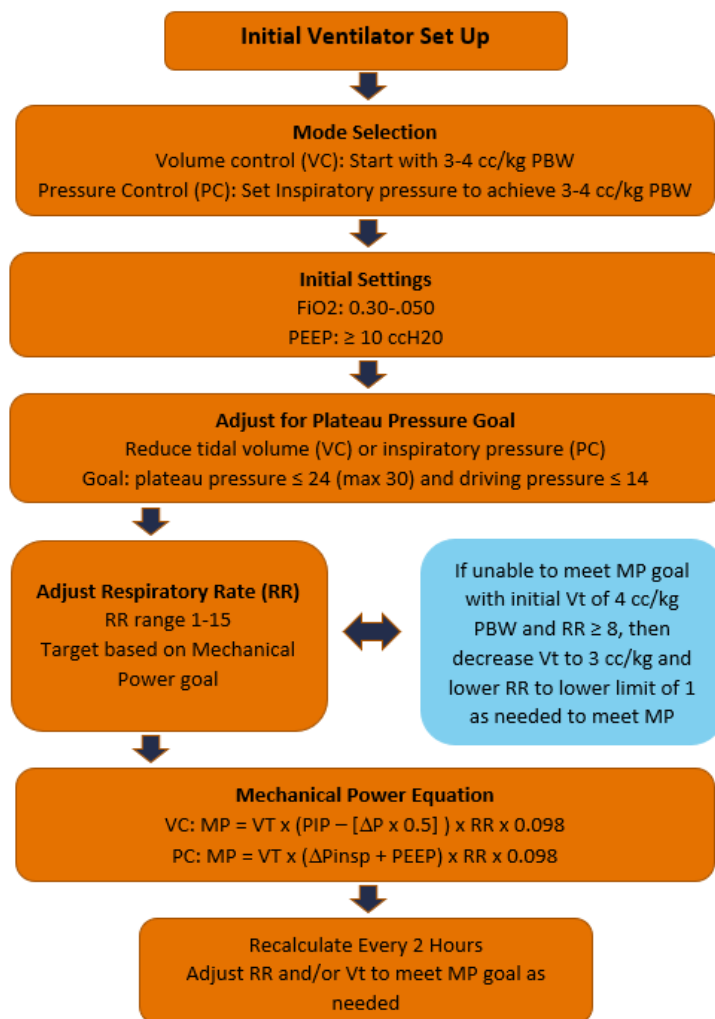


Figure 3. Flow diagram for steps to meet the assigned mechanical power range for both volume control and pressure control ventilation.

ECMO Management

ECMO management including flow, FiO₂ and sweep gas flow will be titrated to meet defined systemic oxygenation (saturation goal of >85-88%, PaO₂ between 50-90 mm Hg, SvO₂ >70%) and ventilation (pH 7.30-7.45, PaCO₂ goal of 35-50 mm Hg) goals. Adjustment and optimization of ECMO oxygenation (through flow, FiO₂, mitigation of recirculation) and ventilation (through sweep gas flow) are prioritized as the primary means to meet these goals, followed by additional sedation ± partial paralysis to decrease metabolic demand (as detailed below), with increases in ventilatory support only to be done when these goals cannot be met with the first two options exhausted. The hemoglobin threshold while on ECMO should be >7-8 g/dl but may be increased to 10 g/dl if persistent hypoxemia is present. ECMO should be run at normal body temperature (37C). Systemic anticoagulation will be left to the treating clinician. Should the ECMO circuit oxygenator or other circuit component need to be exchanged for any reason during the

intervention timeframe, the patient may be allowed to deviate from their assigned MV strategy as deemed necessary to provide native pulmonary gas exchange and allow for safe exchange of the oxygenator or other circuit components without counting as time spent outside the assigned MP target if in the intervention arm. Patients in both arms should be returned to their assigned treatment strategy thereafter as soon as is deemed safe by the treating clinician.

