

Domain Protocol:  
**OZUHN-004-3**

**Invasive Mechanical Ventilation (IMV) Strategies  
Domain**

Platform Master Protocol:  
OZUHN-004

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

**Protocol Version #:** 3.0  
**Protocol Date:** 08-Aug-2025  
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**Protocol History**

**Original:** Version 1.0; dated 22-Dec-2022  
*U.S. Only:* Version 1.1; dated 22-Mar-2024

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Amendment #1: Version 2.0; dated 15-Aug-2024

Amendment #2: Version 3.0; dated 08-Aug-2025

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**Sponsor's Agreement to Domain Protocol #OZUHN-004-3 Version 3.0, Dated 08-Aug-2025 and all current Intervention-Specific Appendices**

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Date of Approval: 01-OCT-2025  
DD-MMM-YYYY

**SYNOPSIS**

<b>Master Protocol Title</b>	Platform of <b>R</b> andomized <b>A</b> daptive <b>C</b> linical <b>T</b> rials <b>I</b> n <b>C</b> ritical Illness (PRACTICAL) Randomized Control Trial
<b>Domain Protocol Title</b>	<b>Invasive Mechanical Ventilation (IMV) Strategies Domain</b>
<b>Eligible Platform-Defined Patient States</b>	<p>This domain includes patients in the following platform defined states:</p> <ol style="list-style-type: none"> <li>1. Intubated patients, not on ECLS, with low normalized respiratory elastance (&lt;2.5 cm H<sub>2</sub>O/(mL/kg predicted body weight))</li> <li>2. Intubated patients, not on ECLS, with high normalized respiratory system elastance (≥2.5 cm H<sub>2</sub>O/(mL/kg predicted body weight))</li> <li>3. Patients on ECLS</li> </ol> <p>There may be additional restrictions based on state that are applicable for certain sites, depending on the intervention arms they are participating in. Refer to the Intervention Appendices and Current Interventions protocol supplement for additional information.</p>
<b>Domain Primary Objective</b>	<p>The primary objective for the domain is to identify the IMV strategy that most effectively improves patient outcomes among a range of strategies including conventional lung-protective ventilation. This overarching primary objective will apply to all interventions being evaluated in phase III.</p> <p>For interventions being evaluated in the pilot/feasibility phase or phase II, comparison-specific primary objectives are defined in the Current Interventions protocol supplement.</p>
<b>Domain Secondary Objectives</b>	<p>To establish the feasibility and tolerability of novel mechanical ventilation strategies in terms of protocol adherence and serious adverse event rates (pilot/feasibility phase interventions).</p> <p>To define the physiological and biological effects of different invasive mechanical ventilation strategies (phase II interventions).</p>
<b>Domain Design</b>	An interventional, open-label, multi-arm adaptive randomized clinical trial.
<b>Duration</b>	This domain will enroll perpetually as current interventions are discontinued and new interventions are added in the future.

<p><b>Planned Total Sample Size</b></p>	<p>For interventions being evaluated at phase III, sample size is not fixed. Unless otherwise specified, interventions evaluated in phase III will be evaluated using a single Bayesian hierarchical statistical model. Sample size for each intervention will be determined by pre-defined stopping rules specified in terms of probabilities of superiority, futility, equivalence, and inferiority with respect to the domain primary endpoint computed from this statistical model.</p> <p>For interventions evaluated in phase II or in the pilot/feasibility phase, sample size requirements are detailed in the applicable intervention-specific appendix.</p>
<p><b>Inclusion/Exclusion Criteria</b></p>	<p>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.</p>
<p><b>Randomization:</b></p>	<p>For any given state and site, patients will be randomised equally between all interventions for which they are eligible. . All sites will randomize to the control arm and at least one other arm.</p>
<p><b>Study Assessments:</b></p>	<p>Study assessments are depicted in the Study Plan.</p>
<p><b>Efficacy Assessments &amp; Analysis</b></p>	<p>Assessments will occur on various comparisons between the different interventions.</p>
<p><b>Statistical Analysis:</b></p>	<p>The statistical analysis plan (SAP) for this domain follows the approach specified by the master SAP and the domain specific SAP.</p> <p>The domain will estimate the superiority, equivalence, futility, or inferiority of each intervention in comparison to others undergoing evaluation in phase III.</p> <p>The SAP for interventions evaluated at phase II or in the pilot/feasibility phase is detailed in the intervention-specific appendices.</p>

