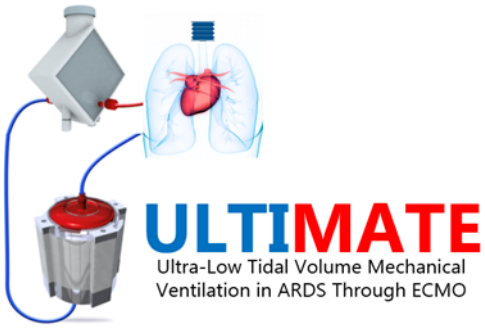
PRACTICAL
Platform Randomized Trial



Master Protocol:
OZUHN-004

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

Domain Protocol:
OZUHN-004-2

Ultra-Low Tidal Volume Mechanical Ventilation in ARDS through ECMO (ULTIMATE) Trial

Protocol Version #: 2.0

Protocol Date: 16-Mar-2023

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Protocol History

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Sponsor's Agreement to Domain Protocol #OZUHN-004-2 v. 2.0 dated 16-Mar-2023

Name of Authorized Personnel (Print) _____

Title of Authorized Personnel (Print) _____

Signature of Authorized Personnel: _____

Date of Approval: _____
DD-MMM-YYYY

Domain Lead Investigators' Agreement to the Domain Protocol OZUHN-004-2 v.2.0, dated 16-Mar-2023

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Signature and Date: _____

Name and Title (print): _____

Signature and Date: _____

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:	Ultra-Low Tidal Volume Mechanical Ventilation in ARDS through ECMO (ULTIMATE) Trial
Primary Objective:	To determine the feasibility of recruiting 72 ARDS patients across sites given 1 year of active enrolment per site, as well as assess the rate of participant recruitment and understand the barriers to enrolment.
Secondary Objectives:	➢ To assess adherence to our explicit mechanical ventilation protocols, with particular focus on delivered tidal volumes in both groups and measured ΔP and estimated $\Delta P_{L\text{-}dyn}$ in the ECMO group. ➢ To measure and understand the reasons for crossovers in each group.
Exploratory Objectives:	➢ Monitor safety issues, recording Serious Adverse Events (SAEs) in both groups. ➢ Quantify cytokine levels to further understand the inflammatory processes involved.
Patient States:	This domain will enrol patients in the following platform defined state; ➢ Intubated patients, not on extracorporeal life support, with high normalized respiratory system elastance (≥2.5 cm H_2O/(ml/kg predicted body weight)).
Study Design:	An interventional, open-label, randomized, multi-site feasibility study.
Duration:	The duration of this study will include an estimated 1 year of recruitment for each site to reach overall target sample size, and a 6 month post-randomization follow up for patients.
Planned Total Sample Size:	Approximately 72 evaluable patients will be randomized in this domain protocol.

Intervention:	Participants will be randomized to receive either the experimental group: ultra-protective ventilation facilitated by an ECMO device or the control group: conventional lung-protective ventilation (LPV).
Inclusion/Exclusion Criteria:	Patients will be eligible for randomization in this domain if they meet PRACTICAL platform eligibility criteria **as well as** ULTIMATE specific eligibility criteria. PRACTICAL Inclusion Criteria: 1. Acute hypoxemic respiratory failure meeting all of the following criteria; ○ New or worsening respiratory symptoms developing within 2 weeks prior to the onset of need for oxygen or respiratory support, ○ 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, ○ 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 PRACTICAL Exclusion Criteria: 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. ULTIMATE Inclusion Criteria: 1. Endotracheal mechanical ventilation for ≤5 days. 2. Early moderate-severe hypoxemic respiratory failure with a $PaO_2/FiO_2 \leq 200$ mmHg for at least 6 hours. ULTIMATE Exclusion Criteria: 1. Patients over 65 years of age. 2. Currently receiving any form of ECMO (ex. venovenous, venoarterial, or hybrid configuration). 3. $\Delta P_{L\text{-}dyn} \leq 20$ or Static $\Delta P \leq 15$ cm H_2O while receiving V_T 6mL/kg (i.e. normalized elastance < 2.5 cmH_2O/mL/kg). 4. Chronic hypercapnic respiratory failure defined as $PaCO_2$>60mmHg in the outpatient setting. 5. Home mechanical ventilation (non-invasive ventilation or via tracheotomy), not CPAP. 6. Actual body weight exceeding 1kg per centimeter of height. 7. More than 48 hours have passed since meeting inclusion criteria. 8. Severe hypoxemia with PaO_2/FiO_2<80mmHg for >6 hours at time of screening. 9. Severe hypercapnic respiratory failure with pH<7.15 and $PaCO_2$>60mmHg for >6 hours at time of screening.