Sedation Management

Sedation targets will be set using the Richmond Agitation-Sedation Scale (RASS), with medications titrated to the desired sedation level. In the early period after ECLS initiation, deep sedation is commonly required and favored to maintain lung rest and ventilator synchrony. An important consideration of this study is examining the relative sedative requirements needed to achieve the assigned MP range, with the idea that titrations in sweep gas flow on the ECMO circuit to normalize pH will partially offset the need for excessive sedation to meet the desired MP. Therefore, in the intervention arm, a 48-hour period of mandated deep sedation (RASS -3 to -5 with the addition of neuromuscular blockade, if required) will be obtained to ensure delivery of the assigned mechanical power range, with sedation titrated as needed to provide complete ventilator synchrony. Following this, as deemed safe by the treating clinician, patients will target a RASS goal of 0 to -2. Again, the ECMO circuit will be relied upon to achieve adequate systemic oxygenation and ventilation, partially decreasing excessive respiratory drive and patient self-induced lung injury (pSILI). If the mechanical power range is unable to be maintained despite optimal ECMO support due to excessive patient effort, the RASS goal will be sequentially increased again, ultimately ending with a RASS of -5 and partial to full neuromuscular blockade if required. The daily RASS score will be calculated and reported for each patient in addition to the number of days in which continuous sedation and/or neuromuscular blockade was employed.

Weaning Criteria and ECMO Decannulation

Weaning from VV ECMO is a multi-part process; consisting of 1) recognizing lung recovery, 2) sequential decreases of oxygenation and ventilation support provided by the ECMO circuit (via a combination of reducing extracorporeal blood flow, sweep gas flow, and fraction of delivered oxygen in the sweep gas) as native lung function improves and is able to assume more responsibility for gas exchange while still meeting defined lung protective ventilation, 3) performing a sweep gas off trial, and 4) decannulation and liberation from ECMO.

Appropriateness for liberation trials is dependent on clinical stability and on indicators of adequate native lung function. While readiness has traditionally been determined by the treating clinicians' judgement of recovery and no well-validated weaning criteria exist, for the purposes of this trial readiness for the initiation of ECMO weaning will be standardized in both arms and defined by maintenance of: 1) pH of 7.30-7.45 with a sweep gas flow of ≤ 2.5 L/min, 2) $\text{PaO}_2 \geq 60$ mmHg with ECMO F_iO_2 of ≤ 0.4 and ventilator F_iO_2 of ≤ 0.5 , and 3) lung compliance ≥ 20 mL/cmH₂O for at least 4 hours. Once patients meet all these criteria, the intervention period will end, and the subject will be allowed to deviate from the assigned MP target during a "sweep gas off trial (SGOT)" to facilitate further ECMO weaning and liberation while still meeting conventional lung protective ventilation settings. Should the patient fail the SGOT trial for any

reason they should return to their assigned MP target until the next SGOT trial. If for any reason a SGOT trial is not performed while meeting the below weaning targets, the patient's ventilator parameters should remain within their assigned MP range until a SGOT is performed. The duration of the SGOT and ultimate decision and timing to decannulate from VV ECMO is at the discretion of the treating clinician.

Weaning Trial Targets	
Parameter	Target for Weaning Trial
ECMO Sweep Gas Flow	< 2.5 L/min
ECMO FiO ₂	≤ 0.4
Ventilator FiO ₂	≤ 0.5
PaO ₂	≥ 60 mmHg
pH	7.30- 7.45
Compliance	≥ 20 mL/cmH ₂ O

Table 1. Checklist of criteria to end intervention period and initiate ECMO weaning.

If patients in the intervention arm have not yet met weaning criteria by the end of day 7, the intervention window will end, and management of the mechanical ventilator settings will be left entirely at the discretion of the treating clinician.