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**LIST OF ABBREVIATIONS**

ABG	Arterial Blood Gases
AE	Adverse Event
ADR	Adverse Device Reaction
AHRF	Acute Hypoxemic Respiratory Failure
ARDS	Acute Respiratory Distress Syndrome
aPTT	Activated Partial Thromboplastin Time
CRF	Case Report Form
CPAP	Continuous Positive Airway Pressure
DSMB	Data Safety Monitoring Board
$\Delta P_{L-dyn}$	Dynamic Trans-Pulmonary Driving Pressure
ECLS	Extra-corporeal Life Support
ECCO <sub>2</sub> R	Extracorporeal CO <sub>2</sub> Removal
FDO <sub>2</sub>	Optical Oxygen Gas Sensor
FiO <sub>2</sub>	Fraction of Inspired Oxygen
ICU	Intensive Care Unit
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
PaCO <sub>2</sub>	Partial pressure of carbon dioxide
PaO <sub>2</sub>	Partial pressure of Oxygen
P/F	PaO <sub>2</sub> /FiO <sub>2</sub>
PEEP	Positive End Expiratory Pressure
P <sub>PLAT</sub>	Plateau Pressure
RCT	Randomized Clinical Trial
SAE	Serious Adverse Events

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SAP	Statistical Analysis Plan
SDM	Substitute Decision Maker
S/F	SpO <sub>2</sub> /FiO <sub>2</sub>
SOC	Standard of Care
SpO <sub>2</sub>	Oxygen Saturation by Pulse Oximetry
TEE	Trans-Esophageal Echocardiography
VILI	Ventilator Induced Lung Injury
VIDD	Ventilator Induced Diaphragm Dysfunction
V <sub>T</sub>	Tidal Volume
VV-ECMO	Veno-Venous Extracorporeal Membrane Oxygenation

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## BACKGROUND

General information on the background and rationale for the design of the **Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL)** Randomized Control Trial is provided in the Master Protocol. That information includes discussion of the clinical problems of **ventilator-induced lung injury (VILI)**, **ventilator-induced diaphragm dysfunction (VIDD)**, and **patient self-inflicted lung injury (P-SILI)**. These clinical problems are the context for the specific interventions to be evaluated in this domain.

Refer to the intervention-specific appendices for additional background and rationale for each intervention.

### **Acute hypoxemic respiratory failure and iatrogenic injury during mechanical ventilation**

Patients with acute hypoxemic respiratory failure (AHRF) including those with severe COVID-19 are at high risk of lung and diaphragm injury from mechanical ventilation and sedation. Approximately 65,000 Canadians develop acute respiratory failure and require invasive mechanical ventilation annually;<sup>1</sup> mortality varies between 20-50%.<sup>2</sup> While life-sustaining, mechanical ventilation can further injure the lung and the diaphragm. **VILI** occurs when mechanical inflation causes excessive stress ('overdistention') within the lung.<sup>3</sup> This induces pulmonary and systemic inflammation leading to multi-organ failure,<sup>4</sup> death, or prolonged ventilation with long-term disability.<sup>5,6</sup> Limiting tidal volume and inspiratory pressure (4-8 mL/kg predicted body weight; plateau pressure  $\leq 30$  cm H<sub>2</sub>O) mitigates lung injury and reduces mortality and is considered the standard of care (SOC).<sup>7</sup>

To achieve low tidal volumes, however, conventional lung-protective ventilation often requires suppression of patient respiratory effort through heavy sedation.<sup>8,9</sup> Suppressing patient respiratory effort can impair hemodynamics and gas exchange<sup>10</sup> and leads to rapid **disuse atrophy of the diaphragm**, resulting in **VIDD**.<sup>11</sup> Diaphragm dysfunction affects nearly two thirds of ventilated patients.<sup>12</sup> Over 50% of ventilated patients included in our physiological observational cohorts (n=216) developed diaphragm atrophy or injury<sup>13</sup> and this was associated with prolonged mechanical ventilation (>14 days) and a higher risk of requiring reintubation or tracheostomy.<sup>14</sup> Prolonged ventilation, in turn, leads to intensive care unit (ICU)-acquired weakness, an increased risk of ventilator-associated pneumonia, death, and long-term disability.<sup>15-19</sup> On the other hand, restoring patient respiratory effort to prevent diaphragm disuse atrophy is challenging because respiratory effort, when present, is frequently excessive. Excessive respiratory effort can cause **P-SILI** by increasing the pressure applied to the lungs.<sup>10,20</sup> It can also cause load-induced diaphragm injury (**myotrauma**)<sup>21,22</sup> and is associated with prolonged ventilation.<sup>14,23</sup>

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## Domain Design

This domain is a multi-centre, randomized, open-label trial that will evaluate multiple novel invasive ventilation strategies in comparison to conventional lung-protective ventilation in patients with AHRF. This domain will enroll perpetually, as interventions are added, continued, or discontinued. In general, domains encompass mutually exclusive interventions that target the same clinical problem.

