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Domain Protocol:  
**OZUHN-004-11**

**Inspiratory Muscle Training in Patients Receiving  
Ongoing Mechanical Ventilation: the IMPROV Pilot  
and Feasibility Randomized Clinical Trial**

Platform Master Protocol:  
OZUHN-004

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

**Protocol Version #:** 1.0

**Protocol Date:** 14-Aug-2025

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**Sponsor's Agreement to Domain Protocol #OZUHN-004-11 Version 1.0, Dated 14-Aug-2025  
and all current Intervention-Specific Appendices**

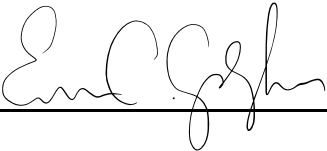
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Date of Approval:

15-Aug-2025

**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>	Inspiratory <b>M</b> uscle Training in <b>P</b> atients <b>R</b> eceiving <b>O</b> ngoing Mechanical Ventilation: the <b>I</b> MPROV Pilot and Feasibility Randomized Clinical Trial
<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 extracorporeal life support, with low normalized respiratory system elastance (&lt;2.5 cm H<sub>2</sub>O/(ml/kg predicted body weight));</li> <li>2. Intubated patients, not on extracorporeal life support, with high normalized respiratory system elastance (≥2.5 cm H<sub>2</sub>O/(ml/kg predicted body weight));</li> <li>3. Patients on extracorporeal life support.             <ul style="list-style-type: none"> <li>○ <i>Note: Only intubated extracorporeal support patients can be considered for this domain.</i></li> </ul> </li> </ol>
<b>Interventions</b>	<p>The interventions currently being studied as part of this domain are:</p> <ol style="list-style-type: none"> <li>1. <b>Intervention Group:</b> Early Routine IMT             <ul style="list-style-type: none"> <li>• 3 sets of 10 breaths, delivered each morning and evening using a device placed at the airway opening to apply an external resistive pressure load, until hospital discharge, death, or day 45 after randomization, whichever occurs first.</li> <li>• Device load will initially be set to 30% of the MIP.</li> <li>• Device load will be titrated upward (in increments of 5-10% of MIP, to a maximum of 60% of MIP) as needed to achieve a modified Borg dyspnea score of 7/10 or visible accessory muscle use.</li> </ul> </li> <li>2. <b>Control Group:</b> Usual Care             <ul style="list-style-type: none"> <li>• Patient to receive usual care</li> </ul> </li> </ol> <p><i>Details specific to each group can be found in the Trial Interventions section below.</i></p>
<b>Domain Primary Outcome</b>	<p>The primary outcome in this pilot and feasibility RCT is feasibility, defined as achieving all of the following endpoints:</p> <ol style="list-style-type: none"> <li>1. ≥0.75 patients randomized per site per month.</li> <li>2. ≥80% average protocol adherence across participants.</li> </ol>

	<p>3. ≥89% ascertainment of vital status and days alive and at home at day 90.</p> <p><i>Refer to the main body of the protocol for domain secondary outcomes.</i></p>
<b>Domain Design</b>	This domain is a multicentre, allocation-concealed RCT.
<b>Duration</b>	Recruitment period of 20 months, with a 6-month follow-up period, for a total study duration of approximately 26 months. If feasibility is demonstrated, patients enrolled in the pilot trial will be included as a vanguard cohort in the full-scale RCT.
<b>Planned Total Sample Size</b>	60 patients from approximately 4 Canadian sites.
<b>Inclusion/Exclusion Criteria</b>	Patients will be eligible for enrolment in this domain if they meet platform- and domain-specific eligibility criteria (refer to main body of protocol for the list of criteria).
<b>Randomization</b>	Patients will be randomized equally (1:1) to each group using undisclosed variable block sizes, stratified by site to account for variation in liberation practices between sites.
<b>Study Assessments</b>	Study assessments are depicted in the Study Plan.

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## LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Device Reaction
AHRF	Acute Hypoxemic Respiratory Failure
ARDS	Acute Respiratory Distress Syndrome
eCRF	eCase 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
FDO <sub>2</sub>	Optical Oxygen Gas Sensor
FiO <sub>2</sub>	Fraction of Inspired Oxygen
Hb	Hemoglobin
ICU	Intensive Care Unit
LAR	Legally Acceptable Representative
mMRC	Modified Medical Research Council
PAC	Pre-Anesthesia Check-up
PaCO <sub>2</sub>	Partial pressure of carbon dioxide
PaO <sub>2</sub>	Partial pressure of Oxygen
PAPm	Pulmonary Artery Pressure Measurement
PCWP	Pulmonary Capillary Wedge Pressure
PT	Physiotherapist
P/F	PaO <sub>2</sub> /FiO <sub>2</sub>
RCT	Randomized Clinical Trial

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RT	Respiratory Therapist
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBT	Spontaneous Breathing Trials
SDM	Substitute Decision Maker
S/F	SpO <sub>2</sub> /FiO <sub>2</sub>
SMO <sub>2</sub>	Saturation of Oxygen in Muscles
SOC	Standard of Care
SpO <sub>2</sub>	Oxygen Saturation by Pulse Oximetry

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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.