Biomarker Collection

Multiple biomarkers have shown a strong correlation with patient centered outcomes in ARDS, and have been increasingly relied upon to define sub-phenotypes of patients and predict response to various interventions. Of these, plasma levels of IL-6, IL-8 (markers of inflammation and predictive of ARDS survival in a reanalysis of ARMA and ALVEOLI); IL-18 (generated by inflammasome activation in lung parenchyma responsible for driving inflammation in acute lung injury/ARDS); TNF- α (increased production by alveolar macrophages in patients with ARDS and closely correlated with IL-10 levels); soluble intracellular adhesion molecule-1 (sICAM-1), angiopoietin-2 (Ang-2) (both markers of lung endothelial injury and barrier dysfunction); soluble receptor for advanced glycation end products (sRAGE), and surfactant protein-d (SP-D) (specific indicators of type I and type II alveolar and epithelial cell injury) have the most data evaluating and associating them with clinically significant lung injury and patient outcomes. Therefore, patients will have 12-ml of blood obtained on day 0 (as soon as feasible after randomization but no sooner than 6 hours following ECMO cannulation), and days 1, 3, 5, and 7 to evaluate the comparative effects of a low mechanical power strategy versus usual care to reduce biomarkers of lung injury during the intervention period to provide additional insight to this novel approach to mechanical ventilation. These eight biomarkers will be measured together in batches at interim analysis and the end of the study period (Creative Proteomics Human Luminex Multiplex Assay Panel). In cases where the subject is experiencing clinically relevant worsening anemia due to ongoing massive resuscitation, the treating physician can omit any study lab draw necessary for clinical care.

Patient Follow-Up

All enrolled patients will have long-term follow-up at post-ICU outpatient clinic as standard of care for this patient population. This clinic is focused on supporting the recovery of patients with severe respiratory failure, in particular those who had required ECMO. The goal for the clinic is to see the patients about 8-12 weeks after discharge, and the visit will be reviewed by the study team to assess for any ongoing or unresolved Adverse Events and for all-cause mortality.

6.2 Registration and Randomization

For patients meeting inclusion and no exclusion criteria, we will obtain written informed consent from the patient or their legally authorized representative (LAR). After obtaining consent, subjects will be randomized to either a low mechanical power targeted strategy (2-4 J/min) or usual care. Participants in the study will be randomized with the minimization method based on three baseline covariates: age (<45, or ≥ 45 years), gender (male or female), and baseline compliance (< 25 ml/cm H₂O or ≥ 25 ml/cm H₂O). Minimization randomization is a dynamic randomization option that assigns a new participant to one of the two comparison groups (e.g., low mechanical power vs. usual care) based on their covariate factors and the number of participants already randomized in the clinical trial. For the study we will utilize MinimPy (Source Forge, San Diego, CA), a desktop application that allows minimization randomization as proposed. Patients will be allocated into two groups with a 1:1 allocation ratio, with a total of 12 patients assigned to each arm.

6.3 Concomitant Therapy

All other treatment decisions during the intervention period not otherwise specified above will be left at the discretion of the treating clinician, including but not limited to the use of corticosteroids, inhaled pulmonary vasodilators, neuromuscular blockade, fluid administration and diuresis, prone positioning, and antibiotic administration. Beyond the intervention period, all patient management decisions will be left to the treating clinician(s). Patients will be monitored continuously as is standard of care for ICU-level patients.

7 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION or WITHDRAWAL

7.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the National Heart, Lung, and Blood Institute (NHLBI). If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and will provide the

reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

7.2 Participant Discontinuation/Withdrawal

The principal investigator can discontinue any patient at any time if deemed medically necessary. It will be documented whether or not each patient completed the protocol. If, for any patient, treatment or observations were discontinued, the reason will be recorded. The reason for participant discontinuation or withdrawal from study treatment will be recorded on the ECF “Note to file”. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form and are randomized and receive the study intervention and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced. Participants who withdraw from the study will not be contacted for any further study visits.

Reasons that a patient may discontinue include:

- Serious adverse event(s)
- Abnormal test procedure result(s)
- Protocol violation
- Withdrawal of consent by the patient or their legally authorized representative if they do not have decision making capacity
- Any event or issue deemed appropriate by the investigator(s)
- Discontinuation of the protocol by the investigator(s)

7.3 Procedures for Discontinuation of Study Intervention

Discontinuation from low mechanical power targeted strategy does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding may be reported as an adverse event (AE) – see [section 9.1.7](#).