As multiple optimal strategies for mechanical ventilation have been proposed, and the optimal approach is unknown, an efficient strategy is to compare multiple potential approaches simultaneously to determine more rapidly (a) which interventions are least effective (and should be dropped), and (b) which interventions are most effective among all options (and should become SOC in the domain). Because different subgroups of patients may be more or less responsive to interventions, testing multiple interventions simultaneously in a single domain facilitates identification of relevant subgroups for more targeted interventional approaches.

Another strategy to increase the efficiency of trial design is to create a ‘pipeline’ structure to evaluate interventions within the same platform and domain across multiple phases of investigation. By utilizing the same trial infrastructure to evaluate the intervention at different stages, it is easier in terms of logistics and site recruitment to progress interventions to more advanced phases of evaluation. This progression can be operationalized as ‘seamless graduation’ according to pre-specified triggers for graduation. This seamless approach can facilitate the incorporation of patients enrolled in the earlier phase in the trial population under analysis in the later phase. Progression can also be operationalized without formal rules for graduation in order to allow full analysis of available data to inform the decision as to whether an intervention warrants evaluation in a more advanced phase. Interventions may be progressed only in promising patient subgroups, where evidence of differential treatment effects emerge during phase II evaluation. Phase II evaluations can be designed in such a way as to increase statistical power to identify promising subgroups (e.g. by the use of continuous endpoints). A general principle of this domain is that interventions will graduate to phase III evaluation only if they have already demonstrated promising evidence of physiological or biological effect in a phase II evaluation.

The domain protocol is designed to be easy to adapt as interventions may be removed or added, therefore, details specific to each intervention are included in the Current Interventions supplement document and the intervention-specific appendices. This domain will be conducted in compliance with the PRACTICAL Master Protocol, this domain protocol, intervention-specific appendices, applicable ICH-GCP guidelines and applicable regulatory requirements.

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## RESEARCH OBJECTIVES

*Listed below are objectives that apply to the entire domain. Refer to the statistical analysis section for the phases and comparisons that are currently being studied for each of the interventions.*

*Refer to the PRACTICAL Master Protocol for the list of platform-wide endpoints.*

### Domain Primary Objective

The primary objective for the domain is to identify the invasive mechanical ventilation strategy that most effectively improves patient outcomes among a range of strategies including conventional lung-protective ventilation. This objective will apply to all interventions being evaluated in phase III.

For interventions being evaluated in the pilot/feasibility phase or in phase II, comparison-specific primary objectives are defined in the intervention-specific appendix for each such intervention.

### Domain Secondary Objectives

1. To establish the feasibility and tolerability of novel mechanical ventilation strategies in terms of protocol adherence and serious adverse event rates (pilot/feasibility phase interventions).
2. To define the physiological and biological effects of different invasive mechanical ventilation strategies (phase II interventions).

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## PATIENT POPULATION, ELIGIBILITY AND ENROLLMENT

### Patient population

This domain will enrol patients in the following platform-defined states:

1. Intubated patients, not on ECLS, with low normalized respiratory elastance (<2.5 cm H<sub>2</sub>O/(mL/kg predicted body weight))
2. Intubated patients, not on ECLS, with high normalized respiratory system elastance (≥2.5 cm H<sub>2</sub>O/(mL/kg predicted body weight))
3. Patients on ECLS

There may be additional restrictions based on state that are applicable for certain sites, depending on the intervention arms they are participating in. Refer to the Intervention Appendices and Current Interventions protocol supplement for additional information.

If, during an interim analysis, a trial conclusion is met in one of the patient states for an intervention, patients in that state may no longer be able to be randomized to that intervention.

Patients who satisfy both platform- and domain-specific eligibility criteria will be considered for enrolment. As mentioned above, there may be additional restrictions based on state that are applicable for certain interventions (refer to the Intervention Appendices and Current Interventions documents). **Sites should refer to the supplementary Eligibility Checklist documents for the extensive list of criteria applicable to their site based on the interventions they are participating in.**

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

### PRACTICAL Platform Eligibility Criteria

#### Platform Inclusion Criteria

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  $\text{FiO}_2 \geq 0.40$  (for venturi mask, high flow nasal cannula, or invasive or non-invasive ventilation) or oxygen flow rate  $\geq 10$  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  $\geq 18$  years

#### Platform 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

#### **Domain-Specific Eligibility Criteria**

##### Domain Inclusion Criteria

1. Patient is in an eligible platform-defined severity state by being either;
  - a) Intubated and not on ECLS at the time of eligibility assessment

