Domain Protocol:
OZUHN-004-2

Expanded ECLS Criteria and Strategies Domain (Expand-ECLS)

Platform Master Protocol:
OZUHN-004

Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL) Randomized Control Trial

Protocol Version #: 3.0

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Clinical Trial Management

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Sponsor's Agreement to Domain Protocol #OZUHN-004-2 v. 3.0 dated 08-Apr-2025

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Date of Approval: 08-May-2025
DD-MMM-YYYY

Domain Lead Investigators' Agreement to the Domain Protocol OZUHN-004-2 v.3.0, dated 08-Apr-2025

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1 SYNOPSIS

Master Protocol Title:	**P**latform of **R**andomized **A**daptive **C**linical **T**rials **I**n **C**ritic**al** Illness (PRACTICAL) Randomized Control Trial
Domain Protocol Title:	Expanded ECLS Criteria and Strategies Domain
Eligible Platform Defined Patient States	This domain includes patients in the following platform defined state: 1. Intubated patients, not on ECLS, with low normalized respiratory elastance (<2.5 cm H_2O/(mL/kg predicted body weight)) 2. Intubated patients, not on ECLS, with high normalized respiratory system elastance (≥2.5 cm H_2O/(mL/kg predicted body weight))
Domain Arms	The arms being studied as part of this domain are: 1. Ultra-protective Ventilation facilitated by VV-ECMO (ULTIMATE) (intervention arm) 2. VV-ECMO-facilitated strategy of earlier awakening, extubation, and rehabilitation (PROACTIVE) (intervention arm) 3. Conventional Lung-Protective Ventilation (LPV) (control arm)
Domain Primary Outcome:	The primary outcome of this pilot study is feasibility, which includes 3 components; 1. *Successful patient recruitment* defined as enrolment of 100 AHRF patients from sites over 2 years 2. *Adherence to protocol* defined as >80% of patients having <20% of monitored values determined to be major protocol deviations 3. *Success for lack of crossovers* defined as <10% of crossovers between groups (when not allowed by protocol) in either direction *Refer to main body of protocol for a list of secondary and exploratory outcomes.*
Domain Design:	An interventional, open-label, randomized, multi-site feasibility study.

Duration:	2 years of accrual and 6 month follow-up for a total study duration of approximately 2.5 years
Planned Total Sample Size:	Approximately 100 evaluable patients will be randomized in this domain protocol.
Inclusion/Exclusion Criteria:	Patients will be eligible for enrolment in this domain if they meet platform- and domain-specific eligibility criteria. See main body of protocol for the list of criteria.
Randomization	Patients will be randomized to the control arm and applicable intervention(s) available. Each site will randomize patients into the control arm, and at least one intervention arm. At sites randomizing to both intervention arms, patients will be randomized using a 1:2:2 ratio, with the control arm receiving the 1 allocation and each of the two intervention arms receiving the 2 allocation. At sites randomizing to only one intervention arm, patients will be randomized in a 1:2 ratio between the control arm and the single intervention arm, with the control arm receiving the 1 allocation. Unequal randomization is used to prioritize and maximize data collection for the intervention arms, as their feasibility is the primary focus. This approach ensures sufficient data is gathered to evaluate the intervention arms, while the well-established feasibility of the control arm requires less emphasis.
Study Assessments:	Study assessments are depicted in the Study Plan (Section 7).
Statistical Analysis:	A target sample size of 100 AHRF patients will be randomized over a period of 2 years. This timeline will determine feasibility, as well as test the validity of our eligibility criteria, ventilation protocols, and study procedures. Descriptive statistical analyses and an intention-to-treat principle will be employed for the pilot phase of the study.

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2 LIST OF ABBREVIATIONS

ABG	Arterial Blood Gases
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
AHRF	Acute Hypoxemic Respiratory failure
aPTT	Activated Partial Thromboplastin
eCRF	Electronic Case Report Form
CPAP	Continuous Positive Airway Pressure
DSMB	Data Safety Monitoring Board
$\Delta P_{L\text{-}dyn}$	Dynamic Trans-Pulmonary Driving Pressure
ECLS	Extra-corporeal Life Support
$ECCO_2R$	Extracorporeal CO_2 Removal
FdO_2	Fraction of Delivered Oxygen
FiO_2	Fraction of Inspired Oxygen
ICU	Intensive Care Unit
MOP	Manual of Procedures
MRP	Most Responsible Physician
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of Oxygen
PEEP	Positive End Expiratory Pressure
P_{PLAT}	Plateau Pressure
REB	Research Ethics Board
RCT	Randomized Controlled Trial
SAE	Serious Adverse Events
SBT	Spontaneous Breathing Trial

SDM	Substitute Decision Maker
SpO_2	Percent Saturation of Oxygen
TEE	Trans-Esophageal Echocardiography
VILI	Ventilator Induced Lung Injury
V_T	Tidal Volume
VV-ECMO	Venovenous Extracorporeal Membrane Oxygenation

3 BACKGROUND

Complete background information of the **P**latform of **R**andomized **A**daptive **C**linical **T**rials **i**n **C**ritic**al** Illness (PRACTICAL) Randomized Control Trial can be found in the Master Protocol.

The problem to be addressed

Acute Respiratory Distress Syndrome is an important public health problem[1,2].ARDS patients account for 10% of all ICU patients and 25% of all patients requiring invasive ventilation[3]. Mortality remains high, from 34 to 65%[4], and up to 10,000 Canadians die with ARDS each year[1,5].

Ventilator-induced lung injury (VILI) contributes to ARDS mortality. While ventilators provide essential life support in ARDS, mechanical ventilation can also perpetuate lung injury[6,7]. In a seminal RCT, a low tidal volume strategy reduced mortality from 40% to 31%, and this strategy is now considered to be the standard of care for ARDS[8,9]. However, usual care, standard ventilation is often still injurious[10]. Driving pressure (ΔP) –a key marker for development of VILI– combines elements of tidal volume and lung compliance and is frequently elevated in clinical practice[11]. Attempts to lower driving pressure and lung stress further have been limited by hypoventilation and respiratory acidosis[12]. More recently we have recognized that the syndrome of Acute Hypoxemic Respiratory failure (AHRF) (excluding heart failure) may be a more useful target than ARDS per se – the only difference between the two syndromes being the chest radiograph criterion, which has known poor reliability.[PMID 10619802] Our group has also recently demonstrated the impact of VILI in populations of AHRF patients, which is similar to that seen in ARDS.[32735841; 36971437]

Current Evidence for the Use of VV-ECMO in Patients with ARDS. Multiple international guidelines recommend use of VV ECMO for severe ARDS.[30-32] There have been two modern RCTs of VV-ECMO in severe ARDS.[33,34] In the larger trial, we demonstrated that VV-ECMO, compared to conventional MV, reduced the ventilator-free days at day 60 and reduced dialysis and vasopressor use, although the trial was stopped early and the primary outcome of 60 day mortality did not reach statistical significance (relative risk 0.76; 95% confidence interval 0.55-1.04; p=0.09).[34] However, subsequent studies, including a post-hoc Bayesian re-analysis[35] and several meta-analyses[36-38] suggested that VV-ECMO decreased mortality in severe ARDS patients. Importantly, the rate of complications (such as cannula site bleeding <12%) were also much reduced highlighting the relatively safety of modern ECMO. Interestingly, subgroup analysis of this landmark trial suggests that mitigation of VILI, not rescue from refractory hypoxemia, was the major driver of benefit in these patients. We also demonstrated in a recent international observational study that ECMO is associated with a mortality benefit in a large cohort of patients with COVID-19-associated respiratory failure.[39] Also in this analysis we observed a significant benefit from ECMO if it were initiated in patients with less severe hypoxemia.

Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) can facilitate ultra-low intensity mechanical ventilation through CO_2 removal. VV-ECMO is a technique that provides artificial respiratory support by adding O_2 and removing CO_2 from blood[13]. In the largest and most recent RCT of VV-ECMO, mortality was reduced with VV-ECMO, and this was most pronounced in patients with higher baseline oxygen levels[14]. This suggests that the effect was mediated through VILI-reduction rather than avoiding death from hypoxemia per se. Driven by these positive results and a large increase in demand driven by the COVID-19 pandemic, many new centres are developing programs to deliver ECMO.

Ultra-low intensity ventilation facilitated by extracorporeal CO_2 removal ($ECCO_2R$) may indeed improve outcomes. There is good physiological rationale to believe that resting the lung further by reducing tidal volume, driving pressure, or respiratory rate– reducing mechanical power – could further lower the clinical impact of VILI[15-17]. Among 10,112 ventilated patients in the Toronto Intensive Care Registry, adjusted for baseline characteristics, higher mechanical power was associated with increased risk of death on any day of ventilation (HR 1.064; 95% CI 1.058 to 1.074 per J/min)[18]. Reducing lung stress and strain is possible by transferring this work to the external artificial membrane lung on VV-ECMO.