The data to be collected and procedures to be completed at the time of study intervention discontinuation are included in the schedule of assessments in [section 13.1](#).

7.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for the scheduled follow up visit at 8 to 12 weeks post discharge and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The clinic will attempt to contact the participant and reschedule the missed visit within 4 weeks..
- Before a participant is deemed lost to follow-up, the investigator or designee will attempt to reach the subject by phone.
- These contact attempts should be documented in the study file.
- Should the participant continue to be unreachable after three phone calls, he/she will be marked as lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Clinical Assessments

Baseline Information to be Collected		
Demographics	Health History	Present Condition
Age	Immunocompromization	ARDS condition diagnosis
Sex	CNS dysfunction	Time since intubation
Weight	Cardiac arrest or Myocardial Infarction	Non- pulmonary infection (Acute)
BMI	Hypertension	Glasgow Coma Score (GCS)
Ethnicity	Diabetes mellitus	SOFA Score
Vital Signs	Chronic liver disease	RESP Score
Mean Arterial Pressure	Congestive heart failure	PRESERVE Score
Temperature	Chronic renal insufficiency	ECMO
Peripheal oxygen saturation		ECMO RPM
Respiratory rate	Mechanical Ventilation	Flow
Laboratory Results	Mode of ventilation	Sweep gas flow
Hemoglobin	Tidal Volume	FiO2
White blood cell count	Positive end expiratory pressure (PEEP)	Interventions
Platelets	Plateau pressure	Vasopressor use
Bilirubin	Driving pressure	Inhaled pulmonary vasodilators
Creatinine	Peak inspiratory pressure (PIP)	Recruitment maneuvers
Arterial blood pH	FiO2	Neuromuscular Blockade
PaO2	P:F Ratio	Corticosteroids
PaCO2	Positioning	Bicarbonate infusion

Figure 4: Baseline clinical information to be collected before and after ECMO cannulation and randomization into study arm.

8.1.1 Clinical Laboratory Assessments

Data to be collected daily from Day 0 randomization through Day 7		
<i>following Day 7 VS and laboratory parameters collected daily at 0800 through day 28</i>		
Vital Signs	Laboratory Data	Serum Biomarkers
0800 and every 6 hours	closest to 0800 daily	0800 daily on days 0, 1, 3, 5, 7
HR	Hemoglobin	IL-6
Systolic BP	White blood cell count	IL-8
Diastolic BP	Platelets	IL-18
Mean arterial pressure	Bilirubin	TNF-alpha
Respiratory rate (actual)	Creatinine	sRAGE
Oxygen saturation	Bicarbonate	sICAM-1
Temperature	Lactate	Ang-2
RASS (0800 and 2000)	LDH	SP-D
	Plasma free hemoglobin	
	Haptoglobin	

Table 2: Laboratory data to be collected from Day 0 through to Day 28. Serum biomarkers to be collected as soon as feasible after randomization but no sooner than 6 hours following ECMO cannulation for Day 0, then closest to 0800 on the following calendar day for Days 1 onwards.

8.1.2 Other Clinical Assessments

Data to be collected daily from Day 0 randomization through Day 7		
<i>following Day 7 all parameters collected twice daily at 0800 and 2000 through day 28</i>		
Mechanical Ventilation	ECMO Data	Patient Management
0800 and every 2 hours unless otherwise specified	0800 and every 2 hours unless otherwise specified	0800 daily for preceding 24 hours
Mode of mechanical ventilation	RPM	Use of prone positioning on ECMO (Y/N)
Tidal volume (total and in cc/kg PBW)	Flow (L/min)	Use of inhaled pulmonary vasodilators on ECMO (Y/N)
PEEP	FiO2	Use of neuromuscular blockade on ECMO (Y/N)
Set inspiratory pressure support above PEEP (if in Pressure Control)	Sweep gas flow (L/min)	Use of corticosteroids on ECMO (Y/N)
Peak inspiratory pressure (PIP)	Systemic anticoagulation (yes/no) (0800)	Use of bicarbonate infusion on ECMO (Y/N)