**OR**

  - b) On ECLS at the time of eligibility assessment. *Note: Only applicable for sites enrolling in the ECLS severity state (refer to the Intervention Appendices and Eligibility Checklist relevant for your site)*
2. The patient has confirmed hypoxemia, defined by meeting at least one of the following;
  - a)  $\text{PaO}_2/\text{FiO}_2 \leq 300$  mm Hg on most recent ABG. The most recent ABG should be preceding 24 hours to be considered for eligibility. ABG should have been drawn on ventilator settings of at least  $\text{FiO}_2 \geq 40\%$  and  $\text{PEEP} \geq 5$ .
  - b) If  $\text{PaO}_2/\text{FiO}_2$  has not been measured,  $\text{SpO}_2 < 97\%$  on  $\text{FiO}_2 \geq 40\%$  during both of the 2 hours immediately preceding eligibility assessment

- c) Patient is on ECLS for AHRF. *Note: Only applicable for sites enrolling in the ECLS severity state (refer to the Intervention Appendices and Eligibility Checklist relevant for your site).*

#### Domain Exclusion Criteria

1. Chronic hypercapnic respiratory failure defined as PaCO<sub>2</sub>>60mmHg in the outpatient setting
2. Home mechanical ventilation (non-invasive ventilation or via tracheotomy), not including nocturnal CPAP applied by nasal or face mask or home tracheotomy if not ventilated
3. Treating clinician plans to institute VV-ECMO in the next 24 hours, at the time of eligibility assessment
4. Anticipated duration of mechanical ventilation is <48 hours from the time of eligibility assessment
5. Duration of mechanical ventilation during current ICU admission is >72 hours at the time of eligibility assessment
6. Previously diagnosed neuromuscular disorder
7. Current diagnosis of severe acute brain injury (e.g. ischemic or hemorrhagic stroke, traumatic brain injury) with Glasgow Coma Scale ≤ 8
8. Baseline weight prior to or at hospital admission less than 35 kilograms
9. Receiving extracorporeal life support without continuous invasive mechanical ventilatory support
10. Broncho-pleural fistula at the time of eligibility assessment
11. Severe liver disease (Child-Pugh Score ≥10)
12. Known to have been randomized in the IMV strategies domain within the last 12 months

#### **Eligible non-randomized patients**

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

1. Lack of consent from patient or substitute decision maker (SDM) (specifying reason);
2. Refusal from attending physician (specifying reason);
3. Enrolment in a confounding study that does not allow co-enrollment;
4. Research coordinator or study material (e.g. device, study drug) not available

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

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## **Patient Consent**

Consent process will be conducted as per local ethics board requirements and recommendations. Where allowed per the local ethics board, a deferred consent model can be used. This is a minimal risk study, and deferred consent is advantageous because the timeframe from screening to intervention is short, and additional burden on SDMs could be avoided.

It will be the responsibility of the local participating investigator to obtain the necessary clearance and to indicate in writing to Ozmosis Research Inc. or the applicable coordinating center 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 ethics board approval and approved consent form must be sent to Ozmosis Research Inc. or the applicable coordinating center. In settings where deferred consent not approved, patient / SDM (as applicable for patients lacking decision making capacity) consent will be obtained prior to domain-specific enrollment.

## **Patient Enrollment**

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

Eligibility will be assessed by one of the principal investigators or sub-investigators prior to entry into this domain. Eligible and consented patients (as applicable per the section above) will be enrolled into the domain.

Prior to enrolling a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. or the applicable coordinating center, and received a local activation letter. Access to the eCRFs will only be granted once this has been received and enrollment will occur online via the REDCap database.

## **Patient Randomization**

Enrolled patients will be randomized to one of the interventions that are available at that specific site and for the specific patient state **after** the post-enrollment stabilization and pre-randomization assessments (see the Study Plan section).

For any given state and site, patients will be randomized equally between all interventions for which they are eligible. Each site will randomize patients into at least two of the intervention arms, one of which will be the current control arm.

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## 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. Additionally, after discharge, all patients will receive a remote follow-up at 6 months to evaluate vital status and quality of life after hospitalization, which will serve as an opportunity for patients to ask any questions about their recovery process.

## STUDY PLAN

### Study Schedule

As soon as possible following eligibility assessment and enrollment, patients will be placed on standardized ventilator settings according to the following criteria;

- Volume assist-control or pressure assist-control mode
- Tidal volume 6 ml/kg predicted body weight
- PEEP 10 cm H<sub>2</sub>O, which may be higher if necessary to maintain SpO<sub>2</sub> > 90% or lower if necessary to maintain plateau airway pressure ≤30 cm H<sub>2</sub>O
- Respiratory rate set to maintain pH>7.15
- FiO<sub>2</sub> adjusted to maintain SpO<sub>2</sub> ≥90).