At the current time the safest and most feasible manner to deliver CO_2 removal is through higher-flow VV-ECMO. We recently reported that a variety of modern $ECCO_2R$ devices are capable of supporting ultra-low tidal volume ventilation[19]. However, secondary analysis of this study showed that when CO_2 removal was delivered through a VV-ECMO device with capability for higher flow and more CO_2 removal, patients were much more likely to reach V_T of 4 mL/kg (92 vs. 64%) and were less likely to experience complications of hemolysis or bleeding (6 vs 27%)[20].Although flow rates above 1.5L/min may not be required for $ECCO_2R$ with these devices, standard VV-ECMO flows at 3-6L/min may be safer because they avoid the need for more aggressive anticoagulation, minimize pump recirculation and blood trauma[21], and can support hypoxemia that may develop due to hypoventilation in the native lung.

To be effective $ECCO_2R$ must use efficient devices *and* target patients who cannot be safely ventilated with usual standard-of-care ventilation. The recently published REST trial used a low-flow, low-efficiency $ECCO_2R$ device in 412 unselected patients with moderate-severe hypoxemic respiratory failure[22]. There was no difference in mortality between groups, likely driven by fact that only modest reductions in intensity of ventilation were achieved. Tidal volume was only 2 mL/kg lower in the $ECCO_2R$, and moreover this reduced driving pressure by only 3 cm of H_2O. Recent work from our group shows reductions in driving pressure drive mortality benefit from tidal volume reduction[23], and that driving pressure is reduced most by $ECCO_2R$ in patients with low respiratory system compliance (high elastance)[24].

The uncritical adoption of $ECCO_2R$ is premature and problematic. Wide dissemination of VV-ECMO outside the severe ARDS population tested in EOLIA at this time would represent premature adoption of a complex technology without rigorous evaluation of associated risks and benefits. A systematic review of $ECCO_2R$ identified 14 studies (2 RCTs) including only 495 patients and concluded that there is a "paucity of high-quality data and significant variation in technology used among studies"[25]. Recent editorialists on the REST Trial also conclude that "Future studies that harness the potential benefits of $ECCO_2R$ without increasing the risk of other complications are needed".

VV-ECMO can facilitate a strategy of early awakening, liberation from mechanical ventilation, and mobilization which may improve morbidity in survivors. A pilot RCT by our team demonstrated that early mobility is safe and feasible in patients on ECMO and may improve physical function in survivors.[28,29,40] These studies focused on using ECMO in severe ARDS patients provide reassuring efficacy and safety data.

Importantly, a recent study by Mustafa et al. provides proof of concept that a strategy ECMO-facilitated awakening, extubation, and rehabilitation is feasible in patients with severe respiratory failure due to COVID-19.[41,42] In this single-centre case series, 40 patients (median age 51 [IQR 22-64]) with severe acute respiratory failure were placed on VV-ECMO relatively soon after intubation (mean 4 ± 0.5 days). Despite severe lung injury at baseline (mean PaO2/FiO2 69 ± 3.1) the investigators demonstrated that: 1) ECMO was safe; 2) awakening, extubation and rehabilitation were achieved in almost all patients; 3) only 1 patient required a tracheostomy; and 4) mortality was only 18%, lower than would be expected given the baseline severity of illness. This study used a single access, dual stage right atrium-to-pulmonary artery cannula for VV-ECMO. We plan to use this cannula in our study because it has the following potential advantages compared to other dual-lumen or 2 cannulae configurations: 1) direct pulmonary artery flow, leading to low recirculation and more stable oxygenation support; 2) facilitates early mobility once off MV with single, upper body configuration; 3) fewer cannula associated complications or revisions than with femoral cannulations[43]; and 4) support of the right heart in case of RV dysfunction, which is very common in patients with ARDS.[44]

Any potential benefit of VV-ECMO must be weighed against device-associated complications including bleeding, hemolysis, and cannulation complications.[45] Our recently completed international RCT (EOLIA) using VV-ECMO in patients with severe ARDS (n = 249) reported fewer serious adverse events with ECMO compared to conventional MV.[34] We also expect less patient ventilator asynchrony with VV-ECMO than conventional MV strategy, which may improve safety and outcomes.[46] Our study will collect detailed data on complications in both VV-ECMO and MV groups.

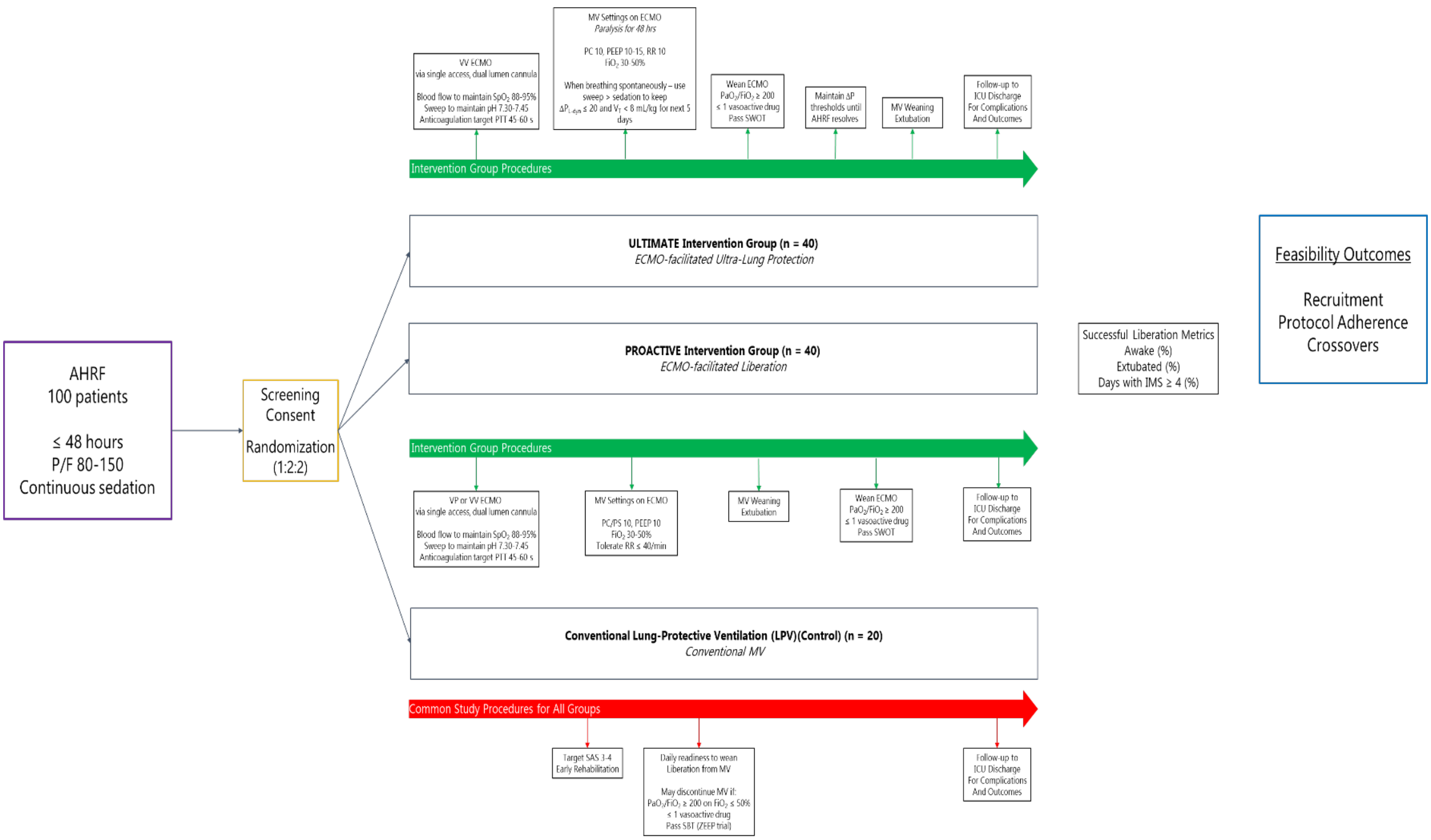
Summary

Extracorporeal support can facilitate ultra-low intensity ventilation while simultaneously avoiding harmful hypercapnia and acidosis. At the current time the safest and most feasible manner to deliver CO_2 removal is through higher-flow VV-ECMO. This approach, termed 'ultra-protective' ventilation, may indeed improve outcomes in patients with moderate-severe ARDS. We therefore propose the Ultra-Low Tidal Volume Mechanical Ventilation in ARDS Through ECMO (ULTIMATE) intervention.