Plateau pressure	Any ECMO related complication in preceding 24 hours (Y/N)	Use of CRRT on ECMO (Y/N)
Driving pressure		Continuous sedatives (propofol, precedex, versed, ketamine) and analgesic (fentanyl, morphine, hydromorphone) over preceding 24 hours (Y/N separately for any sedatives and analgesics)
Mean airway pressure		Vasoactive use (Y/N to each of Norepinephrine, Epinephrine, Vasopressin, Milrinone, and/or Dobutamine)
Respiratory rate (set)		Did patient meet defined weaning criteria (Y/N)
Respiratory rate (actual)		Did patient undergo an ECMO capping/SGOT trial (Y/N)
Minute ventilation		Did the patient undergo a planned ECMO decannulation (Y/N, date and time)
FiO2		Did the patient receive a tracheostomy (Y/N, date and time)
P:F ratio* (0800 and 2000)		
PaO2* (0800 and 2000)		
PaCO2* (0800 and 2000)		
Arterial blood pH* (0800 and 2000)		
Respiratory system compliance (0800 and 2000)		
Mechanical Power (Dynamic)		
Mechanical Power (VC Specific)		
Mechanical Power (PC Specific)		

Table 3: Data to be collected from Day 0 through Day 28

8.2 Research Specimen Collection

8.2.1 Research Blood

Serum biomarkers will be collected via blood draw on days 0, 1, 3, 5, and 7. It is estimated that 12 mLs of blood will be collected per day for a total of 60 mLs of blood per patient for research purposes. All other labs will be collected daily as part of standard procedure.

8.3 Correlative Studies

Blood collected to measure the serum biomarkers will be sent to Creative Proteomics for analyzing. Plasma levels of IL-6, IL-8, IL-18, TNF- α , soluble intracellular adhesion molecule-1 (sICAM-1), angiopoietin-2 (Ang-2), soluble receptor for advanced glycation end products (sRAGE), and surfactant protein-d (SP-D) have the most data evaluating and associating them with clinically significant lung injury and patient outcomes. These eight biomarkers will be measured together in batches at interim analysis of every 12 patients and the end of the study period via Creative Proteomics' Human Luminex Multiplex Assay Panel.

9 DATA AND SAFETY MONITORING PLAN

9.1 Adverse Events and Serious Adverse Events

9.1.1 Definition of Adverse Events (AE)

An adverse event will be considered any undesirable sign, symptom or medical or psychological condition even if the event is not considered to be related to the investigational intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects.

9.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) 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
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.1.3 Classification of an Adverse Event

9.1.3.1 Severity of Event

The severity of AEs will be assessed by the Principal Investigator using the categories below.

- **Mild-** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate-** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs.
- **Severe-** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs.

9.1.3.2 Relationship to Study Intervention

The degree of certainty about causality will be graded using the categories below.

- **Related-** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention and cannot be explained by concurrent disease or other drugs or chemicals.
- **Possibly Related-** There is some evidence to suggest a causal relationship. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "Possibly Related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "Related" as appropriate.
- **Not Yet Determined-** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable but not impossible and in which other drugs or chemicals or underlying disease provides plausible explanations. Although an AE may rate as "Not Yet Determined" soon after discovery, it can be flagged as requiring more information and later be upgraded to "Possibly related" or "Related" as appropriate.
- **Not Related-** The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.1.3.3 Expectedness

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.1.4 Abnormal Laboratory Values

Abnormal lab test values will not be reported as AEs unless they are considered clinically significant, meaning one or more of the following are true: there is an associated clinical condition for which the patient is being monitored or given treatment, the event indicates further testing to assess for a related clinical condition, concomitant treatment is altered, or the event is

considered a serious adverse event. Abnormal lab values that are reported as AEs should be reported as described in [section 9.1.7](#).