After 30 minutes on these settings, measurements will be collected and the following pre-randomization assessments will be performed.

1. Measurement of airway opening pressure. *This is not required if patient is receiving assisted ventilation (triggering the ventilator) (detailed in Manual of Procedures)*
2. Measurements required for computation of respiratory system elastance (detailed in Manual of Procedures)
3. Arterial blood gases. *Required to be done for patients that have an arterial line, not required to be done for patients that do not have an arterial line.*

The patient will then be randomized. Randomization should occur as soon as possible after the pre-randomization measurements have been completed. As soon as possible after randomization, the applicable intervention should be initiated. Please refer to the intervention-specific appendix for details on intervention duration and stopping criteria. If a patient is

randomized but withdraws for any reason prior to meeting one of the stopping criteria, they will not be replaced.

Daily data will be collected twice a day while the patient is receiving the intervention, and once a day post-intervention during ICU admission until Day 28. Thereafter, we will follow patients to the time of hospital discharge and record ICU/hospital survival. Patient vital status will be assessed remotely 6 months after randomization, and this will include completion of a health related quality of life questionnaire.

### Study Schema

This Study Schema applies to all patients enrolled in this domain **with the exception of some study assessments that are required on a site-specific basis based on the intervention arms that the site is participating in**. Refer to the applicable intervention appendices for any additional assessments required.

Required Procedures*	Baseline	Enrolment	Pre-Randomization (Enrolled patients only)	Randomization (Day 0)	Daily: <i>During Intervention</i> (First day of intervention to last day of intervention)	Daily: <i>Post-Intervention in ICU</i> (Day after the last day of intervention up to Day 28)	6 months (180 days) from Randomization (Remote contact)
<b>Window</b>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>	<i>-22/+60 days</i>
Consent <sup>1</sup>	X						
Demographics <sup>2</sup>	X						
Medical History <sup>3</sup>	X						
Vitals <sup>4</sup>	X				X		
Chest X-Ray <sup>15</sup>	X						
Hemodynamics <sup>5</sup>	X				X		
Respiratory Data <sup>6</sup>	X		X	X	X	X	
Hematology <sup>7</sup>	X				X		
Biochemistry <sup>8</sup>	X				X		
Arterial Blood Gases (ABG) <sup>9</sup>	X		X		X		
Blood Sample Collection (Optional)			X		X <sup>12</sup>		
Enrollment (REDCap)		X					

Stabilization on standard ventilator settings (30 minutes) followed by pre-randomization measurements			X				
Randomization (REDCap)				X			
Mechanical ventilation management according to randomized intervention					X		
Daily assessment of readiness-to-wean criteria AND Spontaneous Breathing Trial (SBT) when readiness-to-wean criteria are met					X <sup>10</sup>	X	
Sedation score (SAS, RASS)					X		
HrQOLs (EQ-5D-5L)							X
Vital status							X
Serious Adverse events/safety data <sup>11</sup>				X			
Primary and Secondary Outcomes				X			
Concomitant Medications			X				

