Cover Letter

Official Title of the study: Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation: The PROMIZING Study

NCT number: NCT02447692

Document: Clinical Study Protocol

Date of document: 01 December 2019

Clinical Study Protocol

Proportional Assist Ventilation for
Minimizing the Duration of Mechanical Ventilation:
The PROMIZING Study

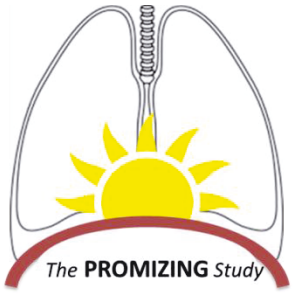
Co-Principal Sponsor-Investigators: Dr. Karen Bosma and Dr. Laurent Brochard

In Collaboration with: The Canadian Critical Care Trials Group (CCCTG)
Réseau Européen de Recherche en Ventilation Artificielle (REVA)

Study Type Randomized Controlled Trial

Funding Entity: CIHR-industry-partnered operating grant (2014-2018)
CIHR project grant (2019-2022)

Version Date: December 1, 2019
Version Number: 5.0



Signature Page for Sponsor

Study Title:	**Pro**portional Assist Ventilation for Mini**mizing** the Duration of Mechanical Ventilation: The PROMIZING Study
Version:	5.0
Version Date:	December 1, 2019

Approved by the following:

September 11, 2020

Dr. Karen Bosma, MD, FRCPC
Co-Principal Sponsor-Investigator

Date
(please print)

September 11, 2020

Dr. Laurent Brochard, MD
Co-Principal Sponsor-Investigator

Date
(please print)

Signature Page for Investigator

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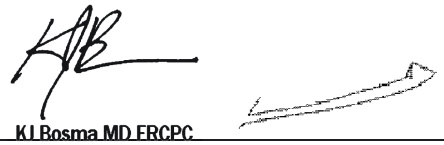
I have read and understand this protocol and concur with the study design. I agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP) and relevant local regulatory requirements that govern the conduct of clinical research.



September 11, 2020

Investigator Name (please print)	Signature	Date (please print)

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1.0 Key Study Contacts

Sponsor and Co-Principal Investigators	Dr. Karen Bosma, Dr. Laurent Brochard
Coordinating Centre	Lawson Health Research Institute, London, Ontario (contracts, trial insurance, financial disbursements) Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute, Toronto (trial coordination, study monitoring and data management)
Executive Steering Committee	Dr. Karen Bosma, Dr. Laurent Brochard, Dr. Karen Burns, Dr. Claudio Martin, Dr. Jordi Mancebo, Dr. Yoanna Skrobik, AHRC Statistician (Kevin Thorpe), AHRC Project Manager (Stephanie DeMasi , Sarah Douglas, Shristi Bhatia, Nicole Cooke)
Data Safety Monitoring Board Members	Dr. Taylor Thompson (Chair) Dr. Maureen Meade Dr. Jean-Daniel Chiche

2.0 Synopsis

Short Title	The PROMIZING Study
Study Title	Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation: The PROMIZING Study
Trial Design	Multi-centre, open-label RCT
Study Participants	Adult patients receiving MV for acute respiratory failure who are ventilated in A/C mode, ready to be maintained with partial ventilatory support (PSV) but not yet ready for extubation (not yet ready for an SBT or failed an SBT)
Investigational Product/Device	Proportional Assist Ventilation with load-adjustable gain factors (PAV+), PB 840 or 980 ventilator, (Covidien LP, a Medtronic company)
Investigational Intervention	Study participants will be randomized to one of two arms. The control is the standard of care PSV ventilation strategy, designed to adjust the level of support according to usual clinical parameters. The intervention is a PAV+ ventilation strategy, designed to adjust the level of support (gain) to target a predefined range of respiratory muscle pressure.
Planned Sample Size	558(279 each PAV+ and PSV) is the minimum planned sample size.
Treatment/Follow up Duration	The expected duration of patient participation is approximately 21-90 days, including screening and follow-up procedures and depends on the length of time the patient remains on MV in the ICU. Patients will be followed with daily data collection until they remain free of invasive mechanical ventilation for 7 days. Date of live ICU discharge or ICU death, live hospital discharge or hospital death will also be recorded for each randomized patient. Vital status will be determined at 14, 21, 28 and 90 days post randomization.
Planned Study Period	Planned enrolment period is Sept 2016- Sept 2021. The study will continue to enrol patients until we have complete data on participants containing required number of events for analysis. Patient follow up is targeted to end December 2021.
Primary Outcome	Time from randomization to successful liberation from invasive mechanical ventilation