9.1.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during chart review and study visits, or upon review by a study monitor.

AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs occurring while on study must be documented appropriately regardless of relationship. AEs will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not recorded as an AE. However, if the study participant's baseline medical condition worsens at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The CRC will record all reportable events with start dates occurring any time after informed consent is obtained until 21 days after the last day of study treatment for review by the PI. Events will be followed for outcome information until resolution or stabilization. While the study team is not required to monitor participants for SAEs after the specified reporting period, if the study team becomes aware of an SAE considered at least possibly related to study participation, the study team should record this event.

9.1.6 Adverse Event Reporting

AEs must be recorded into the University of Virginia IRB, REDCap, and case report forms within 24 hours from when the study team receives knowledge of an AE that is Related to the study, and within 7 days from when the study team receives knowledge of the event for all other classification categories.

9.1.7 Serious Adverse Event Reporting

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the primary investigator deems the event to be chronic or the participant is stable.

- Internal Event Resulting in death that is deemed Related to (caused by) study participation

- Report to the UVA IRB-HSR within 24 hours. Report within 24 hours using IRB Online and a phone call.
- Internal, Serious, Unexpected, Related
 - Report to the UVA IRB-HSR within 7 days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB Online.

9.2 Reporting Events to Participants

If there is any new information relevant to the participant's willingness to continue to participate in the study, such as if there are new risks of the study treatment identified that were not included on the consent form that the participant signed, the study team will contact the participant to discuss this information. If the participant is still receiving study treatment, the study team will present the participant with an updated consent and confirm that he or she wants to continue receiving study treatment.

9.3 Unanticipated Problems

9.3.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs)(may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.3.2 Unanticipated Problem Reporting

- Report UPs that are not adverse events, protocol deviations, or data breaches to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.
- Report UPs that are SAEs in accordance with the guidelines for SAE reporting.

9.3.3 Reporting Unanticipated Problems to Participants

If during the course of the study there is an unanticipated problem that affects current or past participants, affected participants will be contacted if needed.

9.4 Data Breach

9.4.1 Definition of Data Breach

An unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

9.4.2 Reporting a Data Breach

- Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.
 - 924 2938 is UVA Health reporting (if information from UVA patients is involved)
 - 243 8992 is academic reporting (if no information from UVA patients is involved)
 - Additional information (or the initial report if no one is reached at the telephone number) may be sent to
ComplianceandPrivacyMedicalCenter@hscmail.mcc.virginia.edu
- Report to InfoSec if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified.
 - If the breach includes UVA patient data:
<https://hit.healthsystem.virginia.edu/index.cfm/departments/security/computer-security-incident-report/>
 - If the breach does NOT include UVA patient data:
[Information Security Incident Report Form | UVA Information Security \(virginia.edu\)](#)
- Report to UVA police if the breach includes such things as stolen computers. Report by telephone.

9.5 Protocol Deviation

9.5.1 Definition of Protocol Deviation

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVA staff. These protocol violations may be major or minor violations.

9.5.2 Reporting of a Protocol Deviation

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to UVA IRB-HSR and to the NIH NHLBI.

- Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.
- Report major deviations on the eCRF within 7 calendar days from the time the study team received knowledge of the event.
- For minor deviations, please reference the IRB-HSR for tips for recording minor deviations. These deviations should be recorded in a log.

9.6 Participant Withdrawals/Dropouts Prior to Study Completion

Participants who withdraw consent and those dropping out of the study secondary to an AE will be reported to the IRB of record according to IRB guidelines.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The primary outcome is adherence, defined as a binary measure in which a patient's mechanical power remains within the target zone 2-4 J/min for $\geq 90\%$ of the ventilation time. We hypothesize that patients in the low mechanical power group are more likely to adhere than those receiving standard care.