Additionally, VV-ECMO provides a theoretically appealing alternative whereby patients could be awake and breathing spontaneously without a ventilator thus avoiding many of the complications of excess sedation and immobility from bed rest, while still being able to maintain safe oxygenation and ventilation. While based on sound principles, it is currently unknown if this approach improves outcomes. This is the basis of the Prevent Reduced Outcomes in ARDS by Transitioning from Invasive Ventilation to ECMO (PROACTIVE) intervention.

This study will be conducted in compliance with the PRACTICAL Master Protocol, this domain protocol and applicable ICH-GCP guidelines.

4 STUDY SCHEMA



5 RESEARCH OUTCOMES

Listed below are outcomes that apply to the entire domain. Refer to the PRACTICAL Master Protocol for the list of platform-wide endpoints.

Domain Primary Outcome

The primary outcome of this pilot study is feasibility, which includes 3 components;

1. *Successful patient recruitment* defined as enrolment of 100 AHRF patients from sites over 2 years
2. *Adherence to protocol* defined as >80% of patients having <20% of monitored values determined to be major protocol deviations
3. *Success for lack of crossovers* defined as <10% of crossovers between groups (when not allowed by protocol) in either direction

For control and each intervention arm, if feasibility is demonstrated and major protocol changes are not required, patients randomized into this domain will be rolled over and form the vanguard phase of the definitive Expanded ECLS Criteria and Strategies Domain RCT.

Domain Secondary Outcomes

1. Duration of hospital stay
2. Duration of ECMO support
3. Barotrauma
4. ECMO-associated complications (i.e. Mechanical, Hemorrhagic, Renal)
5. Tracheostomy
6. Mortality (28-day, 60-day)
7. Manual muscle strength (MRC Scale) and diaphragm/quadriceps ultrasound at ICU discharge in participating centers.
8. Highest level of activity (IMS) at ICU discharge
9. Health-related QOL (EQ-5D) at Day 60 and 6 months

<u>PROACTIVE Secondary Outcomes:</u>

1. Proportion of patients who are awake, extubated, and able to participate in rehabilitation by study Day 7

Our exploratory outcomes include monitoring safety issues, by recording serious adverse events in all groups as well as quantifying cytokine levels to further understand the inflammatory processes involved.

6 PATIENT POPULATION, ELIGIBILITY AND ENROLLMENT

Patient population

This domain includes patients in the following platform defined states:

1. Intubated patients, not on ECLS, with low normalized respiratory elastance (<2.5 cm H2O/(mL/kg predicted body weight))
2. Intubated patients, not on ECLS, with high normalized respiratory system elastance (≥2.5 cm H_2O/(mL/kg predicted body weight)).

Patients who satisfy both platform- and domain-specific eligibility criteria will be considered for enrolment.

Any questions about eligibility criteria must be addressed ***prior*** to patient randomization.

PRACTICAL Platform Eligibility Criteria

<u>PRACTICAL Inclusion Criteria</u>

1. Acute hypoxemic respiratory failure meeting all of the following criteria;
    a. New or worsening respiratory symptoms developing within 2 weeks prior to the onset of need for oxygen or respiratory support,
    b. Receiving any of the following types of oxygen or respiratory support for at least 4 hours prior to the time of randomization; supplemental oxygen at 10 L/min or higher, high flow nasal oxygen (at any flow rate), invasive ventilator support, extra-corporeal life support (ECLS), or non-invasive ventilator support,
    c. Minimum $FiO_2 \geq 0.40$ (for venturi mask, high flow nasal cannula, or invasive or non-invasive ventilation) or oxygen flow rate ≥10 L/min on face mask for at least 4 hours at the time of evaluation for eligibility unless already on extra-corporeal life support.
2. Age ≥ 18 years.

<u>PRACTICAL Exclusion Criteria</u>

1. Hypoxemia is **primarily** attributable to acute heart failure or fluid overload.
2. Hypoxemia is **primarily** attributable to pulmonary embolism.

3. Hypoxemia is **primarily** attributable to status asthmaticus.
4. Extubation is planned or anticipated on the day of screening.
5. ICU discharge is planned or anticipated on the day of screening.
6. The patient is moribund and deemed unlikely to survive past 24 hours (as determined by the clinical team).
7. The patient is being transitioned to a fully palliative philosophy of care.

Domain-Specific Eligibility Criteria

Domain Inclusion Criteria

1. Receiving invasive mechanical ventilation for ≤ 72 hours.
2. moderate-severe hypoxemic respiratory failure with a $PaO_2/FiO_2 \leq 150$ mmHg for at least 6 hours.

Domain Exclusion Criteria

1. Patients over 70 years of age.
2. Currently receiving any form of ECLS (e.g., Venovenous, venoarterial, or hybrid configuration).
3. Chronic hypercapnic respiratory failure defined as $PaCO_2 > 60$ mmHg in the outpatient setting.
4. Home mechanical ventilation (non-invasive ventilation or via tracheotomy) except for CPAP/BiPAP used solely for sleep-disordered breathing.
5. Actual body weight exceeding 1 kg per centimeter of height.
6. More than 48 hours have passed since meeting inclusion criteria.
7. Severe hypoxemia with $PaO_2/FiO_2 < 80$mmHg for > 6 hours at time of screening.
8. Severe hypercapnic respiratory failure with pH < 7.25 and $PaCO_2 > 60$ mmHg for > 6 hours at time of screening.
9. Expected mechanical ventilation duration < 48 hours at time of screening.
10. Confirmed diffuse alveolar hemorrhage from vasculitis.
11. Contraindications to limited anticoagulation (e.g., active GI bleeding, bleeding diathesis).
12. Previous hypersensitivity/anaphylactic reaction to heparin or heparin-induced thrombocytopenia
13. Neurologic conditions at risk for or undergoing treatment for intracranial hypertension
14. Underlying illness with life expectancy < 1 year
15. Pregnancy (due to unknown effects of $PaCO_2$ changes on placental blood flow)

16. Respiratory failure known or suspected to be caused by COVID-19.

Eligible non-randomized patients will be identified and reasons for non-enrolment classified as:

1. Lack of consent from patient or substitute decision maker (specifying reason);
2. Refusal from attending physician (specifying reason);
3. Enrolment in a confounding RCT;
4. Research coordinator or device not available.

Patient Consent

The consent process will be conducted as per local ethics board requirements and recommendations. Patient / substitute decision maker (SDM) (for patients lacking decision-making capacity) consent must be obtained prior to any domain-specific procedures, randomization and start of the study intervention.

It will be the responsibility of the local participating investigator to obtain the necessary institutional approval, and to indicate in writing to Ozmosis Research Inc. that such clearance has been obtained before the study can commence at that site. Sample English consent forms for the study will be provided. A copy of the initial full ethics board approval and approved consent form(s) must be sent to Ozmosis Research Inc.

All study sites are required to obtain full board ethics approval of the protocol and consent form by the appropriate ethics board prior to commencement of the clinical trial at each site. Annual (or as required by the ethics board) re-approval may be required for as long as patients are being followed on protocol. It will be the Principal Investigator’s responsibility to apply for and obtain the re-approval.

Patient Enrollment and Randomization

General registration information can be found in the PRACTICAL Master Protocol.

Mechanically ventilated patients will be screened by research personnel for the Platform and Domain Inclusion and Exclusion criteria. Eligibility will be confirmed by the applicable site investigator and approval of the most responsible physician (MRP) will be sought and documented, ensuring that participation is aligned with patient’s best clinical interest. Patients with that documented approval will be approached (or their SDMs as applicable) for informed consent. Eligible and consented (as applicable per the section above) patients may be randomized into this domain. Patients who meet inclusion criteria but are not randomized will be recorded in the screening log, along with the reason for non-randomization (e.g. meeting one or more exclusion criteria, lack of consent, etc) clearly recorded.

Prior to screening and consenting patients, each institution must have submitted all the necessary regulatory documentation to Ozmosis Research Inc. and received a local activation letter. Access to the eCRF will only be granted once this has been received and randomization will occur online via the REDCap database.

Patients can be randomized into this domain only once. Patients who are randomized into this study, discharged from the ICU, and then re-admitted at a later date cannot be randomized into this study a second time. If a patient is randomized into another domain within the PRACTICAL platform trial, and becomes eligible for this domain during a subsequent ICU admission or due to a change of severity state, the patient can be randomized (for the first time).

Patients will be randomized to the control arm and applicable intervention(s) available. Each site will randomize patients into the control arm and at least one intervention arm.