### Why is this study needed?

Approximately 15 million patients around the world require mechanical ventilation for acute respiratory failure every year (including approximately 100,000 Canadians)<sup>1</sup>. Over 25% of these patients experience difficulties being liberated from mechanical ventilation,<sup>2</sup> increasing the risks of prolonged intensive care unit (ICU) admission, nosocomial complications, and death<sup>3,4</sup>. Survivors of prolonged mechanical ventilation experience substantial long-term disability and impaired health-related quality of life<sup>4-7</sup>. Prolonged mechanical ventilation also markedly increases healthcare utilization and costs.

The diaphragm and other respiratory muscles determine a patient's ability to be liberated from the ventilator<sup>8</sup>. Over 60% of mechanically ventilated patients develop *de novo* respiratory muscle weakness by the time they reach the weaning phase<sup>8,9</sup>. This weakness develops as a consequence of sepsis, medication exposures, muscle disuse, critical illness polyneuropathy, or even excess muscular loading<sup>8</sup>. Reduced diaphragm muscle mass at the outset of mechanical ventilation predicts reduced survival and prolonged ventilation<sup>10</sup>. Diaphragm atrophy and respiratory muscle weakness are associated with increased risks of prolonged ventilation<sup>8,11-13</sup>, one-year mortality<sup>14</sup>, and functional disability at 5 years<sup>15</sup>. Persistent exertional dyspnea one year after moderate or severe Covid-19 infection was recently shown to result in part from diaphragm weakness<sup>16</sup>, highlighting the relevance of persistent respiratory muscle dysfunction after acute illness to long-term functional outcomes and quality of life.

***There are no established strategies for rehabilitating the respiratory muscles in mechanically ventilated patients.*** Restoring spontaneous respiratory effort may mitigate diaphragm atrophy and weakness, but the benefit and feasibility of this strategy remains uncertain<sup>17</sup>. Pharmacological therapies such as phosphodiesterase antagonists<sup>18</sup> or calcium sensitizer levosimendan<sup>19</sup> have not been shown to improve clinical outcomes. Phrenic nerve stimulation may enhance diaphragmatic strength, but its clinical benefit has not been established<sup>20</sup>. Current practice guidelines on mechanical ventilation do not recommend any specific strategies for respiratory muscle rehabilitation<sup>21-23</sup>.

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### **Rationale for the Intervention**

***Inspiratory muscle training is a simple and inexpensive intervention to enhance respiratory muscle function.*** Inspiratory muscle training (IMT) aims to rehabilitate the respiratory muscles, including the diaphragm and accessory muscles, through the transient application of increased inspiratory loading using a simple device. IMT increases respiratory muscle strength by several mechanisms including (1) stimulating muscle hypertrophy, (2) increasing proportion of type I fibers, (3) increasing type II fiber size within the external intercostal muscles, (4) attenuating the respiratory muscle metaboreflex (which reduces perfusion to limb muscles in the presence of elevated respiratory effort), and (5)<sup>24-27</sup> IMT enhances expiratory muscle function as reflected by increased maximal expiratory pressure<sup>28</sup>. The expiratory muscles play a crucial role in sustaining loaded breathing and coughing function<sup>29,30</sup>. Improved respiratory muscle strength and endurance enable patients to tolerate higher ventilatory loads. This may accelerate recovery, reduce recurrence of respiratory failure, reduce the duration of hospital stay, and improve functional status after hospital discharge.