As a secondary outcome we will assess whether there is a difference in the average mechanical power zone between the low power group and the standard care group. We hypothesize that the low power group will have lower average power than the standard care group.

10.2 Sample Size Determination

For this early phase trial, we propose to recruit a target total sample size of $N = 24$ over a 24-month period based on fiscal and clinical feasibility. At our institution, the annual number of adult VV ECMO runs ranged from $n = 10$ to 38 between 2020 and 2024, averaging to $n = 24$ per year. A preliminary review suggested $\sim 66\text{--}75\%$ of these patients ($\sim n = 16\text{--}18$) would meet the proposed inclusion criteria and be eligible for recruitment. As such, if 75% of the eligible patients were enrolled in the proposed study, we would meet our target total sample size of $N = 24$ over a 24-month period.

10.2.1 Randomization and Measures to Minimize Bias

Participants in the study will be randomized with the minimization method based on three baseline covariates: age (< 45 , or ≥ 45 years), gender (male or female), and baseline compliance (< 25 ml/cm H₂O or ≥ 25 ml/cm H₂O). Minimization randomization is a dynamic randomization option that assigns a new participant to one of the two comparison groups (e.g., low mechanical power vs. usual care) based on their covariate factors and the number of participants already randomized in the clinical trial. For the study we will utilize MinimPy (Source Forge, San Diego,

CA), a desktop application that allows minimization randomization as proposed. Patients will be allocated into two groups with a 1:1 allocation ratio, with a total of 12 patients assigned to each arm.

10.3 Statistical Analyses

In general, efficacy outcome analyses will follow the intent-to-treat principle, in which participants will be analyzed according to the randomized groups, regardless of treatment received. Safety outcome will be analyzed primarily in the as-treated population, defined as participants who actually received intervention. Analysis of the Primary Efficacy Endpoint(s)

To assess selection bias, descriptive statistics for key clinical characteristics will be summarized and stratified by patients' eligibility status. Then descriptive statistics will be calculated stratified by intervention group. Means, standard deviations, medians, and interquartile ranges (IQRs) will be summarized for continuous variables, and frequencies and proportions will be summarized for categorical variables. Differences in patient characteristics and ventilation parameters between the two intervention arms will be evaluated using the Chi-square test for categorical variables and two-sample t-test or Wilcoxon rank sum test for continuous measures. The primary endpoint, adherence to $\geq 90\%$ time in mechanical power range 2-4J/min, will be assessed using logistic regression. The odds ratio of achieving the target zone vs. standard care, along with its 95% confidence interval, will be reported both unadjusted and adjusted for patient characteristics and ventilation parameters.

10.3.1 Analysis of the Secondary Endpoint(s)

Descriptive statistics will be summarized similarly as described in Section 10.3. above. Secondary endpoints (mechanical power, RASS score, use of neuromuscular blockage, plasma biomarkers) will be measured at multiple time points, requiring the use of generalized linear mixed effects regression models (GLMERs) to assess the extent to which the changes in the outcome measure differ between the two groups. The fixed effects of interest will be group (low mechanical power vs usual care), time, and their interaction. Patient ID will be included as a random effect to account for within-patient correlations over time. As with the primary endpoint, analyses will be performed in both the intention-to-treat and as-treated populations.

Model fit will be assessed with model fit indices (e.g., AIC, BIC) and proportion of variance explained (e.g., R^2), and model comparison will be performed to determine the best fitting model for the data. Results from these models will provide us with an estimate of effect size for each of the outcome variables of interest, which will allow us to estimate the sample size needed to detect the corresponding clinically meaningful effect sizes for future studies.

10.3.2 Safety Analyses

Safety analyses will be performed by tracking the adverse events described above as descriptive statistics. No statistical analysis is planned.

10.3.3 Baseline Descriptive Statistics

Baseline descriptive statistics will be computed as described in Sections 10.3 and 10.3.1 above.

10.3.4 Planned Interim Analyses

There is no interim analysis planned.