At sites randomizing to both intervention arms, patients will be randomized using a 1:2:2 ratio, with the control arm receiving the 1 allocation and each of the two intervention arms receiving the 2 allocation. At sites randomizing to only one intervention arm, patients will be randomized in a 1:2 ratio between the control arm and the single intervention arm, with the control arm receiving the 1 allocation.

Unequal randomization is used to prioritize and maximize data collection for the intervention arms, as their feasibility is the primary focus. This approach ensures sufficient data is gathered to evaluate the intervention arms, while the well-established feasibility of the control arm requires less emphasis.

Benefits to Patients

The intervention may or may not be of direct benefit to patients. The information learned from this study will contribute to better care for patients with AHRF in the future. There is an intent to benefit all patients regardless of the assigned intervention. Patients will receive daily intensive monitoring by the research team, in addition to routine monitoring by the clinical team.

7 STUDY PLAN

Study Schedule

Patients randomized to the ULTIMATE intervention arm will receive ultra-protective ventilation using VV-ECMO. Patients randomized to the PROACTIVE intervention arm will receive a VV-ECMO-facilitated strategy of earlier awakening, extubation, and rehabilitation. Patients randomized to the control arm will receive Conventional Lung-Protective Ventilation (LPV). Patients randomized to either intervention arm should be cannulated and go on ECMO as soon as possible. In the event of an unavoidable significant delay in receiving ECMO following randomization to an intervention arm, confirm with the clinical team that it remains appropriate for the patient to receive the intervention.

Study procedures common to all groups will continue for the duration of the ICU stay up to day 28. We will collect daily data during mechanical ventilation until Day 28. Thereafter, we will follow patients to the time of hospital discharge and record ICU/hospital survival. We will also assess health-related quality of life through remote contact at Day 60 and Day 180 from randomization. Refer to Section 3 (Study Schema) above for a general overview of the study timelines and procedures. Refer to Section 8 for details on management of the intervention and control arms.

Study Calendar

Required Procedures*	Baseline	Daily to day 28 or ICU discharge, whichever comes first	Day 60	6 months (180 days) from Randomization (Remote contact)
Window	*N/A*	*N/A*	+10 days	*-22 days, +60 days*
Consent & Randomization [1]	X			
Demographics [2]	X			
Medical History [3]	X			
Vitals [4]	X	X		
Hemodynamics [5]	X	X		
Respiratory Data [6]	X	X		
Hematology [7]	X	X		
Biochemistry [8]	X	X		

Arterial Blood Gases (ABG) [9]	X	X		
Pregnancy Test (urine/serum)	X			
Optional: Blood Sample Collection [10]	X	X (Day 3 (+/- 1 day), Day 7 (+/- 1 day), and ICU Discharge)		
Management according to randomized arm[12]		X		
Modified Rankin Scale (MRS)		X (At ICU Discharge in participating centers)		
Highest level of activity (IMS)[18]		X (At ICU Discharge)		
Diaphragm/quadriceps ultrasound[21]		X (At ICU Discharge in participating centers)		
MV Readiness to Wean	X	X		
Spontaneous Breathing Trial [13]		X		
Sweep Gas Off Trials (SWOTs)[14]		X		
HrQOL(EQ-5D-5L)[15]			X	X[15]
Vital Status		X (At Day 28 or ICU discharge, whichever comes first)	X[19]	X
Ventilation assessment worksheet completion (ULTIMATE patients only)		X[20]		
Glasgow Coma Scale and Sofa Score	X	X		
Serious Adverse Events [16]		X		
Outcomes[22]		*As applicable*		
Concomitant Medications [17]	X			

[1] Consent should be obtained prior to any study-specific baseline assessments and according to site institutional timelines.

[2] Demographics include age, gender, height, and weight. Race and ethnicity will be reported only for patients who have consented to the collection of this data.

[3] Hospital and ICU admission information (including date/time), Diagnosis/Cause of AHRF, APACHE IV, Clinical Frailty Score, , COVID-19 infection status.

[4] Vitals include temperature, heart rate, respiratory rate, and blood pressure.

[5] Hemodynamics include BP, PAPm, PCWP, SvO_2 and will reported in the database if collected.

[6] Respiratory data include mode of ventilation, FiO_2, PEEP, PIP, RR, ventilation rate, tidal volume, plateau and driving pressure, oxygen saturation, and expiratory occlusion pressure (P_{occ}).

[7] Hematology reporting on Hg, WBCs, and platelets. If not done daily per clinical standard-of-care procedures, sites are not required to have these tests done specifically for study purposes, and this will not be considered a protocol deviation.

[8] Biochemistry will include reporting the following values: INR, PTT, activated clotting time, Fibrinogen, Antithrombin III, D-Dimers, plasma-free hemoglobin, sodium, glucose, creatinine, albumin, bilirubin, potassium, bicarbonate, creatinine kinase, troponin, phosphate, total calcium. If not done daily per standard-of-care procedures, sites are not required to have these tests done specifically for study purposes, and this will not be considered a protocol deviation.

[9] ABG testing will include the following parameters: pH, $PaCO_2$, HCO_3, base excess, SaO_2, lactate, hemoglobin. Venous blood gas (VBG) testing may be used as an alternative. If not done per standard of care, sites are not required to have ABG/VBG testing done specifically for the study and this will not be a protocol deviation.

[10] Blood sample collection is optional and will proceed only if patient or their SDM signs the optional consent form. Blood samples collection will occur at baseline, on Day 3 (+/- 1 day), Day 7 (+/- 1 day) and ICU discharge

[11] Patient will be on mechanical ventilation, regardless of randomization, and will be assessed daily for readiness to wean.

[12] Patients randomized to the ULTIMATE intervention arm will receive ultra-protective ventilation using VV-ECMO. Patients randomized to the PROACTIVE intervention arm will receive a VV- ECMO -–facilitated strategy of earlier awakening, extubation, and rehabilitation. Patients randomized to the control arm will receive Conventional Lung-Protective Ventilation (LPV). Patients randomized to either intervention arm (ULTIMATE/PROACTIVE) should be cannulated and go on ECMO as soon as possible.

[13] Spontaneous breathing trials (SBTs) will be conducted only when patient is deemed ready for weaning from MV and per standard of care and/or institutional guidelines.

[14] Patients who have received ≥ 48 hours of ECMO therapy will be assessed daily for ECMO discontinuation with SWOTs. This assessment will be considered successful if patients tolerate SWOTs for ≥12 hrs with no significant hypoxemia, respiratory acidosis, or work of breathing.

[15] HrQOL questionnaires (EQ-5D-5L) will be administered through remote contact at Day 60 and Day 180 from randomization. Vital status (patient dead or alive) will also be reported at this timepoint.

[16] SAEs will be reported at the start of randomization and for a period of up to 28 days, or while in ICU, whichever is shorter.

[17] Concomitant medications listed in section 8 will only be captured, if taken. Concomitant medications will be collected for study purposes from time of consent to time of ICU discharge or for 28 days, whichever is shorter.

[18] Highest level of activity (IMS) recorded daily.

[19] The Day 60 vital status check can be done based on review of medical records if the site has access. In those cases, it is not necessary to contact the patient.

	[20]Ventilation assessment worksheet should be completed once daily for patients that are randomized to the ULTIMATE intervention for the duration of the intervention. [21] Diaphragm/quadriceps ultrasound measurements done at ICU discharge in participating centers. • Maximum thickening fraction should be measured at the earliest opportunity once patient has their first SBT [22]Outcomes include duration of ECMO Support, ECMO-associated complications, Tracheostomy, Biotrauma (as measured by plasma cytokines) in participating centers, Barotrauma, and Organ Dysfunction (as measured by SOFA score). * All blue fields are standard-of-care assessments and data being collected for study purposes.

Optional Correlative Sample Collection

Blood sample collection for the assessment of biomarkers and other future research studies will occur at the time points indicated within the Study Calendar. It is not mandatory for all sites to participate in the collection of correlative samples and each sites' willingness and ability to participate will be discussed individually. In participating sites, patients will be provided with an informed consent form to review and indicate their willingness to participate in this optional sample collection.

Further details are available in the MOP.

8 CONCOMITANT MEDICATION/ PROCEDURES

The administration of the following concomitant medications will be collected for study purposes from time of consent to time of ICU discharge or for 28 days, whichever is shorter.