	10. Expected mechanical ventilation duration <48 hours at time of screening. 11. Confirmed diffuse alveolar hemorrhage from vasculitis. 12. Contraindications to limited anticoagulation (ex. active GI bleeding, bleeding diathesis). 13. Pregnancy—due to unknown effects of $PaCO_2$ changes on placental blood flow. 14. Respiratory failure known or suspected to be caused by COVID-19.
Study Assessments:	Study assessments are depicted in the study schema (Section 5.2).
Safety Variables & Analysis:	The safety and tolerability of VV-ECMO will be evaluated by means of recording serious adverse events in both groups and monitoring the predicted physiological response (reduced driving pressure ΔP) to CO_2 removal by VV-ECMO.
Efficacy Assessments & Analysis	The efficacy of VV-ECMO will be evaluated by means of assessing delivered tidal volumes in both groups and magnitude of physiological response (reduced driving pressure ΔP) to CO_2 removal by VV-ECMO.
Statistical Analysis:	A target sample size of 72 ARDS patients will be randomized across sites given 1 year of active enrollment per site. 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 trial.

TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

ABG	Arterial Blood Gases
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
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
$PaCO_2$	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
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.

3.1 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]

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]

3.2 Why is a trial needed now?

VV-ECMO reduces mortality in very severe ARDS patients and its use is rapidly expanding. 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".

In summary, $ECCO_2R$ 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) Trial.

4 PRIMARY RESEARCH QUESTIONS AND STUDY OBJECTIVES

4.1 Definitive ULTIMATE Trial

Primary Research Question:

What is the effect of ultra-protective ventilation facilitated by CO_2 removal through VV-ECMO versus best current standard ventilation on all-cause hospital mortality among patients with early moderate-severe hypoxemic respiratory failure receiving potentially injurious mechanical ventilation?

Secondary Research Questions:

Among these same patients, what is the effect of ultra-protective ventilation versus best current standard ventilation on: (1) duration of mechanical ventilation; (2) duration of ICU and hospital stay; (3) organ dysfunction; (4) barotrauma; and (5) mortality at other time-points (ICU discharge, 28-day, 60-day)?

4.2 The ULTIMATE Pilot Study

Before embarking on a definitive multinational trial to address the questions listed above, the ULTIMATE Pilot Study has these 3 specific feasibility objectives:

1. To assess the feasibility of recruiting 72 ARDS patients across sites over a period of 1-year of active enrollment per site, as well as estimate the rate of patient recruitment and understand barriers to recruitment;
2. To assess adherence to our explicit mechanical ventilation protocols, with particular focus on delivered tidal volumes in both groups and measured ΔP and estimated $\Delta P_{L\text{-}dyn}$ in the ECMO group; and lastly,
3. To measure and understand the reasons for crossovers in each group.

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

If feasibility is demonstrated and major protocol changes are not required, patients randomized into the ULTIMATE Pilot Study will be rolled over and form the vanguard phase of the definitive ULTIMATE RCT.

5 STUDY DESIGN

The ULTIMATE Pilot Study is a multi-centre, randomized, open-label trial, embedded as a domain within the PRACTICAL platform trial. This domain will be conducted in compliance with the protocol and GCP guidelines.