10.3.5 Sub-Group Analyses

Sub-group analyses will be limited to descriptive statistics, in which descriptive statistics will be reported by eligibility group and by intervention group.

10.3.6 Tabulation of Individual Participant Data

There will be no tabulation of individual participant data. All data will be aggregated by group.

10.3.7 Exploratory Analyses

Exploratory analyses will be performed as described in Section 10.3.1 above.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory and Ethical Considerations

11.1.1 Informed Consent Document

Consent forms will be written in accord with federal regulations and will be reviewed and approved by the UVA IRB-HSR prior to use. Signed consent forms and other research records will be retained in a confidential manner.

11.1.2 Consent Procedures and Documentation

Given the critical illness and sedation levels of the study patient population, most participants will be unable to provide informed consent at enrollment. In this case, surrogate consent will be obtained from legally authorized representatives (LARs) per institutional policy and IRB approval. A member of the study team will explain the research study to the participant and/or their LAR and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants or their LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant or LAR will sign the informed consent document prior to any procedures being done specifically for the study. Results from procedures completed prior to consent for standard of care purposes may be used for research purposes. Participants and LARs must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date),

and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them and their LAR that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. When possible, specimens will be coded with IDs (not MRN or name). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the investigator.

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Virginia School of Medicine Clinical Trials Unit (UVA SOM CTU). Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by UVA SOM CTU research staff will be secured and password protected.

11.1.4 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The DSMB will review all serious adverse events (SAEs) that occur after every 6 patients enrolled. If unexpected safety concerns arise, the study team will promptly report them to the DSMB within 48 hours and the UVA IRB within 7 days per institutional guidelines. The DSMB will have the authority to pause the study if any significant safety concerns arise.

11.1.5 Site Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with

International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). The research team will monitor the trial for all safety and adverse events or any unanticipated problems involving risk to the patients or others. The DSMB will review all serious adverse events (SAEs) as they are reported and cumulatively at each 6 patients enrolled. The trial may also be selected for review by the UVA IRB-HSR PAM & Ed program, which chooses trials at random for auditing.

11.1.6 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.2 Data Handling and Record Keeping

11.2.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Study data will be deidentified for analysis and entered into an electronic case report form (CRF) in UVA REDCap ensuring secure, password protected collection of HIPAA compliant data.

11.2.2 Study Records Retention

Once the study has been completed, a CSV file will be generated from REDCap and will be modified into a fully deidentified analytic dataset. Within one month of creating the final analytic dataset it will be publicly shared in a repository (BioData Catalyst) along with a copy of the CRF. The dataset will remain publicly available for at least five years for those who want to perform secondary data analysis, if they have IRB approval for their research. When the study is published, a link to the data repository will be made available in the article.

11.3 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

11.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the institution has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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13 APPENDICES

13.1 Reporting Table

Sponsor/UVA CTU MPM Reporting to UVA IRB-HSR: Applicable only for sites relying on the UVA IRB-HSR as their IRB of record

Type of Event	To whom will it be reported:	Time frame for reporting:	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation <i>An internal event is one that occurs in a subject enrolled in a UVA protocol</i>	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event <i>Note; if in the text and in the UVA application only unexpected, serious, and RELATED AEs are being reported to UVA IRB-HSR, then make this consistent.</i> <i>Be sure the text in this section matches the text in the SAE reporting section.</i>	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. <i>Timeline includes submission of signed hardcopy of AE form.</i>	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form

Protocol Deviations/Noncompliance <i>The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.</i>	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach	The UVa Corporate Compliance and Privacy Office	As soon as possible and no later than 24 hours from the time the incident is identified.	UVa Corporate Compliance and Privacy Office- Phone (434) 924-2938
	ITC: if breach involves electronic data	As soon as possible and no later than 24 hours from the time the incident is identified.	ITC: Information Security Incident Reporting procedure , https://security.virginia.edu/report-information-security-incident
	UVA Police if breach includes such things as stolen computers	IMMEDIATELY.	UVA Police-Phone- (434) 924-7166

13.2 Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

[illegible]