- Neuromuscular blocking agents (e.g., rocuronium, cisatracurium)
- Sedatives and analgesics (e.g., propofol, fentanyl, hydromorphone, midazolam, ketamine)
- Corticosteroids (e.g., methylprednisolone, prednisone, dexamethasone, hydrocortisone)
- Inotropes (e.g., dobutamine, milrinone)
- Vasopressors (e.g., norepinephrine, vasopressin, epinephrine)
- Diuretics (e.g., furosemide, metalazone)
- Inhaled pulmonary vasodilators (e.g. nitric oxide, flolan)

Additionally, the following procedures are to be documented:

- Prone positioning
- Renal replacement therapy

9 TRIAL INTERVENTIONS

Intervention Arms (ULTIMATE/PROACTIVE): Stabilization and ECMO Initiation

If not already done, patients randomized to either of the two intervention arms will be deeply sedated to a Sedation Agitation Scale (SAS) = 1 and then be paralyzed with a neuromuscular blocking agent (NMBA). Baseline usual care standard ventilation will then be set as follows:

- Mode: Volume Assist-Control
- FiO_2 1.0;
- PEEP 10-15 cm H_2O or higher as needed to maintain $SpO_2 > 92\%$;
- V_T = 6 mL/kg PBW and adjusted to maintain $P_{PLAT} \leq 30$ cm H_2O
- Inspiratory to expiratory (I:E) ratio 1:1 to 1:3, avoiding auto-PEEP
- Respiratory rate set to match previous minute ventilation to maximum of 35 breaths/min and targeting a pH > 7.25

These initial adjustments may occur over a period of a few minutes to a couple of hours, depending upon the baseline V_T and the ability of the patient to tolerate sudden changes. In keeping with routine clinical practices, an arterial blood gas should be drawn within 1 hour of transitioning onto the study protocol to assess both oxygenation and ventilation.

As soon as the patient is stable (based on the standard settings described above), the clinical team will measure the patient's respiratory elastance using the following equation:

$$Elastance = \frac{Driving\ Pressure}{\frac{Tidal\,Volume}{PBW}} = \frac{Pplat - PEEP\ total}{\frac{VT}{PBW}}$$

9.1 **ULTIMATE Intervention Arm:** Ultra-protective Ventilation using ECMO devices

Our goal for this arm is to study ultra-protective ventilation (i.e., low driving pressure, tidal volume, and respiratory rate) facilitated by ECMO devices compared to Conventional Lung Protective Ventilation (LPV). The overarching goal of ULTIMATE is to deliver lung protective ventilation to improve outcomes. This consists of ECLS-facilitated ultra-low driving pressure ventilation in the early phase, followed by low driving pressure ventilation in the post-ECLS phase. This will ensure adequate adherence to an optimal lung protective strategy for the intervention group and better align with our primary outcome.

Patients randomized to this experimental arm will receive VV-ECMO with cannula(e) configuration at the discretion of the treating center. We will employ an explicit protocol outlined below that draws heavily on our previous ECMO protocols,[14, 19] and on expert consensus.[15]

Proceed with cannulation and connection to the VV-ECMO circuit using sterile technique and monitoring according to usual practice (e.g. ultrasound-guided puncture, radiography, trans-esophageal echocardiography (TEE), or fluoroscopic cannula positioning). We recommend use of the study-supplied dual-lumen bicaval Crescent cannula connected to the Nautilus oxygenator, but the clinical team may choose any VV-ECMO configuration that facilitates 3-5 L/min blood flow.

VV-ECMO will then be initiated with pump speed set to deliver blood flow of 3-5 L/min and sweep gas flow of 1 L/min of 100% oxygen.

The mechanical ventilator will then be adjusted as follows:

- Mode: Pressure Control
- FiO_2 0.5
- Set Driving Pressure to 10 cmH_2O
- PEEP 10-15 cm H_2O
- Inspiratory time 0.7-1 second
- Respiratory rate 10 breaths/min

As per usual care, an arterial blood gas will be drawn after 15-30 minutes, and sweep gas flow will be adjusted to target a $PaCO_2$ of 40-60 mmHg; if the baseline $PaCO_2$ is above 60 we will target lowering it slowly by no more than 10-20 per 12 hours.[19] We will maintain a FdO_2 of 1.0 on the circuit and adjust blood flow rates to maintain SpO_2 92-97%.

<u>Maintenance and Weaning of Ultra-Protective Ventilation</u>:

Deep sedation, paralysis, and these low-intensity mechanical ventilation settings will be maintained for at least 48 hours after ECMO initiation. The clinical team will make adjustments to the VV-ECMO settings to maintain the same $PaCO_2$, pH and PaO_2 and SpO_2 targets as above. These adjustments to VV-ECMO sweep gas or blood flow will be dictated by ABG results drawn as clinically indicated.

Anticoagulation with intravenous heparin infusion during VV-ECMO will be recommended at a level to target aPTT 1.5-2 times normal but will be ultimately managed at the discretion of the attending physician.

On study day 3, patients will then enter the maintenance and weaning phase – neuromuscular blockade will be discontinued, and lighter sedation levels (SAS 2-3) will be targeted unless otherwise decided by the attending physician.

During the first 14 days after randomization and once neuromuscular blockade is stopped and patients are making spontaneous breathing efforts, we will use sweep gas flow (primary) and sedation (secondary) to modulate spontaneous efforts to maintain low intensity ventilation, targeting the estimated dynamic trans-pulmonary driving pressure ($\Delta P_{L\text{-}dyn}$) and tidal volume.

During each major ventilation round and at least twice daily, clinicians will measure patient respiratory effort by calculating ΔP_{occ} (which is always zero or negative):[26]

- Perform expiratory hold and record trough pressure with next effort (record as = PEEP if no efforts made)
- Calculate ΔP_{occ} = trough pressure - PEEP
- Calculate $\Delta P_{L\text{-}dyn}$ = (Peak airway pressure – PEEP) – 0.67 x ΔP_{occ}

To maintain $\Delta P_{L\text{-}dyn} \leq 23$ cm H_2O while patients are breathing spontaneously, the treating team will adjust in the following order: a) the mechanical ventilator and/or the sweep gas flow, and b) sedation levels.

The following table outlines the ECMO and ventilator settings and targets during the ECMO maintenance and weaning phase (Days 3-14)

Mode of mechanical ventilation	Pressure-control or Pressure Support
Tidal volume	**During controlled ventilation (Pocc = 0 cm H2O): resultant Vt from PC 10 cm H2O** **During assisted ventilation (Pocc < 0 cm H2O): adjusted to maintain dynamic transpulmonary ΔP ≤20 cm H2O**
Plateau airway pressure	**Target of ≤25 cm H2O** (measured during assisted ventilation, when possible)
pH	Target >7.15
Respiratory rate	**≤30 breaths per minute** (measured during assisted ventilation, when possible*)*
Positive end-expiratory pressure (PEEP)	Adjusted according to local site practice
Ventilator Fraction of inspired oxygen (FiO2)	Adjusted to maintain peripheral oxygen saturation (SpO2) ≥ 90% , unless otherwise specified by this protocol

Plateau pressure monitoring protocol	Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)
ECMO Blood Flow	**RPMs adjusted to 3-5 L/min to achieve SpO2>90%**
ECMO FdO2	**Set at 1.0**
ECMO Sweep Gas	**Adjusted to maintain PaCO2, pH and ∆PL in target range**
Expiratory occlusion pressure (Pocc) monitoring protocol	**Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)**
Dynamic transpulmonary driving pressure (∆PL) monitoring protocol	**Computed in real time at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution). If Pocc = 0 cm H2O, ∆PL cannot be estimated and does not apply.**
Adjustment for severe respiratory acidosis (pH<7.15) with respiratory rate adjusted to maximum of 40 breaths per minute	Increase sweep gas up to 10L/min – if pH still below target check membrane function Clinician may treat with intravenous bicarbonate. If pH remains below 7.15 tidal volume may be increased in 1 mL/kg increments to achieve pH target (under these conditions plateau pressure targets may be exceeded)
Adjustment for plateau airway pressure above target during controlled ventilation (Pocc = 0 cm H2O)	1) PEEP will be titrated downward as tolerated, 2) Tidal volume will be reduced as permitted by pH; sweep gas will be increased as needed
Adjustment for dynamic transpulmonary ∆PL>20 cm H2O during assisted ventilation (Pocc <0 cm H2O)	1) **increase sweep gas flow in increments of 2 L/min to a maximum of 10 L/min and assess dynamic transpulmonary ∆PL at each step. Stop when limited by pH (> 7.5) or hypocapnia (PaCO2 < 30 mm Hg) . If limited by pH and bicarbonate is >35 mmol/L clinician can consider administration of acetazolamide**

	2) PEEP will be titrated upward or downward to determine whether dynamic transpulmonary ∆P can be reduced by optimizing compliance and respiratory effort 3) Inspiratory pressure/flow will be decreased as permitted by pH and tidal volume limits (can be skipped if the patient's respiratory effort is already significantly elevated (i.e., Pocc more negative than –20 cm H2O) 4) If Pocc is more negative than –20 cm H2O, FiO2 will be increased by 20% to increase PaO2 to assess whether this reduces respiratory drive and effort 5) If pH < 7.3, consider bicarbonate infusion 6) Sedation will be increased when deemed necessary by the clinicians to reduce respiratory effort in order to reduce dynamic transpulmonary ∆P to acceptable limits 6) Consider neuromuscular blockade if dynamic transpulmonary ∆PL remains above target because of persistently excessive respiratory effort despite deep sedation
Sedation targets	The sedation regimen will be managed by the clinical team to target light levels of sedation (typically SAS 3 to 4 or RASS -2 to 0) via targeted sedation or daily interruption, unless otherwise indicated, as per PADIS guidelines. During assisted ventilation, if dynamic transpulmonary deltaPL exceeds 20 cm H2O due to excessive respiratory effort, and this cannot be resolved by adjusting ECMO or the ventilator, the clinical team will be directed to adjust sedation according to their best judgment to reduce respiratory effort and achieve dynamic transpulmonary ∆PL target. Sedation to apnea (Pocc = 0 cm H2O) is permitted if necessary to achieve targets.