<sup>1</sup> Consent should be done prior to any study specific assessments and according to site institutional timelines.  
<sup>2</sup> Demographics including race, ethnicity, age, sex, height, and weight.  
<sup>3</sup> Hospital and ICU admission information (including date and time), APACHE IV, Clinical Frailty Scale, Glasgow Coma Scale, COVID-19 infection status.  
<sup>4</sup> Vitals include temperature, heart rate, respiratory rate, and blood pressure.  
<sup>5</sup> Hemodynamics include BP and, if available, PAPm, PAC, PCWP, SmvO<sub>2</sub>.  
<sup>6</sup> Respiratory data including mode of ventilation, FiO<sub>2</sub>, PEEP, PIP, RR, tidal volume, plateau and driving pressure, oxygen saturation, expiratory occlusion pressure (P<sub>occ</sub>), and airway occlusion pressure (P<sub>0.1</sub>). P<sub>occ</sub> and P<sub>0.1</sub> are optional after the intervention period and will be collected if available.  
<sup>7</sup> Hematology reporting on Hb, WBCs, and platelets. *If not done daily per SOC, sites are not required to have the tests done specifically for the study and this will not be a protocol deviation.*  
<sup>8</sup> Biochemistry will include reporting the following values: INR, PTT, sodium, glucose, creatinine, albumin, bilirubin, potassium, bicarbonate, troponin, phosphate, total calcium. *If not done daily per SOC, sites are not required to have the tests done specifically for the study and this will not be a protocol deviation.*  
<sup>9</sup> ABG testing will include the following parameters: pH, PaCO<sub>2</sub>, HCO<sub>3</sub>, base excess, SaO<sub>2</sub> and, if available, lactate, hemoglobin. ABG testing is a required assessment at the pre-randomization time-point for patients that already have an arterial line, not required to be done for patients that do not already have an arterial line. *For all other time points, if not done SOC, sites are not required to have the tests done specifically for the study and this will not be a protocol deviation.*  
<sup>10</sup> Spontaneous breathing trials will be conducted only when patient is deemed ready for weaning and per standard of care and/or institutional guidelines.  
<sup>11</sup> SAEs will be reported from the start of randomization and for a period of up to 28 days, or while in ICU, whichever is shorter. Sites participating in the CAV intervention will document occurrence of refractory hypoxemia (SpO<sub>2</sub> < 88% despite increase of FiO<sub>2</sub>) and persistent hypotension (MAP<55 despite fluid administration and/or vasopressors).  
<sup>12</sup> Beyond baseline, optional correlative blood samples are only to be collected on Day 3 (+/- 1 day) and Day 7 (+/- 1 day).  
<sup>13</sup> Chest X-ray data will be completed if the X-ray is being performed as a standard-of-care assessment. It is not required as a study specific assessment.  
 \* All blue fields are standard-of-care assessments and data being collected for study purposes.

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### **Optional Correlative Sample Collection**

Blood sample collection, for the assessment of lung, muscle, and brain injury biomarkers, and other future research studies will occur at the time points indicated in the Study Schema for patients that have provided informed consent on the optional consent for blood sample collection according to the approved consenting process at each site, which may include a deferred consent model. 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 on a case-by-case basis. Further details are available in the Manual of Procedures.

### **CONCOMITANT MEDICATION/ PROCEDURES**

The administration of the following concomitant medications will be collected for study purposes from baseline to time of ICU discharge or for 28 days from randomization (Day 0), whichever is shorter.

- Neuromuscular blocking agents (e.g., rocuronium, cisatracurium)
- Sedatives (e.g., propofol, fentanyl, midazolam)
- Analgesics (e.g., fentanyl, morphine, hydromorphone)
- Corticosteroids (e.g., methylprednisolone, prednisone, dexamethasone)
- Inotropes (e.g., dobutamine, milrinone)
- Vasopressors (e.g., norepinephrine, vasopressin, epinephrine)
- Antipsychotics (e.g., haloperidol, quetiapine, risperidone)

Additionally, the following procedures are to be documented:

- Prone positioning
- Renal replacement therapy
- ECMO

## TRIAL INTERVENTIONS

Refer to the intervention-specific appendices for details on each current intervention.

### Co-Intervention Management

Management of co-interventions will be conducted according to the protocols specified in the following table and will be applied until one of the following stopping criteria are met.

- Death
- Extubation
- Day 28 of mechanical ventilation. If a patient is re-intubated anytime within 28 days during the index ICU admission, they will resume the protocol.

Co-Intervention Management	
Weaning: assessment for readiness-to-wean criteria	<p>Readiness to wean will be assessed on a daily basis. Assessment for readiness to wean will include the following standard criteria:</p> <ul style="list-style-type: none"> <li>• <math>FiO_2 \leq 0.5</math></li> <li>• <math>PEEP \leq 10</math> cm H<sub>2</sub>O</li> <li>• Patient continuously triggering the ventilator (in any mode)</li> <li>• On a single vasopressor with the dose not rapidly escalating</li> </ul>
Weaning: spontaneous breathing trials (SBT)	<p>Spontaneous breathing trials will be conducted if the patient meets readiness-to-wean criteria. The spontaneous breathing trials will be conducted using ventilator settings specified according to local site practice. If a site does not have a protocol for SBT they will follow the protocol provided below.</p>
Best practice in acute hypoxemic respiratory failure: Prone positioning	<p>Prone position will be routinely implemented for 16-18 hours daily when <math>PaO_2/FiO_2</math> is below 100 mm Hg, in accordance with clinical practice guidelines. Prone positioning will be permitted and recommended when the <math>PaO_2/FiO_2</math> is between 100-150 mm Hg according to clinician discretion.</p>
Best practice in acute hypoxemic respiratory failure: Extracorporeal life support	<p>Referral for extracorporeal life support should be considered if the patient meets the following criteria:</p> <ul style="list-style-type: none"> <li>• Very severe hypoxemia (<math>PaO_2/FiO_2 &lt; 80</math> mm Hg) for at least 6 hours</li> <li>• Refractory hypoxemia (<math>PaO_2/FiO_2 &lt; 55</math> mm Hg) at any time</li> <li>• Severe hypercapnic acidosis (<math>PaCO_2 &gt; 60</math> mm Hg and <math>pH &lt; 7.25</math> with plateau airway pressure above 35 cm H<sub>2</sub>O and respiratory rate at 40 breaths per minute)</li> </ul>