5.1 Patient population

This domain will enrol patients in the following platform defined state;

- Intubated patients, not on extracorporeal life support (ECLS), with high normalized respiratory system elastance (≥2.5 cm H_2O/(ml/kg predicted body weight)).

Patients must meet both the PRACTICAL platform eligibility criteria (section 3.2) and the domain-specific ULTIMATE eligibility criteria (section 3.3) prior to randomization. Any questions about eligibility criteria must be addressed prior to patient randomization.

5.2 PRACTICAL Platform Eligibility Criteria

5.2.1 PRACTICAL Inclusion Criteria

1. Acute hypoxemic respiratory failure meeting all of the following criteria;
    - New or worsening respiratory symptoms developing within 2 weeks prior to the onset of need for oxygen or respiratory support,
    - 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,
    - Minimum FiO_2 ≥ 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.

5.2.2 PRACTICAL Exclusion Criteria

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.

5.3 ULTIMATE Domain Eligibility Criteria

5.3.1 Inclusion Criteria

1. Endotracheal mechanical ventilation for ≤5 days.
2. Early moderate-severe hypoxemic respiratory failure with a PaO_2/FiO_2≤200 mmHg for at least 6 hours.

5.3.2 Exclusion Criteria

1. Patients over 65 years of age.
2. Currently receiving any form of ECMO (ex. venovenous, venoarterial, or hybrid configuration).
3. $\Delta P_{L\text{-}dyn}$ ≤20 or Static ΔP ≤15 cmH_2O while receiving V_T 6mL/kg (i.e. normalized elastance < 2.5 cmH_2O/mL/kg).
4. Chronic hypercapnic respiratory failure defined as $PaCO_2$> 60mmHg in the outpatient setting.
5. Home mechanical ventilation (non-invasive ventilation or via tracheotomy), not CPAP.
6. Actual body weight exceeding 1kg per centimeter of height.
7. More than 48 hours have passed since meeting inclusion criteria.
8. Severe hypoxemia with PaO_2/FiO_2 <80mmHg for >6 hours at time of screening.
9. Severe hypercapnic respiratory failure with pH<7.15 and $PaCO_2$> 60mmHg for >6 hours at time of screening.
10. Expected mechanical ventilation duration <48 hours at time of screening.
11. Confirmed diffuse alveolar hemorrhage from vasculitis.
12. Contraindications to limited anticoagulation (ex. active GI bleeding, bleeding diathesis).
13. Pregnancy—due to unknown effects of $PaCO_2$ changes on placental blood flow.
14. 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.

To better characterize the generalisability of our randomized population, baseline, demographic, and outcome data will be recorded on all eligible non-randomized patients.

5.4 Patient Consent

Patient / substitute decision maker (SDM) (for patients lacking decision-making capacity) consent must be obtained according to local institutional and/or University Human Experimentation Committee requirements prior to randomization into the ULTIMATE domain 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 trial can commence at that centre. Sample English consent forms for the trial will be provided. A copy of the initial full board REB approval and approved consent forms must be sent to Ozmosis Research Inc. Consent process will be conducted as per Health Canada's notice "Management of Clinical Trials during the COVID-19 pandemic: Notice to clinical trial sponsors" updated May 6, 2021, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators, and Institutional Review Boards March 2020 or REB recommendations.

Eligibility will be assessed by one of the site principal investigators or sub-investigators prior to entry into this domain. An explanation of the study and discussion of the expected side effects and full disclosure of the "informed consent" documents will then take place.

Each institution must have submitted all the necessary regulatory documentation to Ozmosis Research Inc. prior to randomizing consented and eligible patients via the REDCap database. General registration information can be found in the PRACTICAL Master Protocol.