***Previous trials have shown that IMT improves respiratory muscle function in patients undergoing invasive mechanical ventilation.*** In a 2018 systematic review of clinical trials examining IMT during mechanical ventilation (including 28 studies of 1,185 critically patients), we found that IMT was associated with improvements in both inspiratory muscle strength and expiratory muscle strength in comparison to control (usual care or sham IMT), although there was substantial clinical and methodological heterogeneity between studies<sup>28</sup>. Subsequently, three newer RCTs of ICU patients have been published. One RCT found that IMT increased maximal inspiratory pressure (MIP)<sup>26</sup>, another found no increase in MIP<sup>31</sup>, and the third reported improved accessory muscle oxygen utilization with IMT<sup>32</sup>. A 2025 systematic review of RCTs confirmed the findings of the 2018 review<sup>55</sup>; meta-analysis of 18 RCTs (N=716) found IMT was associated with higher maximal inspiratory pressure (very low certainty)<sup>55</sup>. This review also identified gaps in the IMT literature, including a lack of trials that continue IMT beyond ICU discharge.

***IMT appears to be safe and well-tolerated in mechanically ventilated patients.*** In our systematic review<sup>28</sup>, adverse events associated with IMT were rare and protocol adherence rates were generally high (11 studies, median 95% adherence). Adverse events have only been reported with IMT strategies employing prolonged periods of loading (i.e.  $\geq 5$  mins). By contrast, there were no reported adverse events in 7 trials that used brief IMT sessions (i.e. 10-20 breaths per set). A recent observational study found that IMT was feasible and well-tolerated in patients requiring at least 5 days of mechanical ventilation using an IMT strategy similar to the one to be employed in our trial (197 of the planned 242 IMT sessions successfully completed)<sup>33</sup>. In that study, all patients (n=13) reported that IMT was highly acceptable.

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***IMT improves patient-centered outcomes in other acute care settings.*** IMT is recommended by the American Society of Anesthesiologists (ASA) guidelines for “prehabilitation” prior to major cardiothoracic surgery based on evidence from clinical trials showing that pre-operative IMT reduces the probability of post-operative pulmonary complications<sup>34</sup>.

***Despite compelling evidence that IMT increases respiratory muscle strength in mechanically ventilated patients, the impact of IMT on patient-centered outcomes has not been established.*** Our systematic review found that IMT was associated with reduced duration of mechanical ventilation (4 days fewer, 95% CI 1-7 days fewer, 9 studies, total n=345 patients, very low certainty), but the results were no longer statistically significant when trials deemed to be at high risk of bias were excluded<sup>28</sup>. There was no important difference in survival to hospital discharge with IMT versus control, although the effect estimates were not sufficiently precise to exclude clinically relevant benefit or harm. One subsequent RCT reported a reduction in duration of ventilation (8 vs. 11 days, n=79 patients, p<0.01)<sup>31</sup>. Another RCT found that IMT improves dyspnea and quality of life (EQ-5D) after ICU discharge (n=70)<sup>35</sup>. Few studies have evaluated outcomes beyond hospitalization; one trial reported that IMT increased short-term quality of life 2 weeks after ICU discharge<sup>36</sup>.

***Use of IMT during mechanical ventilation varies widely around the world; it is rarely employed in Canada.*** IMT is not widely adopted as standard practice in most ICUs worldwide. ICU rehabilitation programs have paid relatively little attention to IMT, and the most recent guidelines<sup>37</sup> for ICU rehabilitation do not mention IMT. Survey data suggests 63% of ICU physiotherapists around the world occasionally incorporate IMT into their practice, but there was marked geographic variation<sup>38</sup>. Of Canadian physiotherapists surveyed (N=14), only 2 reported ever using IMT<sup>38</sup>. This variation in practice and limited use in Canada is likely attributable to the lack of a large, definitive RCT evaluating IMT in the ICU.

***Early routine IMT may attenuate ventilator complications.*** Following initiation of mechanical ventilation, rapid disuse atrophy of the diaphragm may develop<sup>44</sup>. This atrophy is associated with prolonged mechanical ventilation and a higher risk of nosocomial complications<sup>14</sup>. Exercising the diaphragm muscle with IMT as early as safely permissible during mechanical ventilation may attenuate this atrophy and restore diaphragm muscle mass and strength. On this basis, early intervention may be critical to the success of the intervention.

***A large high quality multicenter RCT is required to definitively establish whether IMT during and after mechanical ventilation can improve patient-centered outcomes for respiratory failure patients around the world.*** Before seeking funding for the full-scale RCT, we wish to examine trial feasibility in terms of recruitment rate, protocol adherence, and 90-day outcome ascertainment.

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### Domain Design

This domain is a pilot and feasibility RCT, designed as a pragmatic trial with reference to the CONSORT guidelines for pilot and feasibility RCTs<sup>42</sup>. It is a multicentre, allocation-concealed RCT. This domain will be conducted in compliance with the PRACTICAL Master Protocol, this domain protocol, applicable ICH-GCP guidelines and applicable regulatory requirements.