We will wean ECMO prior to liberating from mechanical ventilation and provide explicit protocols for weaning ECMO (See Manual of Procedures). Briefly, patients will be assessed daily for ability to discontinue ECMO – all patients who are not paralyzed and are breathing spontaneously on sweep gas flow of 4 L/min or less, and who are receiving an FiO_2 of ≤ 0.6 on the mechanical ventilator with a PaO_2/FiO_2 > 150 will undergo a trial of sweep gas off on ECMO. ECMO will be discontinued if patients tolerate sweep gas off for at least 12 hours (i.e., no significant hypoxemia, respiratory acidosis, or increased work of breathing).

After patients are decannulated from VV-ECMO or at day 14 these patients will be managed by the IMV Driving Pressure Limited (DPL) protocol. If patients remain on ECMO after day 14, ECMO settings will be determined by the treating team but sweep gas off trials will continue to occur daily if applicable as above.

Management details that differ from Conventional Lung-Protective Ventilation (LPV) (control arm) are bolded in the table below.

Intervention Management – Driving Pressure Limited (DPL)	
Mode of mechanical ventilation	Pressure-targeted or volume-cycled ventilation modes as per clinician preference (e.g. pressure control, volume control, pressure support, etc.)
Tidal volume	**During controlled ventilation (Pocc = 0 cm H2O): adjusted to maintain ∆P ≤15 cm H2O** **During assisted ventilation (Pocc < 0 cm H2O): adjusted to maintain dynamic transpulmonary ∆P ≤23 cm H2O**
Plateau airway pressure	**Target of ≤35 cm H2O**
pH	Target >7.15
Respiratory rate	**≤40 breaths per minute**
Positive end-expiratory pressure (PEEP)	Adjusted according to local site practice

Fraction of inspired oxygen (FiO2)	Adjusted to maintain peripheral oxygen saturation (SpO2) ≥ 90% , unless otherwise specified by this protocol
Plateau pressure monitoring protocol	Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)
Driving pressure (∆P) monitoring protocol	**Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)**
Expiratory occlusion pressure (Pocc) monitoring protocol	**Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)**
Dynamic transpulmonary driving pressure (ΔP_L) monitoring protocol	**Computed in real time at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution). If Pocc = 0 cm H2O, ∆PL cannot be estimated and does not apply.**
Adjustment for severe respiratory acidosis (pH<7.15) with respiratory rate adjusted to maximum of 40 breaths per minute	Clinician may treat with intravenous bicarbonate. If pH remains below 7.15 tidal volume may be increased in 1 mL/kg increments to achieve pH target (under these conditions plateau pressure targets may be exceeded)
Adjustment for airway ∆P >15 cm H2O during controlled ventilation (Pocc = 0 cm H2O)	**1) PEEP will be titrated upward or downward to determine whether ∆P can be reduced by optimizing compliance** **2) Tidal volume will be decreased as permitted by pH; respiratory rate will be increased to a maximum of 40 breaths per minute if needed to permit reductions in tidal volume**

Adjustment for plateau airway pressure above target during controlled ventilation (Pocc = 0 cm H2O)	**1) PEEP will be titrated downward as tolerated, provided oxygenation does not worsen significantly (i.e. increase in FiO2 requirement) and ∆P does not increase to ≥15 cm H2O.** **2) Tidal volume will be reduced as permitted by pH; respiratory rate will be increased to a maximum of 40 breaths per minute if needed to permit reductions in tidal volume**
Adjustment for dynamic transpulmonary ∆PL>23 cm H2O during assisted ventilation (Pocc <0 cm H2O)	**1) PEEP will be titrated upward or downward to determine whether dynamic transpulmonary ∆P can be reduced by optimizing compliance and respiratory effort** **2) Inspiratory pressure/flow will be decreased as permitted by pH and tidal volume limits (can be skipped if the patient's respiratory effort is already significantly elevated (i.e., Pocc more negative than –20 cm H2O)** **3) If Pocc is more negative than –20 cm H2O, FiO2 will be increased by 20% to increase PaO2 to assess whether this reduces respiratory drive and effort** **4) If pH < 7.3, consider bicarbonate infusion** **5) Sedation will be increased when deemed necessary by the clinicians to reduce respiratory effort in order to reduce dynamic transpulmonary ∆P to acceptable limits** **6) Consider neuromuscular blockade if dynamic transpulmonary ∆PL remains above target because of persistently excessive respiratory effort despite deep sedation**

Sedation targets	**The sedation regimen will be managed by the clinical team to target light levels of sedation (typically SAS 3 to 4 or RASS -2 to 0) via targeted sedation or daily interruption, unless otherwise indicated, as per PADIS guidelines.** **During assisted ventilation, if dynamic transpulmonary ΔPL exceeds 23 cm H2O due to excessive respiratory effort, and this cannot be resolved by adjusting the ventilator, the clinical team will be directed to adjust sedation according to their best judgment to reduce respiratory effort and achieve dynamic transpulmonary ΔPL target. Sedation to apnea (Pocc = 0 cm H2O) is permitted if necessary to achieve targets.**

The intervention will be applied until one of the following criteria are met;

1. Death
2. Day 28 of mechanical ventilation
    - If re-intubated within the 28 days during the index hospitalization, resume intervention if the patient has hypoxemic respiratory failure (i.e. they do not meet the criteria for resolution of hypoxemic respiratory failure in #3 below)
3. No longer in hypoxemic respiratory failure. We define patients as no longer in hypoxemic respiratory failure when they meet ALL of the following criteria for at least 2 hours:
    a. Patient triggering the ventilator continuously in an assisted mode of ventilation
    b. FiO2 ≤ 0.4
    c. PEEP ≤ 8 cm H2O
    d. SpO2 >90%
    e. Inspiratory pressure (peak pressure – PEEP) ≤10 cm H2O; or Pressure Support ≤10 cm H2O
    f. Inhaled nitric oxide and/or extracorporeal membrane oxygenation have been discontinued

For the duration of the intervention period (noted in #2 above), if hypoxemic respiratory failure recurs (i.e. patients no longer meet these criteria for discontinuing the intervention for at least 2 hours), then ventilator settings should again be managed according to protocol as specified for this intervention.

4. If the goals of care are modified such that no escalations in ventilator support will be permitted

Once one of these criteria are met, ventilator settings will be managed according to clinician discretion, while still following the domain protocol for co-interventions including weaning practices, if applicable.

9.2 **PROACTIVE Intervention Arm**: VV ECMO-facilitated strategy of earlier awakening, extubation and rehabilitation

Patients will have been sedated and paralysed and placed on the following standard settings outlined in more detail at the beginning of Section 9

- Mode: Volume Assist-Control
- FiO_2 1.0;
- PEEP 10-15 cm H_2O or higher as needed to maintain $SpO_2 > 92\%$;
- V_T = 6 mL/kg PBW and adjusted to maintain $P_{PLAT} \leq 30$ cm H_2O
- Inspiratory to expiratory (I:E) ratio 1:1 to 1:3, avoiding auto-PEEP
- Respiratory rate set to match previous minute ventilation to maximum of 35 breaths/min and targeting a pH > 7.25

As soon as the patient is stable and as soon as possible after randomization, patients assigned to this intervention arm will be cannulated and receive VV-ECMO via a 29 or 31 Fr single access, dual-lumen Protek Duo cannula (LivaNova) inserted into the right internal jugular vein. If this cannula is unavailable or can't be inserted due to technical limitations, other 29-32 Fr single access, dual-lumen cannulae may be used, or if not possible then Fem-IJ cannulation can also be used. VV-ECMO will then be initiated with pump speed set to deliver blood flow of 3-5 L/min and sweep gas flow of 1 L/min of 100% oxygen.