Rescue strategies for refractory hypoxemia: neuromuscular blockade	Neuromuscular blockade will be permitted when patients develop severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg) or for refractory patient-ventilator dyssynchrony. However it is not mandatory.
Rescue strategies for refractory hypoxemia: inhaled pulmonary vasodilators	Inhaled pulmonary vasodilators will be permitted when $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg at clinician discretion or for right ventricular failure at clinician discretion.
Rescue strategies for refractory hypoxemia: lung recruitment maneuvers	The use of lung recruitment maneuvers will be discouraged based on best available evidence.
Sedative agents	Selected according to clinician discretion and local site usual practice.
Sedation targets	Sedation will be managed by targeting light levels of sedation via targeted sedation or daily interruption, unless otherwise contraindicated, as per PADIS guidelines, or unless otherwise specified by the intervention specific appendices. <i>When sedation is used to control excessive respiratory effort, based on available physiological data we suggest that clinicians consider using propofol in preference to other sedatives. We suggest that the propofol infusion rate can be titrated up gradually in increments of 10 mcg/kg/min every 10-15 minutes or per local site protocol until the respiratory effort target is reached to minimize adverse hemodynamic effects.</i>
Analgesia targets	Pain will be assessed and managed according to local usual practice. Use of a standardized pain assessment tool (e.g., CPOT) is recommended.

### Spontaneous Breathing Trials

Spontaneous breathing trials (SBTs) should be conducted according to usual local site practice provided practice is standardized and will be the same for all patients enrolled at the site. At sites that do not have a standardized protocol, SBTs will be conducted using the following ventilator settings:

- PSV or CPAP mode
- PSV 0 cm H<sub>2</sub>O
- PEEP 0 cm H<sub>2</sub>O
- $\text{FiO}_2 \leq 0.5$

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## Cross Overs

Cross overs are not planned for this trial. Protocol deviations may be documented if the ventilation targets are not met in the arm assigned.

## SAFETY AND REPORTING REQUIREMENTS

The critically ill patient population is 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 lung injury; 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, adverse events will not be collected for this study and only related serious adverse events (SAEs) will be collected (see section below).

### Serious Adverse Event

An 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 the randomized study intervention

*\*A related event is an event in which there is a reasonable possibility that the randomized study intervention 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 intervention;*
- *There is a plausible biological mechanism through which the intervention may have caused or contributed to the SAE.*

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## Reporting Serious Adverse Events or Serious Adverse Device Effects

All SAEs as defined in the section above must be recorded on the eCRF. In addition, they must be reported by using the SAE form and must be submitted to Ozmosis. SAEs should be reported within 24 hours of becoming aware of the event.

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.  
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 SAE 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

## Procedure for Expedited Reporting

### Responsibility for Reporting SAEs 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 Lead Investigators within 24hrs after receipt of the SAE form at Ozmosis.

### Reporting SAEs to Local Research Ethics Boards

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Investigators must notify their ethics board as applicable per their guidelines and file the report in their Investigator Site File. Documentation that SAEs have been reported to the ethics board must be kept on file at Ozmosis. Documentation can be any of the following:

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

All expedited SAEs occurring within a centre should also be reported to the local ethics board.

### **Reporting & Follow up of SAEs**

SAEs must be reported from the 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.

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## STATISTICAL ANALYSES

Additional details including stopping criteria and procedures of accounting for missing, unused and spurious data are included in the master and domain-specific SAPs.

Any deviations from the finalized SAPs will be described in the final reports.

### Sample Size

For interventions being evaluated at phase III in this domain, sample size is not fixed. Interventions evaluated in phase III will be evaluated using a single Bayesian hierarchical statistical model. Sample size for each intervention will be determined by stopping rules defined in terms of probabilities of superiority, futility, equivalence, and inferiority with respect to the domain primary endpoint computed from this statistical model.

For interventions being evaluated at phase III in this domain but analyzed in a separate trial under a multi-platform approach, the sample size is governed by the trial design specified for the primary platform.

For interventions evaluated in phase II or in the pilot/feasibility phase, sample size requirements are detailed in intervention-specific appendices.