### RESEARCH OBJECTIVES

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

### Domain Primary Outcome

The primary outcome in this pilot and feasibility RCT is feasibility, defined as achieving all of the following endpoints (refer to the Statistical Analysis section for additional details):

1.  $\geq 0.75$  patients randomized per site per month.
2.  $\geq 80\%$  average protocol adherence across participants.
3.  $\geq 89\%$  ascertainment of vital status and days alive and at home at day 90.

### Domain Secondary Outcomes

**Clinical Outcomes:** We will collect clinical outcomes in anticipation of the future full-scale RCT, including:

- Number of reintubations up to tracheostomy during index hospitalization
- Occurrence of tracheostomy during index hospitalization
- Number of days from first SBT to disconnection from mechanical ventilation (final date of extubation or the first day of continuous tracheostomy mask for at least 24 hours, provided ventilator support is not resumed during the index ICU admission)
- Barotrauma during hospital admission (pneumothorax, pneumomediastinum, subcutaneous emphysema)
- Cardiac arrest during hospital admission
- Discharge disposition (rehabilitation facility, long-term care, home)
- 30 second sit to stand test at ICU discharge and hospital discharge
  - *Note: this test is to be done by blinded personnel, see study calendar for additional details*
- Health-related quality of life (EQ-5D-5L) at days 90 and 180
- Modified Medical Research Council (mMRC) Dyspnea Scale at ICU discharge and days 90 and 180
- Physical function (Activity Measure for Post-Acute Care) at ICU discharge and days 90 and 180
- Hospital free days to day 90
- Mortality at 90 days

**Physiological outcomes:** We will quantify the effect of therapy on respiratory muscle strength based on scheduled measurements of MIP in both the Early Routine IMT and Usual Care groups by the respiratory therapist (RT). Dyspnea will be measured daily using a Modified Borg Rating of Perceived Exertion scale and the respiratory distress observation scale<sup>49</sup> validated for mechanically ventilated patients. Diaphragm function will be measured at select sites at the same time as MIP measurements.

**Safety outcomes:** Investigators will be required to report serious adverse events (SAEs) that are plausibly related to the administration of IMT or other study procedure. Reported SAEs will be reviewed by the Sponsor and Domain Lead Investigators to confirm relatedness. SAEs and clinical outcomes (which also assess overall safety) will be reviewed by the data safety monitoring board (DSMB) according to the DSMB charter.

## **PATIENT POPULATION, ELIGIBILITY AND ENROLMENT**

### **Patient Population**

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

- Intubated patients, not on extracorporeal life support, with low normalized respiratory system elastance (<2.5 cm H<sub>2</sub>O/(ml/kg predicted body weight));
- Intubated patients, not on extracorporeal life support, with high normalized respiratory system elastance (≥2.5 cm H<sub>2</sub>O/(ml/kg predicted body weight));
- Patients on extracorporeal life support.
  - *Note: Only intubated extracorporeal support patients can be considered for this domain.*

All eligibility criteria will be assessed prior to patient enrollment. The eligibility criteria noted with an (\*) at the end below should be re-checked prior to randomization, as there can be some time between enrollment and randomization in this domain. This includes platform exclusion 6 and 7, and domain exclusion 4.

### **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)\* (*re-check right prior to randomization*)
7. The patient is being transitioned to a fully palliative philosophy of care\* (*re-check right prior to randomization*)

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

##### Domain Inclusion Criteria

1. Patients receiving invasive mechanical ventilation for AHRF as defined by the PRACTICAL platform trial criteria above.
2. Within 7 calendar days of intubation

##### Domain Exclusion Criteria

1. Patient is expected to be liberated from mechanical ventilation within 24 hours
2. Known or suspected chronic hypercapnic respiratory failure defined as  $\text{PaCO}_2 > 60$  mmHg in the outpatient setting
3. 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
4. Known pneumothorax or pneumomediastinum without chest tube placement sustained during current ICU admission\* (*re-confirm immediately prior to randomization*)
5. Patient is admitted primarily for acute brain injury (stroke, traumatic brain injury, etc.)
6. Previously diagnosed chronic neuromuscular disorder

7. Patient has an implantable cardiac defibrillator or pacemaker
8. Planned to be transferred to another hospital before ICU discharge
9. Already receiving a regimen of inspiratory muscle training using external resistive device or diaphragm neurostimulation

### **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 (specifying reason);
2. Refusal from attending physician (specifying reason);
3. Enrolment in a confounding study that does not allow co-enrolment;
4. Research coordinator or study material (e.g. device, study drug) not available
5. Intervention providers do not have capacity to enrol another participant

### **Patient Consent**

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

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 minimally invasive intervention, and previous trials report good tolerability and safety. If enrolled by deferred consent, participants will be followed to obtain consent once they regain capacity. All attempts to contact the SDM for study consent should be documented in the patient chart and/or site study binder.