Secondary Outcomes	(i) Ventilator-free days at day 14, 21,28 days post randomization, (ii) Time from randomization to live ICU discharge (up to day 90), (iii) Time from randomization to live hospital discharge (up to day 90), (iv) Mortality, measured as ICU mortality; hospital mortality; 14, 21, 28, and 90 day mortality (v) Weaning Progress, measured as time from randomization to: first SBT; first successful SBT; first extubation. (vi) Weaning Difficulties, measured as the number of patients failing first SBT or first extubation attempt and requiring up to 7 days to extubate (difficult weaning group/ group 2); failing first SBT or first extubation attempt and requiring more than 7 days to extubate (prolonged weaning group/ group 3), (vii) Weaning Complications, measured as the number of patients: requiring non-invasive ventilation post-extubation; ventilated more than 7 days post randomization, ventilated more than 21 days from time of intubation (prolonged MV group); receiving tracheostomy post randomization, requiring reintubation (up to 7d after planned extubation) (viii) Tolerance of modes, measured as number of patients ever requiring A/C mode post randomization; number of patient-days requiring A/C mode post randomization, (ix) Cumulative dose of narcotics (converted to morphine equivalents); benzodiazepines (converted to midazolam equivalents); propofol, and dexmedetomidine (x) Number of patients and number of patient-days receiving any antipsychotic medication (xi) Sensitivity analyses of primary and secondary outcomes defining "successful extubation" as "48 hours without reintubation" (xii) Sensitivity analyses of primary and secondary outcomes assigning a value of 0 ventilator-free days to any participant who dies at any time during the study period
A priori Subgroup Analyses	(i) duration of MV prior to randomization greater than 5 days (ii) failed SBT vs. failed CPAP 0 trial vs. failed weaning criteria prior to randomization (iii) failed extubation prior to randomization (iv) mild, moderate, severe frailty

3.0 Abbreviations

A/C	Assist/Control
AE	Adverse Event
AHRC	Applied Health Research Centre
CC	Coordinating Centre
CMV	Controlled Mechanical Ventilation
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
EC	Executive Committee
eCRF	Electronic Case Report Form
ICU	Intensive Care Unit
MV	Mechanical Ventilation
PAV+	Proportional Assist Ventilation with load-adjustable gain factors
PEEP	Positive End-Expiratory Pressure
PSV	Pressure Support Ventilation
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SDM	Substitute Decision Maker
VFD	Ventilator-Free Day

4.0 Introduction

4.1 Study Conduct

This study will be conducted in compliance with the protocol approved by Research Ethics Boards (REBs) and according to ICH Good Clinical Practice standards.

The study has been registered on www.clinicaltrials.gov prior to participant enrolment (NCT02447692).

4.2 Background

4.2.1 Study Rationale

Patients with acute respiratory failure require invasive mechanical ventilation (MV) to support their work of breathing and provide adequate gas exchange until they recover from their acute illness. Upon initiation of invasive MV, the goal is to wean and liberate patients from MV as soon as they can manage breathing unsupported. However, MV itself may induce respiratory muscle weakness,[1-3] patient-ventilator dyssynchrony,[4;5] and necessitate the administration of sedative drugs, all of which have been associated with a prolonged duration of dependence on MV. Prolonged dependence on MV contributes to increased patient complication rates, intensive care unit (ICU) length of stay, and is associated with increased mortality.[6;7] Therefore, a major goal in caring for patients with acute respiratory failure is to reduce the duration of weaning and increase the number of patients successfully liberated from MV[8]. Avoidance of respiratory muscle atrophy, patient-ventilator dyssynchrony, and heavy sedation are potential means of achieving this goal, although this has not been definitively proven. Theoretically, respiratory muscle atrophy and patient-ventilator dyssynchrony should be minimized if the level of ventilator assistance is adjusted to target normal or reasonable levels of respiratory effort.[5;9;10]