The mechanical ventilator will then be adjusted as follows:

- Mode: Pressure Control
- FiO_2 0.5
- Set Driving Pressure 10 cmH_2O

- PEEP 10-15 cmH_2O
- Inspiratory time 0.7-1 second
- Respiratory rate 10 breaths/min

As per usual care an arterial blood gas will be drawn after 15-30 minutes, and sweep gas flow will be adjusted to target a pH 7.30-7.45; if the baseline $PaCO_2$ is above 60 we will target lowering it slowly by no more than 10-20 per 12 hours.[19] We will maintain a FdO_2 of 1.0 on the circuit and adjust blood flow rates to maintain SpO_2 92-97%. In the absence of contraindications, anticoagulation with unfractionated heparin will commence at VV ECMO initiation, targeting an aPTT 1.5-2 times normal (or equivalent).

Once the patient is stabilized on ECMO, the sedation will be weaned to off as soon as possible. Concomitantly the mechanical ventilator settings will be transitioned to facilitate spontaneous breathing and MV will then be weaned, making adjustments to ECMO flow and sweep gas as needed to facilitate ventilator weaning. Spontaneous breathing trials will be conducted at least twice daily in this phase and the patient will be extubated as soon as possible after passing an SBT and being able to maintain airway protection. Respiratory support will be maintained with VV ECMO.

Graded rehabilitation and mobilization will be performed under the supervision of an experienced physical therapist (PT) as per usual institutional protocols including prior to extubation. Prior to PT sessions with mobilization (i.e., sit at edge of the bed or higher level of activity), the security of the cannula will be inspected by the medical team (or as per usual institutional practice). ECMO will be continued until patients meet readiness to wean criteria (or 14 days of VV ECMO, whichever is sooner) and will be safely discontinued through protocolized sweep off trials (SWOT) – see Manual Of Procedures).

<u>Weaning of Sedation, Paralysis, Mechanical Ventilation, and ECMO:</u>

Deep sedation, paralysis, and these low-intensity mechanical ventilation settings will be weaned following stabilization on VV ECMO. The clinical team will make adjustments to the VV-ECMO settings to maintain the same $PaCO_2$, pH and PaO_2 and SpO_2 targets as above. These adjustments to VV-ECMO sweep gas or blood flow will be dictated by ABG results drawn as clinically indicated. Lighter sedation levels (SAS 3-4) will be targeted unless otherwise decided by the attending physician.

We will provide explicit protocols for weaning ECMO (See Manual of Procedures). Briefly, following <u>liberation from mechanical ventilation,</u> patients will be assessed daily for ability to discontinue ECMO – all patients who are receiving a FiO_2 of ≤ 0.6 via FM/HFNC with a PaO_2/FiO_2

> 150 will undergo a trial of sweep gas off on ECMO. ECMO will be discontinued if patients tolerate sweep gas off for at least 12 hours (i.e., no significant hypoxemia, respiratory acidosis, or work of breathing).

Anticoagulation with intravenous heparin infusion during VV-ECMO will be recommended at a level to target aPTT 1.5-2 times normal (or equivalent) but will be ultimately managed at the discretion of the attending physician.

After 14 days all study-mandated procedures related to ECMO will cease and ongoing management will be determined by the attending physician.

9.3 Control Arm: Conventional Lung-Protective Ventilation (LPV)

Patients randomized to the control group will be treated with the same explicit standard ventilation protocol that we used to good effect in several recent multi-centre trials in ARDS. The overall goals for this strategy are to minimize volutrauma and atelectrauma to the extent possible with standard of care ventilation. This control intervention is the same as that currently being used in the invasive mechanical ventilation strategies domain.

Volume Assist Control will be the default mode and will be set to achieve lower tidal volumes (6mL/kg PBW) and plateau pressures ($P_{PLAT} \leq 30$ cmH_2O). Other modes may also be used at the discretion of the attending physician. The same limits to P_{PLAT} and V_T apply regardless of ventilator mode. Only when the patient is being ventilated with Pressure Support of 10 cmH_2O support or less and with PEEP ≤ 8 cmH_2O and $FiO_2 \leq 0.4$ will these thresholds (P_{PLAT} and V_T) no longer apply. PEEP will be adjusted according to local practice at the discretion of the attending physician. If the plateau pressure target is exceeded, V_T will be reduced as needed to a minimum of 4 mL/kg PBW, and/or PEEP reduced and FiO_2 increased as necessary to achieve $P_{PLAT} \leq 30$ cmH_2O while providing adequate oxygenation.

Ventilation Management for patients randomized to Conventional Lung-Protective Ventilation (LPV)	
Mode of mechanical ventilation	Pressure-targeted or volume-cycled ventilation modes as per clinician preference (e.g. pressure control, volume control, pressure support, etc.)

Tidal volume	Initiated at 6 mL/kg (predicted body weight) Maintained at 6 mL/kg as much as possible Adjusted if needed according to criteria below, permitted range 4-8 mL/kg *For ECLS patients; Adjust according to usual site practice, tidal volume permitted to be less than 4 mL/kg in these patients*
Plateau airway pressure	Target of ≤30 cm H_2O
pH	Target >7.15
Respiratory rate	≤35 breaths per minute
Positive end-expiratory pressure (PEEP)	Adjusted according to local site practice
Fraction of inspired oxygen (FiO_2)	Adjusted to maintain peripheral oxygen saturation ≥90%
Plateau pressure monitoring protocol	Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected once daily on the CRF)
Expiratory occlusion pressure (Pocc) monitoring protocol	Recorded once daily (not used for ventilator titration)
Dynamic transpulmonary driving pressure (ΔP_L) monitoring protocol	Not measured in real time at bedside
Adjustment for severe respiratory acidosis (pH<7.15) with respiratory rate adjusted to maximum of 35 breaths per minute	Clinician may treat with intravenous bicarbonate. If pH remains below 7.15, tidal volume may be increased in 1 mL/kg increments to achieve pH target (under these conditions plateau pressure targets may be exceeded)
Adjustment for $\Delta P \geq 15$ cm H2O	No adjustments
Adjustment for plateau airway pressure above target	1. Tidal volume will be reduced in 1 mL/kg increments as permitted by pH to a minimum of 4 mL/kg; respiratory rate will be increased to a maximum of 35 breaths per minute if needed to facilitate reductions in tidal volume 2. PEEP can be titrated downward as tolerated, provided oxygenation does not worsen significantly (i.e. increase in FiO2 requirement).
Adjustment for dynamic transpulmonary ΔP_L>23 cm	No adjustments

H2O	
Sedation Target	The sedation regimen will be managed by the clinical team to target light levels of sedation (typically SAS 3 to 4 or RASS -2 to 0) via targeted sedation or daily interruption, unless otherwise indicated, as per PADIS guidelines.

If a patient randomized to the control arm worsens and meets entry criteria from the EOLIA trial (persistence of either $PaO_2/FiO_2 < 80$ or pH < 7.15 and $PaCO_2 > 60$) they can receive VV-ECMO (a secondary outcome) at the discretion of the attending physician.

Discontinuing the intervention
The intervention will be applied until one of the following criteria are met;

1. Death
2. Day 28 of mechanical ventilation
   If re-intubated within the 28 days during the index hospitalization, resume intervention if the patient has hypoxemic respiratory failure (i.e. they do not meet the criteria for resolution of hypoxemic respiratory failure in #3 below)
3. No longer in hypoxemic respiratory failure. We define patients as no longer in hypoxemic respiratory failure when they meet ALL of the following criteria for at least 2 hours:
   a. Patient triggering the ventilator continuously in an assisted mode of ventilation
   b. FiO2 ≤ 0.4
   c. PEEP ≤ 8 cm H2O
   d. SpO2 >90%
   e. Inspiratory pressure (peak pressure – PEEP) ≤10 cm H2O; or Pressure Support ≤10 cm H2O
   f. Inhaled nitric oxide and/or extracorporeal membrane oxygenation have been discontinued

   For the duration of the intervention period (noted in #2 above), if hypoxemic respiratory failure recurs (i.e. patients no longer meet these criteria for discontinuing the intervention for at least 2 hours), then ventilator settings should again be managed according to protocol as specified for this intervention.

4. If the goals of care are modified such that no escalations in ventilator support will be permitted

Once one of these criteria are met, ventilator settings will be managed according to clinician discretion, while still following the domain protocol for co-interventions including weaning practices, if applicable.