It will be the responsibility of the local participating investigator to obtain the necessary clearance 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 ethics board approval and approved consent form must be sent to Ozmosis Research Inc. In settings where deferred consent is not approved, patient / SDM (as applicable for patients lacking decision making capacity) consent will be obtained prior to domain-specific enrolment and randomization and start of the study intervention.

### **Patient Enrolment and Randomization**

General enrolment 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 section above) will be

enrolled into the domain via REDCap. Enrolled patients will be randomized once they enter the weaning phase and meet the following readiness-to-wean criteria:

- Spontaneously triggering the ventilator in any mode of ventilation
- Hemodynamically stable (single vasopressor infusion, not requiring rapid upward titration)
- Fraction of inspired oxygen (FiO<sub>2</sub>) ≤0.5
- Positive end-expiratory pressure (PEEP) ≤10 cm H<sub>2</sub>O

Enrolled patients who are not randomized before death or discharge from ICU will have no further follow-up and will not be randomized.

Patients will be randomized equally (1:1) to each group using undisclosed variable block sizes, stratified by site to account for variation in liberation practices between sites.

## **STUDY PLAN**

### **Study Schedule**

Patients will be randomized to receive either Routine Early IMT or Usual Care (see additional details in the Patient Enrollment and Randomization section). If randomized to Routine Early IMT, the intervention should be initiated as soon as possible after randomization, after the patient meets tolerability criteria for training.

Data will be collected until hospital discharge, the end of the intervention, or day 45 (whichever comes first). Patients will be followed to hospital discharge to ascertain vital status at discharge.

Patients will be contacted remotely at 3-months and 6-months post randomization to ascertain vital status, physical function (Activity Measure for Post-Acute Care), modified mMRC dyspnea scale and quality of life (EQ-5D-5L).

**Study Schema**

Required Procedures*	Baseline & Enrollment	Randomization (Day 0)	Daily: During 45 day intervention period – while in the ICU	Daily: During 45 day intervention period – after ICU discharge while in hospital	ICU Discharge	Hospital Discharge	Day 90	6 months (180 days) from Randomization
Window	N/A	N/A	N/A	N/A	N/A	N/A	+ 30 days	-22/+60 days
Consent <sup>1</sup>	X							
Demographics <sup>2</sup>	X							
Medical History <sup>3</sup>	X							
Vitals <sup>4</sup>	X	X <sup>17</sup>	X					
Enrollment	X							
Randomization <sup>14</sup>		X						
Resting oxygen saturation and oxygen requirements	X	X <sup>17</sup>	X					
Hemodynamics <sup>5</sup>	X	X <sup>17</sup>	X					
Respiratory Data <sup>6</sup>	X	X <sup>17</sup>	X					
Mobility Assessment <sup>16</sup>	X	X <sup>17</sup>	X (every 4 days (+/- 1 day) on the same days as MIP)	X (every 4 days (+/- 1 day) on the same days as MIP)				
Hematology <sup>7</sup>	X	X <sup>17</sup>	X					
Biochemistry <sup>8</sup>	X	X <sup>17</sup>	X					
IMT Tolerability Assessments & readiness-to-wean criteria <sup>9</sup> ( <b>Early Routine IMT patients only</b> )			X (2x daily, prior to IMT training)	X (2x daily, prior to IMT training)				
MIP <sup>10</sup> ( <b>All patients</b> )		X	X (every 4 days (+/- 1 day) – preferably in the morning)	X (every 4 days (+/- 1 day) – preferably in the morning)				
Modified Borg Rating of Perceived Exertion Scale (dyspnea) <sup>18</sup> ( <b>All patients</b> )		X	X (every day – preferably in the morning)	X (every day – preferably in the morning)				
IMT Intervention (for patients randomized to this group) <sup>11</sup>			X (2x daily, morning and evening)	X (2x daily, morning and evening)				
<b>Select sites:</b> Diaphragm Ultrasound ( <b>All patients</b> )			X (every 4 days (+/-1 day) at the same time as MIP)	X (every 4 days (+/-1 day) at the same time as MIP)				
Blinded 30 second sit to stand test <sup>15</sup>					X	X		
Vital Status <sup>12</sup>							X	X
Dyspnea (mMRC), and physical function (Activity Measure for Post-Acute Care)					X		X	X
Quality of life (EQ-5D-5L)							X	X
Serious Adverse Events <sup>13</sup>			X	X				