Proportional assist ventilation with load-adjustable gain factors (PAV+) is a mode of mechanical ventilation which delivers assistance to breathe in proportion to the patient's effort. The proportional assistance, called the gain, can be adjusted by the clinician to maintain the patient's respiratory effort or workload within a reasonable range. This is the only mode of ventilation which allows for measurement and targeting of a specific range of respiratory muscle activity by the patient. Pressure support ventilation (PSV) is a mode of ventilation which is considered the current standard of care for assisting breathing of patients during the recovery phase of acute respiratory failure. Several studies have shown short term advantages of PAV over PSV, including improved patient-ventilator synchronization, improved adaptability to changes in patient effort, and improved sleep quality.[5;11-14]

The objective of this multi-centre randomized controlled trial is to determine if, for patients with acute respiratory failure, ventilation with PAV+ will result in a shorter duration of time spent on mechanical ventilation than ventilation with PSV.

4.3 Description of Intervention

The intervention is proportional assist ventilation with load-adjustable gain factors:
PAV+™, Puritan Bennett™ 840 or 980 ventilator (Covidien LP, a Medtronic company, Boulder, USA). Sites will confirm prior to participation that the correct device and settings are available.

This mode of ventilation (PAV+) and this device (Puritan Bennett™ 840 or 980 ventilator) are approved for use in all countries with participating centres:

Health Canada Information: First Issue Date: 19Sep2005, Device name: 840 VENTILATOR SYSTEM - PAV UPGRADE KIT, Device Identifiers are 4-078204-00 and 4-078206-00

Europe Information: Issue Date: 19Jan2005, Release/Change per ECO-R151570, Device name: 840 VENTILATOR SYSTEM, SOFTWARE OPTIONS AND 806 COMPRESSOR, 840 Ventilator CE Marked Software Options , Device Identifiers for PAV+ Option are 4-078195-00 (Spanish), 4-078196-00 (French), 4-078198-00 (Italian) and Device Identifiers for PAV+ Upgrade are 4-078205-00 (Spanish), 4-078206-00 (French) and 4-078208-00 (Italian).

Argentina Information: First Issue Date: 06June2011, Device name: SISTEMA DE VENTILACION 840-KIT DE ACTUALIZACION PAV, Device Identifier is 4-078205-00.

Proportional assist ventilation with load-adjustable gain factors (PAV+) is a unique ventilatory mode that delivers assistance in proportion to patient effort, thereby allowing for titration of the balance between respiratory muscle capacity and load, and ensuring that the respiratory muscles are utilized throughout the breath and not just for triggering the breath. In PAV+ mode, the ventilator measures the instantaneous flow and volume generated by the patient and calculates the instantaneous pressure needed to overcome the elastic and resistive pressures. This is achieved by performing automated and repeated measurements of respiratory system compliance and resistance. This automatic adjustment has been implemented recently, justifying the acronym PAV"+". Assistance (or gain) from the ventilator, which is adjusted by the clinician, is expressed as a percentage of the total pressure needed to inflate the respiratory system. Because of its working principles, PAV+ is the only mode which enables estimation of the pressure generated by the respiratory muscles. This can be made at the bedside from the values of the gain and the driving inspiratory airway pressure.

Patients will be randomized to either the PAV+ Ventilation Strategy, using a Puritan Bennett 840™ ventilator equipped with PAV+™, (intervention arm) or the PSV Ventilation Strategy, using any ventilator equipped with PSV (control arm).

In the PAV+ strategy, the level of support (gain) will be adjusted to target a respiratory muscle pressure within normal range. In the PSV strategy, the level of support will be adjusted according to usual clinical parameters (See Appendix C and Appendix D respectively). In both arms, patients developing respiratory distress or clinical instability will be changed to A/C mode and reassessed within 24 hours for criteria to resume PAV+ or PSV according to treatment allocation.