6 STUDY PLAN

6.1 Study Schedule

Consenting eligible patients will be randomized to either the experimental group or the control group. Patients randomized to the experimental group will receive ultra-protective ventilation using ECMO. Patients requiring ventilation for longer periods may continue ventilation via ECMO or receive Conventional Lung-Protective Ventilation (LPV), as deemed necessary by the treating physician. Patients randomized to the control group will receive LPV. If the patient's clinical status declines and meets the ECMO criteria for ventilation (as established by prior randomized clinical trials), they would be eligible to receive ECMO if their treating physician deems that appropriate. Please see sections 7.2 and 7.4 below.

Study procedures common to both groups will continue for the duration of the ICU stay up to day 30. We will collect daily data during mechanical ventilation until day 30. 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 by telephone interview or via email 6 months after randomization.

6.2 Study Schema

Required Procedures	**Pre-Ventilation (Baseline)**	**Daily***	**Day 1**	**Day 3**	**Day 7**	**ICU Discharge**	**At 6 months post-randomization (Phone Visit)**
Window	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*±14 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	X	X	
For the Control Arm: Conventional Lung Protective Ventilation [11] per section 7.2		X					
For the Experimental Arm: ECMO Intervention [12] per section 7.1		X					
MV Readiness to Wean	X	X					
Spontaneous Breathing Trial [13]		X					
Sweep Gas Off Trials (SGOTs) [14]		X					
HrQOL, Modified Rankin Scale and Vital Status							X[15]
Glasgow Coma Scale and Sofa Score	X	X					
Serious Adverse Events [16]		X					
Concomitant Medications [17]	X						

[1] Consent should be obtained prior to any study-specific baseline assessments and according to site institutional timelines. Randomization in the ULTIMATE domain will occur for consenting eligible patients once elastance has been estimated as high (≥2.5 cmH_2O/ml/kg PBW) per indicated eligibility criteria.

[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 admission (date/time), ICU admission (date/time), APACHE IV, Charlson Comorbidity Index, 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 exclusively for research 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 clinical standard-of-care procedures, sites are not required to have these tests done exclusively for research 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.

[10] Blood sample collection is optional and will proceed only if patient or their SDM signs the optional consent form.

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

[12] ECMO will be administered once patient has stabilized on initial MV settings and will be maintained for at least 48 hours. If patient is unsuccessful on Sweep Gas Off Trials (SGOTs) post 48 hours, then ECMO will continue until no longer needed and per the discretion of the treating physician.

[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 SGOTs. This assessment will be considered successful if patients tolerate SGOTs for ≥12 hrs with no significant hypoxemia, respiratory acidosis, or work of breathing.

[15] HrQOL questionnaires (ADL and EQ-5D-5L) as well as the Modified Rankin Scale (MRS) will be administered via phone or e-mail at 6 months. 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 30 days, or while in ICU, whichever is shorter.

[17] Concomitant medications listed in section 6 will only be captured, if taken.

*Daily data common to both groups will be collected for the duration of intervention administration and ICU stay and up to day 30.

6.3 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 Schema. 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.

7 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 30 days, whichever is shorter.

- Neuromuscular blocking agents (e.g., rocuronium, cisatracurium)
- Sedatives (e.g., propofol, fentanyl, midazolam)
- Corticosteroids (e.g., methylprednisolone, prednisone, dexamethasone)
- Inotropes (e.g., dobutamine, milrinone)
- Vasopressors (e.g., norepinephrine, vasopressin, epinephrine)
- Diuretics (e.g., furosemide, metalazone)

Additionally, the following procedures are to be documented:

- Prone positioning
- Renal replacement therapy

8 TRIAL INTERVENTIONS

Our goal 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.

8.1 Experimental Group: Ultra-protective Ventilation using ECMO devices

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

8.1.1 Stabilization and ECMO Initiation

If not already done, patients will be deeply sedated to a Sedation Assessment 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 bpm and targeting a pH above 7.15

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 on these standard settings, the clinical team will measure the patient's respiratory elastance using the following equation:

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

If the patient's static driving pressure is 15 cmH_2O or lower, then re-assess patient within a 12-hour timeline for ECMO initiation whilst keeping the patient deeply sedated and paralyzed. If patient's static ΔP is 16 cmH_2O or higher, then 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
- PEEP 10-15 cm H_2O
- Inspiratory time 0.7-1 second
- Respiratory rate 10

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%.