Concomitant medications	X		X	X				
<p>1 Consent should be done prior to any study specific assessments (unless a deferred consent model is being used) and according to site institutional timelines.</p> <p>2 Demographics including race, ethnicity, age, sex, height, and weight.</p> <p>3 Hospital and ICU admission information, diagnosis/cause of AHRF, APACHE IV, Clinical Frailty Scale, Charlson Comorbidity Index, and Glasgow Coma Scale. Patient self-reported gender will be collected if available in the patient chart.</p> <p>4 Vitals include temperature, heart rate, respiratory rate, and blood pressure.</p> <p>5 Hemodynamics include BP and, if available, PAPm, PAC, PCWP, SmvO2.</p> <p>6 Respiratory data, sedation and weaning will be monitored as part of SOC at participating site.</p> <p>7 Hematology reporting on Hgb, 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.</p> <p>8 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.</p> <p>9 IMT tolerability to assess respiratory distress (respiratory distress observation scale) or cardiopulmonary instability will occur prior to each IMT training. Readiness to wean criteria must be met prior to IMT training.</p> <p>10 Maximum inspiratory pressure (MIP) will be measured to assess load (“dose”) as needed to achieve a Modified Borg Rating of Perceived Exertion score of 7/10 or visible accessory muscle use. MIP will be measured by Marini maneuver in incapacitated patients. MIP will be re-measured every 4 days (+/- 1 day) and device load will be adjusted as needed. MIP measurements should occur before IMT training.</p> <p>11 IMT will be applied for 3 sets of 10 breaths, delivered each morning and evening. Respiratory therapist (RT) or physical therapist (PT) will reconnect patients to ventilator for 1-2 minutes of rest between each set. See ‘Trial Interventions’ section below for additional details.</p> <p>12 Vital status will be ascertained remotely via telephone at 90 days and 6-months post-randomization.</p> <p>13 SAEs will be reported for the duration of the patient receiving either Early Routine IMT or Usual Care.</p> <p>14 Patients can be randomized once they enter the weaning phase and meet readiness-to-wean criteria.</p> <p>15 The 30 second sit to stand test is to be completed by a site team member blinded to what group the patient was randomized to.</p> <p>16 Mobility assessments will be completed at the same time as MIP assessments during the intervention period. The ICU Mobility Scale will be used for mobility assessment in the ICU, and the Ward Mobility Assessment scale will be used if the patient continues the intervention in the ward.</p> <p>17 As there may be some time in between baseline/enrolment and randomization in this domain, these assessments done at baseline/enrolment should be repeated on the day of randomization if the patient is being randomized 1 or more calendar days after baseline/enrolment.</p> <p>18 Modified Borg Rating of Perceived Exertion score (dyspnea) will be done every day before IMT training. It should occur for a second time each day at peak during training.</p> <p><b>* All blue fields are standard-of-care assessments and data being collected for study purposes.</b></p>								

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## TRIAL INTERVENTIONS

The intervention and control arm protocols are outlined below, along with details regarding co-intervention management recommendations.

### **Intervention Group:** Early Routine IMT

IMT will be delivered using a device placed at the airway opening to apply an external resistive pressure load. IMT devices can be connected to the patient's endotracheal tube or tracheostomy via a filter and a connector. IMT will be delivered by an RT or PT. IMT tolerability and cardiopulmonary stability will be assessed prior to training. If patients deteriorate and no longer meet readiness-to-wean criteria, IMT will be paused until the patient recovers and again meets readiness-to-wean criteria. If a patient is extubated and then reintubated, IMT will continue when the patient meets readiness-to-wean criteria. The same procedures will be employed in patients with a tracheostomy.

IMT load ("dose") will be selected in a similar manner to previous RCTs where IMT was shown to be feasible and physiologically effective<sup>28</sup>. First, MIP will be measured. The device load will initially be set to 30% of the MIP<sup>28,39</sup>. To ensure an adequate training load, the device load will be titrated upward (in increments of 5-10% of MIP, to a maximum of 60% of MIP) as needed to achieve a modified Borg dyspnea score of 7/10 or visible accessory muscle use, as previously described in other trials<sup>32,35</sup>.

Additionally, MIP will be re-measured every 4 days (+/- 1 day) and the device load will be adjusted as needed to ensure that it remains  $\geq 30\%$  of the most recently measured MIP as MIP may progressively increase over time.