9.4 Procedures Common to All Arms – Experimental & Control

For patients in all arms, we will protocolize:

1. Weaning from mechanical ventilation;
2. Prone positioning: a procedure that places the patient face-down for 16-20 hours per day, will be applied daily to patients whose PaO_2/FiO_2 remains < 150 during the first week as dictated by evidence-based practice for the management of hypoxemia and clinician discretion; and
3. Intravenous fluid therapy for patients not in shock. For these patients, a conservative fluid approach will be applied, since this strategy has been shown to reduce the duration of mechanical ventilation for patients with ARDS.

To ensure timely discontinuation of mechanical ventilatory support, patients in all groups will be assessed daily for standard “readiness to wean” criteria. In patients who meet these criteria, a spontaneous breathing trial (SBT) will be performed with no or minimal mechanical ventilation support and those that pass will be promptly extubated (Manual of Procedures).

9.5 Crossovers

We will sub-classify crossovers as consistent with, or in deviation of, the study protocol and will collect detailed reasons for crossovers classified as protocol deviations. Crossovers that are consistent with the protocol include control group patients who receive the VV-ECMO intervention once they meet the EOLIA criteria, or when PROACTIVE group patients have ECMO discontinued after liberation from mechanical ventilation. Crossovers that are in deviation of the protocol will include Conventional Lung-Protective Ventilation (control group) patients being treated with ECMO when not allowed by protocol (do not meet the criteria defined) and PROACTIVE group patients who stop the ECMO intervention prematurely (i.e., before mechanical ventilation is discontinued).

9.6. ECMO Study Device Supply

Supply of the device will be outlined in the site agreement as applicable.

10 SAFETY AND REPORTING REQUIREMENTS

The critically ill patient population are admitted to the ICU for life-sustaining therapies (e.g. mechanical ventilation, vasopressors, renal replacement therapy). Many of the potential subjects will be admitted with the expectation of receiving end-of-life care and possibly dying in the ICU. Furthermore, medical complications are likely to occur in this population, consistent with the nature of their progressive illness (e.g. nosocomial infections; septic shock; multi-organ failure; need for vasopressors; acute renal failure and the need for renal replacement therapy; arrhythmias; cardiac arrest; coma; aspiration; venous thromboembolism). Due to these relatively unique morbidity and mortality expectations in the critically ill patient population and the intervention's safety profile, generic adverse events will not be collected for this study and only study-procedure related SAEs will be collected and reported (see section below). Expected events occurring in the course of life-support patient, and not related to study procedure, will not be reported as SAEs in this domain.

Serious Adverse Event

A serious adverse event (SAE) in this domain is defined as:

a) (any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization,

OR

b) any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above,)

AND

c) which the attending physician believes to be **related*** to a study procedure

**A related event is an event in which there is a reasonable possibility that the study procedure caused or contributed (definitely, probably, or possibly) to the SAE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:*

- *There is a plausible time sequence between onset of the SAE and study procedure;*
- *There is a plausible biological mechanism through which study procedure may have caused or contributed to the SAE;*

The SAEs dictated below are of *particular interest*; however, they are not an exhaustive list of all SAEs that might be identified and reported on the study (please refer to section 11- evaluation of safety for further details):

- death due to the ECMO device (failure, accident, septic shock due to infection at the cannulation site, hemorrhagic shock due to bleeding at the cannulation site, intracranial hemorrhage, massive circuit clotting)
- cardiac arrest due to massive circuit clotting, pneumothorax during cannula insertion, or ECMO device failure/accident
- massive hemorrhage requiring transfusion of ≥10 packed red blood cells
- massive gaseous (air) emboli

Reporting Serious Adverse Events

All serious adverse events (SAEs) as defined in section 10 must be recorded on case report forms. In addition, they must be reported using the SAE form and submitted to Ozmosis within 24 hours of becoming aware of the event.

All SAEs must be reported as follows:

Within 24 hours: Report initial information (on study specific SAE report form) by e-mail to:

Ozmosis Research Inc.
Phone: 416-634-8300
E-mail: ozmsafety@ozmosisresearch.ca

The initial information should always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Mechanical Ventilation Type and Start/Stop Dates

Within 3 calendar days: E-mail completed study-specific Serious Adverse Event form including;

- Any information required per the SAE report form that was not included in the initial report

- Any additional, relevant and **de-identified** clinical notes, diagnostic test results and medical interventions
- Ensure that the patient eCRF pages are complete

Procedures for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Sponsor

Ozmosis will be responsible for submitting SAE reports (Initial and/or Follow-up reports) received from the sites, to the Sponsor and the domain Principal Investigators within 1 business day after receipt of the SAE form at Ozmosis.

Reporting Serious Adverse Events to Data Safety Monitoring Board (DSMB)

Ozmosis will be responsible for submitting SAE reports received from the sites to the DSMB chair. The SAE reports will be sent along with a synthesis from Sponsor and Domain Lead Investigators.

Reporting Serious Adverse Events to Local Research Ethics Boards

Investigators must follow their local ethics board guidelines for SAE reporting. Documentation of correspondence with REBs/IRBs should be forwarded to Ozmosis.

Documentation can be any of the following:

- letter from the ethics board acknowledging receipt
- stamp from the ethics board, signed and dated by ethics board chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board

Reporting and Follow up of Serious Adverse Events

SAEs (as defined in section 10) must be reported from start of randomization to time of ICU discharge or 28 days, whichever is shorter.

The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented in the eCRF.

11 STATISTICAL ANALYSES

Study Population

The number of patients planned to be randomized into this domain protocol is 100. This will allow for testing the validity of our eligibility criteria, ventilation protocols, and study procedures. It will also allow for an assessment of crossovers at numerous sites involving a number of clinicians. The sample size will allow for an assessment of feasibility objectives over a reasonable time period of 2 years as well as allow us to detect an adherence rate of 80% +/- 10% (meaning 80% + /- 10% of study patients will have fewer than 20% of monitored values as major deviations).

Evaluation of Safety

The safety and tolerability of VV-ECMO will be evaluated by means of recording serious adverse events (SAEs) in all groups (frequency and type of SAEs) and monitoring the predicted physiological responses.

In addition, the secondary outcomes listed above (section 5) and the PRACTICAL platform level clinical and safety outcomes also function as safety outcomes.

Proposed Type of Analyses

For the feasibility objectives of this pilot RCT we will present point estimates as proportions with 95% confidence intervals. We will present continuous data as means (standard deviations), or medians (interquartile ranges), as appropriate. We will not undertake formal statistical interference for any outcomes.

Proposed Frequency of Analyses

Due to the small size and short duration of this pilot RCT, we have not planned for any domain-specific interim analyses. We have planned, however, to provide the PRACTICAL Platform Data Safety and Monitoring Board (DSMB) with analyses by group at the completion of this pilot RCT. Further details regarding DSMB commitment are detailed in the DSMB charter. These analyses will include relative use of neuromuscular blockade, sedative infusions, and vasopressor infusions; and relative rates of prone positioning, ECMO, and mortality. In this pilot RCT, we will not undertake any formal statistical inference or testing and will report descriptive statistics as required. Investigators will remain blinded to these clinical results, while the full Expanded ECLS

Criteria and Strategies trial moves forward. Due to the pilot study design of the trial and its short duration, no subgroup analyses are planned.

Feasibility Outcomes

1) Adherence to our explicit ventilation protocols will be adequate if more than 80% of patients have fewer than 20% of monitored values as major protocol deviations.
2) The number of protocol withdrawals or off-protocol treatment with VV-ECMO will be acceptable if fewer than 10% of patients cross over, when not allowed by protocol.
3) Patient accrual will be adequate if we recruit at least 100 patients over 2 year of active site enrolment.

Sites

Multiple centres will participate in this domain. All of these centres have experience in clinical trials of mechanical ventilation, and most have worked closely with us in the LOVS and OSCILLATE Trials. By design, we have included a mix of high-volume ECMO centres; centres doing some ECMO; and centres that do not perform ECMO but have access to an ECMO centre for backup. This is to ensure that feasibility is generalizable and to pre-emptively identify potential roadblocks to the full trial.

Randomization Scheme

We will use web-based, allocation-concealed randomization, stratified by centre, accessible 24 hours per day. We will randomize patients 1:2:2 or 1:2 using a maximum tolerated imbalance approach. Research assistants and/or clinical respiratory therapists will screen all mechanically ventilated patients for eligibility on a daily basis.

12 PUBLICATION POLICIES AND DISCLOSURE OF DATA

This section is in accordance with the PRACTICAL Master Protocol and the PRACTICAL Publication Policy.

Intellectual Property

Intellectual property guidelines will conform with UHN Policy for Principal Investigator.

Data Sharing

Please refer to PRACTICAL Master Protocol for details.

13 REFERENCES

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