4.4 Clinical Data to Date

4.4.1 Clinical Data

Several physiological studies have shown important potential advantages of PAV compared to PSV including improved synchronization adaptation to changes in ventilator demand and improved sleep quality during short term ventilation. A relatively large single centre RCT but limited to a 48 hour period showed that significantly more patients could be ventilated with PAV+ than with PSV (94.4% vs 71.0%, p<0.001) [15] and a pilot single centre RCT by Bosma showed a two day reduction in ICU length of stay with PAV+ compared to PSV (median[IQR] 7.3[5.2-11.4] days on PAV+ vs. 12.4[7.5-30.8] days on PSV, p=0.03.[16]

4.4.2 Safety Data

In the study by Bosma, there were no adverse events (pneumothorax, arrhythmia or death) resulting from the study interventions (n=54 patients) [16]. As a safety mechanism, studies of PAV+ have utilized "intolerance criteria" for switching to another mode of ventilation, typically utilizing assist-control as the default mode for

patients who meet pre-specified criteria for respiratory distress despite optimization of PAV+ or PSV. As such, there are no reported cases of patients experiencing an adverse event as a physiological consequence of excessive work of breathing or instability due to PAV+.

The studies of PAV+ have demonstrated that PAV+ is generally well tolerated in patients meeting enrolment criteria for these studies. In the study by Bosma, patients tolerated PAV+ an average of 18.1 ± 5.9 hours/day and tolerated PSV 18.8 ± 5.0 hours/day in the PSV group (p=0.64). Over the duration of the study, total time spent on PAV+ ranged from 18 to 565 hours, or 10 to 100% of the study period (mean 75.3 ± 24.6%), and in the PSV group, time spent on PSV ranged from 19 to 743 hours, or 28 to 100% of the study period (mean 78.4 ± 21.0%).[16] A study by Xirouchaki et al., which examined tolerance of PAV+ and PSV for 48 hours in critically ill patients, found successful tolerance in 89% and 78% of patients on these respective modes.[15] A pilot study by Carteaux et al. study found one of 53 patients to be intolerant to PAV+; median time spent on PAV+ was 3 days [IQR 1-5] for the remaining 98% of patients who tolerated PAV+ for some duration of the study period.[17]

4.4.3 Pilot Data for this study design

The design of this trial is based upon two pilot studies. The eligibility criteria, method of recruitment, staged enrolment process, randomization to two equivalent ventilation strategies, criteria to initiate and method of weaning were piloted by Bosma and coworkers in the single centre pilot RCT (n=54). [16] The ventilation algorithm to adjust PAV+ gain to maintain respiratory muscle workload within the normal range was piloted by Brochard and colleagues in a multi-centre study (n=52). [17] Most of the centres participating in The PROMIZING Study were involved in one of these two studies. Both studies demonstrated safety, feasibility, and compliance with study protocol.

5.0 Study Objectives

The primary objective of this study is to determine if, for patients with acute respiratory failure, ventilation with PAV+, instituted early in the recovery phase and set to maintain a workload of breathing within the normal range, will result in a shorter duration of time spent on mechanical ventilation than ventilation with PSV.

The secondary objective of the study is to determine if other clinically important outcome measures are better with PAV+ as compared to PSV.

6.0 Study Design

6.1 General Design

This clinical study is a multi-centre open-label, RCT.

6.2 Primary Study Endpoints

The primary outcome is time from randomization to successful liberation from invasive mechanical ventilation.

6.3 Secondary Study Endpoints

The secondary outcome measures are:

(i) Ventilator-free days at day 14, 21 and 28 post randomization,
(ii) Time from randomization to live ICU discharge (up to day 90),
(iii) Time from randomization to live hospital discharge (up to day 90),
(iv) Mortality, measured as ICU mortality; hospital mortality; 14, 21, 28, and 90 day mortality
(v) Weaning Progress, measured as time from randomization to: first SBT; first successful SBT; first extubation.