Before each training session in intubated patients, ventilator support will be briefly reduced to CPAP 0 cm H<sub>2</sub>O for 30 seconds to confirm that the patient can physiologically tolerate IMT. If no distress develops then the IMT session will proceed. IMT sessions should be conducted at least 1 hour before or after the daily spontaneous breathing trial to allow for adequate respiratory muscle rest.

IMT will be applied for 3 sets of 10 breaths, delivered each morning and evening. Between each set, the RT or PT will reconnect the patient to the ventilator for 1-2 minutes of rest<sup>39,40</sup>. IMT sessions will be timed so as not to interfere with other routine care processes.

The session will not commence if the patient has respiratory distress; an uncontrolled tachyarrhythmia; labile blood pressure requiring rapid changes in vasopressors; fever ( $>39^{\circ}$ ); or new sepsis (defined as new diagnosis of sepsis, not yet showing signs of clinical resolution in response to interventions)<sup>26</sup>. Sessions may resume when hemodynamics have stabilized (rapid

changes in vasopressors no longer required), high grade fever is resolved (temperature <39 degrees) and sepsis is resolving (as per clinical judgment based on signs such as pressor requirements decreasing, no longer requiring fluid resuscitation, and/or white blood count decreasing).

A training session may be aborted if patients experience significant dyspnea, cardiopulmonary instability, respiratory distress, or become agitated or refuse to continue<sup>41</sup>. Patients who are incapacitated by delirium or sedation, but have adequate respiratory drive (airway occlusion pressure, P0.1  $\geq$  2 cm H<sub>2</sub>O) will undergo IMT sessions.

After extubation or tracheostomy decannulation, participants will perform IMT using the same device via a mouthpiece. When the patient is discharged to the ward, a trained RT or PT will visit the patient twice per day to supervise each IMT session. MIP will continue to be measured every 4 days (+/- 1 day) to confirm adequacy of training load and load will be titrated upward as tolerated per the targets outlined above. IMT will be discontinued when the patient is discharged from hospital or at 45days from randomization, whichever occurs first.

**Control Group: Usual Care**

Patients will be treated according to usual care. Use of any IMT in the control group is permitted only if it is part of standard of care at the participating site ICU.

**Cross Overs**

Since IMT is not standard of care and is rarely applied in Canadian ICUs, crossovers will not be permitted. None of the participating sites routinely employ IMT in clinical management. Patients may discontinue the intervention, but all will be analyzed according to their randomized treatment assignment under the 'intention to treat' principle.

**Premature Withdrawal/Discontinuation Criteria**

Treating physicians may choose to discontinue the intervention at their discretion, including any situation that occurs such that continued participation in the study would not be in the best interest of the participant.

Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of the intervention regardless of the reason (e.g. patient or physician request, or adverse event), does not constitute study withdrawal. Patient follow-up data will still be collected as planned and analyzed as intent to treat unless the participant withdraws consent for continued follow-up.

Participants that are withdrawn at any time after randomization will not be replaced.

**Co-Intervention Management**

Patients in both groups will receive usual care in terms of mechanical ventilation, sedation, physical therapy, and weaning, as dictated by local site practice in the ICU and on the hospital ward.

<b>Co-Intervention Management</b>	
Weaning: assessment for readiness-to-wean criteria	Readiness to wean will be assessed on a daily basis. Assessment for readiness to wean will include the following standard criteria: <ul style="list-style-type: none"> <li>• FiO<sub>2</sub> ≤0.5</li> <li>• PEEP ≤10 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)	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.
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.

**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 (AEs) will not be collected for this study and only related serious adverse events (SAEs) will be collected (see section below).

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### 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 IMT or other study procedure

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

### 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](mailto: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 24 hours after receipt of the SAE form at Ozmosis.

#### Reporting SAEs to Local Research Ethics Boards

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 for the duration the patient is receiving the IMT.

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, they become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented in the eCRF.

### **STATISTICAL ANALYSES**

Additional details are included in the statistical analysis plan (SAP). Any deviations from the finalized SAP will be described in the final reports.