### Study Population

The study population in this domain will depend on the stage of investigation at which each intervention is being studied as well as the aim of analysis.

The primary analysis of phase III is based on the intention to treat (ITT) population, where all the patients randomized to interventions under evaluation in phase III are included and will be analyzed by the treatment group to which they were assigned at randomization. Patients enrolled in interventions that are being evaluated at phase III will be analyzed using a single statistical model across all the states and eligible interventions. Bayesian hierarchical modelling will be employed to account for differences across the states.

The safety analysis for the phase III interventions will be conducted on the IIT population, where patients will be analyzed according to the treatment actually received, regardless of the treatment assignment.

Patients enrolled in interventions that are being evaluated at **phase II** will be evaluated based on populations defined by the specific phase II analysis plan. The stage of evaluation for each intervention is indicated above and in the intervention-specific appendix to this protocol.

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## Evaluation of Safety

Safety will be analyzed for each intervention based on the clinical and safety endpoints defined in the PRACTICAL Master Protocol.

## Evaluation of Efficacy

Efficacy will be evaluated according to the stage of evaluation defined for each intervention in the following primary analysis section (for phase III) or intervention-specific appendix (for phase II).

## Primary Endpoint

The primary endpoint for interventions being evaluated in phase III in this domain is ventilator-free days to day 28, analysed as an ordinal variable, unless otherwise specified. This endpoint is a composite of death in hospital (assigned a value of  $-1$ ) and, in survivors to hospital discharge, the number of days alive and free of mechanical ventilation to day 28. This definition is given in more detail in the master SAP.

## Secondary Endpoints

Secondary endpoints for this domain include:

- Duration of mechanical ventilation during index ICU admission
- Reintubation during index ICU admission
- Tracheostomy during index ICU admission
- Survival to ICU discharge
- Duration of ICU admission
- Need for ICU readmission prior to hospital discharge
- Survival to hospital discharge
- Duration of hospitalization
- Discharge disposition (home, rehabilitation facility, skilled nursing facility, weaning facility)
- All-cause 60 day mortality
- Barotrauma (i.e. new onset pneumothorax if not directly related to an intervention (e.g. central line insertion))
- Cardiac arrest
- Survival to day 180
- Hospital-free days to day 90

- Quality of life assessed at day 180 (EQ-5-D)
- Daily Sequential Organ Failure Assessment (SOFA) score for duration of intervention
- Daily physiological parameters of respiratory mechanics (driving pressure, P<sub>0.1</sub>, plateau airway pressure) and gas exchange (PaO<sub>2</sub>/FiO<sub>2</sub>, ventilatory ratio) for duration of intervention
- Cumulative fluid balance at day 7 post-randomization
- Daily vasopressor-inotrope score over the first 3 days, computed from the highest hourly infusion rate for each pressor in the 24-hour calendar day
- Daily cardiovascular SOFA score over the first 3 days, computed from the worst hourly values in the 24-hour calendar day

### **Proposed Type of Analyses**

Treatment effect will be analyzed according to the statistical analysis plan specified for the domain, with model design conforming to the platform master statistical analysis plan and appropriate for the endpoint on which treatment effect is primarily evaluated. The treatment effects across the different states will be estimated in a single hierarchical model, which allows for dynamic borrowing across states. Bayesian hierarchical regression models (generalized linear models, survival models, etc.) will be used in the secondary analyses. Subgroup analyses will be conducted by including an interaction term between the treatment effect and the subgroup in the model.

In the future, if additional interventions ( $\geq 3$  total) are evaluated at phase III, the model may be employed to compute the probabilities of inferiority and equivalence, alongside superiority and potentially futility. When additional interventions are included, simulations will be undertaken before beginning enrolment to the added interventions to understand the operating characteristics of the additional comparisons.

For phase II evaluations, we will use Bayesian hierarchical regression models with the specific error function adjusted to reflect the Phase II outcome of interest. Stopping rules for Phase II trials will be specified separately for each phase II intervention and evaluated as needed through simulation before beginning enrollment.

For pilot/feasibility evaluations, descriptive analyses will be conducted on protocol adherence and adverse event rates as specified in the intervention-specific appendix.

More details on analysis design are included in the master and domain SAPs and in the intervention-specific appendices.

### **Proposed Frequency of Analyses**

The primary statistical model will be updated at adaptive interim analyses performed every 3 months (and when at least 50 additional patients are enrolled), unless otherwise specified in the master SAP or domain SAP. All other analyses will be performed once a trial conclusion has been reached in a particular state.

Frequency of analyses are defined in the domain SAP.

### **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 Investigators.

#### **Data Sharing**

Please refer to PRACTICAL Master Protocol for details.

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