(vi) Weaning Difficulties, measured as the number of patients failing first SBT or first extubation attempt and requiring up to 7 days to extubate (difficult weaning group/group 2); failing first SBT or first extubation attempt and requiring more than 7 days to extubate (prolonged weaning group/group 3),
(vii) Weaning Complications, measured as the number of patients: requiring non-invasive ventilation post-extubation; ventilated more than 7 days post randomization, ventilated more than 21 days from time of intubation (prolonged MV group); receiving tracheostomy post-randomization, requiring re-intubation (up to 7d after planned extubation)
(viii) Tolerance of modes, measured as number of patients ever requiring A/C mode post randomization; number of patient-days requiring A/C mode post randomization,
(ix) Cumulative dose of narcotics (converted to morphine equivalents); benzodiazepines (converted to midazolam equivalents); propofol, and dexmedetomidine
(x) Number of patients and number of patient-days receiving any antipsychotic medication
(xi) Sensitivity analyses of primary and secondary outcomes defining "successful extubation" as "48 hours without reintubation"
(xii) Sensitivity analyses of primary and secondary outcomes assigning a value of 0 ventilator-free days to any participant who dies at any time during the study period

The subgroups for a priori subgroup analyses are:
(i) Duration of mechanical ventilation prior to randomization greater than 5 days
(ii) Failed SBT vs. failed CPAP 0 trial vs. failed weaning criteria prior to randomization
(iii) Failed extubation prior to randomization
(iv) Mild, moderate, severe frailty

6.4 Primary Safety Endpoints

Safety analyses will be based on all participants who were randomized to either intervention or control arm, and received either PAV+ or PSV according to study protocol.
Safety will be assessed by evaluating and comparing:

(i) Frequency and incidence of reported serious adverse events between intervention and control groups.
(ii) Mortality difference between intervention and control groups

7.0 Participant Identification

7.1 General Characteristics of the Proposed Participant Population

The participant population will be adult patients receiving invasive MV for acute respiratory failure for at least 24 hours, who are ventilated in A/C mode and ready to be maintained with partial ventilatory support (PSV) but not yet ready for extubation (not yet ready for an SBT or failed an SBT). In summary, we aim to enrol patients as they enter the recovery phase of their illness (see Figure 1 below, which summarizes the MV modes and the goals of MV at each phase of critical illness).

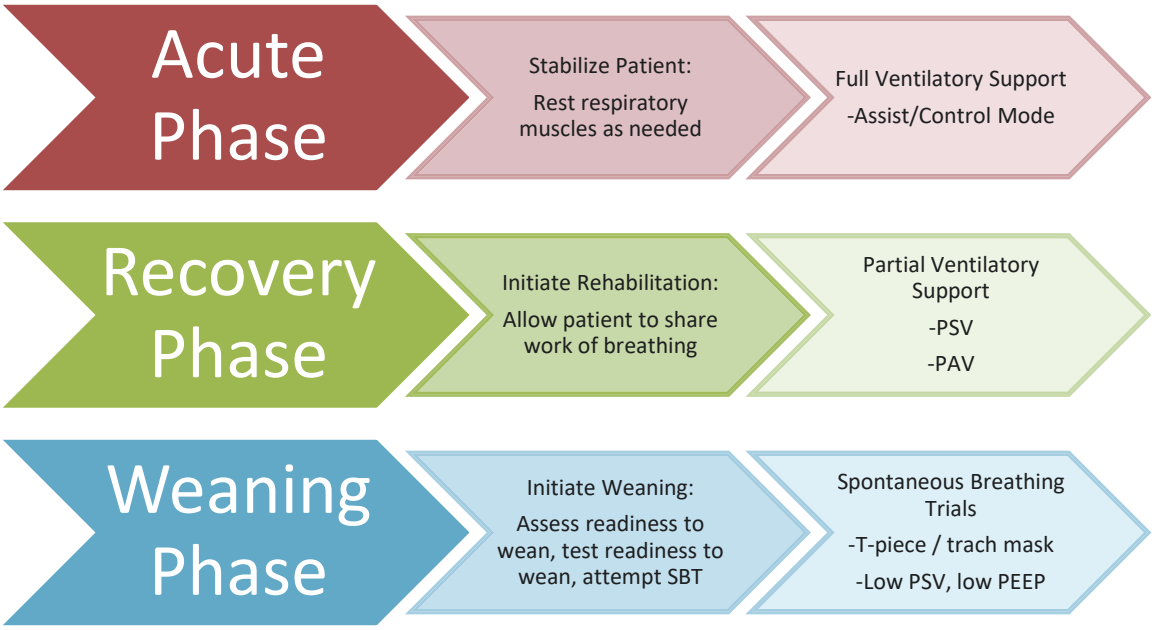

Figure 1

7.2 Anticipated Number of Research Participants

558 (279 each PAV+ and PSV)