8.1.2 Maintenance and Weaning of Ultra-ProtectiveVentilation

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.

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 7 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.

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 maintaining a V_T of 8 ml/kg PBW or lower, the treating team will adjust in the following order: a) the mechanical ventilator, b) the sweep gas flow, and c) sedation levels. After day 7 driving pressure and V_T targets, as well as sweep gas settings will be determined by the attending physician.

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 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 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.

8.2 Control Group: 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.

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 cm H_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 cm H_2O support or less and with PEEP ≤ 8 cm H_2O and $FiO_2 \leq 0.4$ will these thresholds (P_{PLAT} and V_T) no longer apply. We recommend that PEEP and FiO_2 be adjusted according to oxygenation targets using the higher PEEP-FiO_2 table, allowing for use of lower PEEP if clinically indicated. 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 cm H_2O while providing adequate oxygenation.

If a patient's state 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.

8.3 Procedures Common to Both Groups – Experimental & Control

For patients in both groups, 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, all patients in either group not receiving ECMO at that time will be assessed daily for standard "readiness to wean" criteria. In patients who meet these criteria, an SBT will be performed with no or minimal mechanical ventilation support and those that pass will be promptly extubated (Manual of Procedures).

8.4 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 ECMO intervention (experimental group) once they meet the ECMO criteria of hypoxemia (section 7.2) and as part of rescue therapy, or when ECMO is discontinued before day 7 in the experimental group after passing a sweep gas off trial (section 7.1.2). 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 in sections 7.2/3.2/3.3) and ultra-protective ventilation (experimental group) patients who stop the ECMO intervention prematurely.

8.5 ECMO Study Device Supply

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

9 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 the ULTIMATE trial.

9.1 Serious Adverse Event

A serious adverse event (SAE) in the ULTIMATE trial 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 trial (please refer to section 8.2- 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

9.2 Reporting Serious Adverse Events

All serious adverse events (SAEs) as defined in section 8.1 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 trial 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 trial-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

9.3 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 initial SAE report will be sent within 1 business day of receipt of the SAE form at Ozmosis, with follow-up reports and synthesis from Sponsor and Domain Principal Investigators being sent when available.

Reporting Serious Adverse Events to Local Research Ethics Boards

Investigators must follow their local Research Ethics Boards (REBs)/Institutional Review Boards (IRBs) 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 REB/IRB acknowledging receipt
- stamp from the REB/IRB, signed and dated by REB/IRB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board

9.4 Reporting & Follow up of Serious Adverse Events

SAEs (as defined in section 8.1) must be reported from start of randomization to time of ICU discharge or 30 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.

10 STATISTICAL ANALYSES

10.1 Study Population

The number of patients planned to be randomized into this domain protocol is 72. This would 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 would allow for an assessment of feasibility objectives over a reasonable time period of 1 year as well as allow us to detect an adherence rate of 80% + 10% (meaning 80% + 10% of study patients will have fewer than 10% of monitored values as major deviations).

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.

10.2 Evaluation of Safety

The safety and tolerability of VV-ECMO will be evaluated by means of recording SAEs in both groups and monitoring the predicted physiological response (reduced driving pressure ΔP) to CO_2 removal by VV-ECMO.

The following safety outcomes will be evaluated:

- Mechanical complications
- Hemorrhagic complications
- Renal complications
- Cardiovascular complications
- Pulmonary complications
- Metabolic complications
- Neurological complications
- Infections
- Death
- Clinical endpoints as defined in section 9.10.

10.3 Evaluation of Efficacy

The efficacy of VV-ECMO will be evaluated by means of assessing delivered tidal volumes in both groups and magnitude of physiological response (reduced driving pressure ΔP) to CO_2 removal by VV-ECMO.

10.4 Primary Objective

To determine the feasibility of recruiting 72 ARDS patients across sites given 1 year of active enrolment per site, as well as assess the rate of participant recruitment and understand the barriers to enrolment.