### **Sample Size**

We plan to enroll until 60 patients are randomized into the pilot and feasibility RCT. This sample

size will allow us to estimate the randomization rate with a precision of  $\pm 0.25$  patients/site/month, assuming a randomization rate of 1 patient/site/month. The lower bound of this confidence interval coheres with our threshold of 0.75 patients/site/month defining feasibility. This sample size will also allow us to measure protocol adherence and refine strategies to improve implementation based on barriers identified over a reasonable time period (16-20 months). A sample size of 60 randomized patients will enable us to measure protocol adherence with reasonable precision at  $\pm 8\%$  (assuming 90% adherence similar to adherence in previous RCTs, yielding a confidence interval of 82% to 98%). The lower bound of this confidence interval coheres with our threshold of  $\geq 80\%$  defining feasibility (see 2.16). Finally, this sample size will allow us to estimate the 90-day outcome ascertainment rate with precision of  $\pm 5\%$  (assuming 95% ascertainment similar to previous RCTs in the field, yielding a confidence interval of 89% to 100%). The lower bound of this interval coheres with our threshold of  $\geq 89\%$  defining feasibility.

The future full-scale RCT will employ a Bayesian adaptive design powered to detect an improvement in days alive and out of hospital. Preliminary estimates suggest that the maximum sample size required to obtain 80% power in the full-scale RCT would be 1300 patients. This maximum sample size was calculated without adaptations for early stopping, which will be incorporated in the full-scale RCT to decrease the number of required patients. Comprehensive simulations of the design to fully justify sample size will be included in a future funding application for the full-scale RCT.

Risk of ascertainment bias will be mitigated by selecting an objectively defined, clinically indisputable primary endpoint for the future definitive RCT.

### **Primary outcome**

The primary outcome in this pilot and feasibility RCT is feasibility, defined as achieving ALL of the following endpoints:

1.  **$\geq 0.75$  patients randomized per site per month.** This minimum threshold for recruitment rate across 35 centres for 48 months would recruit 1260 patients, which will be sufficient once interim assessments are included in the full-scale trial design.. Randomization rate will be computed as the total number of patients randomized divided by the sum of total months of active recruitment for all participating sites. Randomization rate will be evaluated by recording the number of patients enrolled and the number of active enrolling sites on a weekly basis. Challenges to recruitment will be identified by reviewing screening logs and direct communication with site investigators and research coordinators.
2.  **$\geq 80\%$  average protocol adherence across participants.** Protocol adherence will be quantified as the proportion of scheduled IMT sessions during hospitalization when IMT is delivered. The number of scheduled IMT sessions (the “denominator”) will be computed as the number of twice daily sessions when the patient met criteria to undergo IMT from the

time of initiating IMT to the end of the intervention period as defined above. IMT will be counted as “delivered” in a given session (the “numerator”) if the patient completes at least one set of 10 breaths of IMT. Each session is recorded on the device and the supervising RT or PT will document the outcome of each IMT session in a training diary. Reasons for missed sessions will be recorded to improve training methods and to determine whether lack of adherence is related to lack of tolerability (unable to participate in IMT) or lack of acceptability (unwilling to participate in IMT).

3. **≥89% ascertainment of vital status and hospital-free days at day 90.** This will be the key primary endpoint in the full-scale trial; a high rate of ascertainment is critical for valid results. Reasons for missing data will be assessed by enquiry with site research coordinators.

### **Evaluation of Safety**

Safety will be analysed for each intervention based on the clinical and safety endpoints defined in the PRACTICAL Master Protocol and this domain protocol.

### **Proposed Type of Analyses**

We will present binary data as proportions with 95% confidence intervals. We will present continuous data as means (standard deviations), or medians (interquartile ranges), as appropriate. Comparison of all clinical endpoints between groups will be provided only to the DSMB at the completion of the pilot RCT for assessment of safety. In the future full-scale RCT, days alive and out of hospital at day 90 will be analyzed as a continuous endpoint using a proportional odds model to compare between groups. Patients who die before day 90 will be assigned a value of 0.

***Sex and gender considerations:*** Sex-specific differences in protocol adherence will be assessed. The effect of the intervention on respiratory muscle strength will be stratified by sex to assess for potential sex-specific differences in baseline respiratory muscle strength and in treatment effect on respiratory muscle function. Use of hormones will be collected in the database, and patient self-reported gender will be collected if available in the patient chart.

***Subgroup analyses:*** We will conduct exploratory analyses of protocol adherence rates and the effect of the intervention on respiratory muscle strength across subgroups defined by age, sex, centre, and duration of mechanical ventilation prior to randomization (<7 days or ≥7 days, a recognized threshold for risk of prolonged ventilation)<sup>15</sup>.

### **Proposed Frequency of Analyses**

Data including safety outcomes will be analyzed upon completion of the pilot RCT. SAEs will be reported to the principal investigators in real-time during the trial. SAEs and clinical outcomes will be reviewed by the DSMB as per the charter.

## **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 the University Health Network (UHN) Policy for Principal Investigators.

### **Data Sharing**

Please refer to PRACTICAL Master Protocol for details.

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