10.5 Primary Endpoint

Record total number of patients randomized, total number of patients eligible yet not randomized, and the number of active randomizing sites on a monthly basis. This will include evaluating the validity and impact of inclusion and exclusion criteria, trial acceptability, and the reasons for lack of consent or withdrawal.

10.6 Secondary Objectives

- To assess adherence to our explicit mechanical ventilation protocols, with particular focus on delivered tidal volumes in both groups and estimated $\Delta P_{L\text{-}dyn}$ in the ECMO group
- To measure and understand the reasons for crossovers in each group

10.7 Secondary Endpoints

- Evaluate number of protocol deviations and their causes (control group: V_T>8ml/kg, P_{PLAT}>30cm H_2O; experimental group: V_T>8ml/kg, P_{PLAT}>30cm H_2O, $\Delta P_{L\text{-}dyn}$ >23 cm H_2O) over 2 consecutive data points for a minimum of 48 hours.
- Classify crossovers as consistent with, or in deviation of, the study protocol and detailed documentation will be required for crossovers classified as deviations.

10.8 Exploratory Objectives

- To monitor safety issues, recording serious adverse events in both groups
- Quantify cytokine levels to further understand the inflammatory processes involved

10.9 Exploratory Endpoints

- Frequency and type of SAEs
- Analyze cytokine blood levels

10.10 Clinical Endpoints

The following clinical endpoints will be assessed:

- ICU length of stay
- Survival status at ICU discharge (dead or alive)
- Survival status at hospital discharge (dead or alive)
- Duration of mechanical ventilation
- Survival status at disconnection from mechanical ventilation (dead or alive)
- Ventilator free days to day 28 (an ordinal scale composed of survival to hospital discharge and days alive and free of ventilation where death in the hospital is assigned a score of –1)

10.11 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.

With respect to patient accrual, our goal is to enrol 72 patients across Canadian sites for the pilot study given a period of one year of active enrolment per site. Failure to do so will prompt us to modify our plans for a future trial. If our accrual is as anticipated, or better, we will not modify the eligibility criteria. If our accrual rate is marginal (that is, barely achieves our goals), we will examine the number of patients excluded on the basis of each exclusion criterion and reconsider the necessity for any criterion that has resulted in a large number of excluded patients.

10.12 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 Data Safety and Monitoring Board (DSMB) with analyses by group at the completion of this pilot RCT. Further details regarding DSMB commitment will be 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. We

will also consider controlling for centre and providing both unadjusted analyses and analyses adjusted for age and baseline oxygenation, and duration of ventilation prior to enrolment using Bayesian (generalized) linear models. The results from these models will be summarised using the posterior mean and 95% credible intervals. All these analyses will include all randomised patients adhering to the intention to treat principle. We will use complete case analyses, with the level of missingness reported for each outcome. Investigators will remain blinded to these clinical results, while the full ULTIMATE trial moves forward. Due to the pilot study design of the trial and its short duration, no subgroup analyses are planned.

10.13 Feasibility Outcomes

1) Adherence to our explicit ventilation protocols will be adequate if more than 80% of patients have fewer than 10% 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 60 patients over 1 year of active site enrolment.

10.14 Sites

Multiple centres will participate in the ULTIMATE pilot study. All of these centres have experience in ventilation RCTs, 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.

10.15 Randomization Scheme

We will use web-based, allocation-concealed randomization, stratified by centre, accessible 24 hours per day. We will randomize patients 1:1 (experimental:control) using randomly variable, undisclosed block sizes. Research assistants and/or clinical respiratory therapists will screen all mechanically ventilated patients for eligibility on a daily basis.

11 PUBLICATION POLICIES AND DISCLOSURE OF DATA

This section is in accordance with the PRACTICAL platform protocol and publication policy.

11.1 Intellectual Property

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

11.2 Data Sharing

Please refer to PRACTICAL master protocol for details.

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