7.3 Eligibility Criteria

A staged enrolment process will be used to identify patients eligible to be enrolled and randomized in the study. At each stage of the enrolment process, a patient must meet inclusion criteria and not meet exclusion criteria in order to pass. To progress to the next stage, patients must continue to pass criteria from the prior stages. After enrolment, there are also specific tests to perform (with pass/fail criteria) to determine eligibility to be randomized. The five stages (sets of criteria and tests) are:

A. Screening Criteria
B. Enrolment Criteria and Obtaining Consent
C. Pressure Support Trial Criteria and the Pressure Support Trial
D. Weaning Criteria and the CPAP Trial and the Spontaneous Breathing Trial (SBT)
E. Randomization Criteria

The first stage of enrolment is called (A) Screening. Patients are screened while they are in the acute phase of their respiratory failure.
To be considered eligible for Screening, a participant must satisfy each of the following inclusion criteria:

A. Screening Inclusion Criteria:

A1.	Age ≥18 years
A2.	Intubated and receiving any mode of invasive MV ≥24 hours

All patients admitted to a participating site ICU during the study period meeting the above screening inclusion criteria will be entered into a screening log and followed until they satisfy all inclusion criteria, are enrolled and randomized, or meet an exclusion criterion and exit the screening/enrolment process.

A participant will be ineligible for participation in this study and will be counted as a "screen failure" if he or she satisfies any one or more of the following exclusion criteria:

A. Screening Exclusion Criteria:

A3	Anticipating withdrawal of life support and/or shift to palliation as the goal of care
A4	Severe central neurologic disorder (eg. Hemorrhage, stroke, tumour) causing elevated intracranial pressure, or impaired control of breathing, or requiring specific ventilator adjustments (i.e. To attain specific CO_2 target) or requiring neurosurgical intervention
A5	Known or suspected severe or progressive neuromuscular disorder likely to result in prolonged or chronic ventilator dependence (eg. Guillain-Barré syndrome, Myasthenia Gravis, ALS, MS, high spinal cord injury, kyphoscoliosis, or other restrictive disorder) (Note that obesity hypoventilation syndrome that may be managed with nocturnal non-invasive ventilation is NOT an exclusion under A5)
A6	Severe COPD: Baseline daytime hypercapnea (pCO_2> 50 mmHg) OR GOLD 4 airflow limitation (FEV_1<30% predicted) OR MRC class 4 symptoms ("I am too breathless to leave the house" OR "I am breathless when dressing")
A7	Broncho-pleural fistula
A8	Tracheostomy present at ICU admission for the purpose of chronic or prolonged mechanical ventilation (>21 days). (Note that a patient who was endotracheally intubated for acute respiratory failure and received a tracheostomy during their ICU admission, prior to enrolment, is not excluded under A8).
A9	Current enrolment in a confounding study, as assessed by the steering committee
A10	Previous randomization in the PROMIZING Study
A11	Severe, end-stage, irreversible respiratory or cardiac disease (e.g. interstitial lung disease, pulmonary fibrosis, cardiomyopathy, valvulopathy) likely to result in prolonged or chronic ventilator dependence /unlikely to wean from mechanical ventilation [Note: patients who are candidates for intervention to treat the underlying respiratory/cardiac disease (e.g. lung transplant, heart transplant, cardiac surgery) may be re-evaluated once intervention is complete and they no longer meet criteria A11.]

Patients satisfying all of the Screening inclusion criteria and none of the Screening exclusion criteria will be classified as "eligible" and will be followed daily until they meet **all** of the following criteria to be approached for consent. This is the second stage, called **(B) Enrolment and Obtaining Consent**, and it occurs as the patient approaches the "recovery phase" of his/her critical illness, as defined by passing the "Enrolment Inclusion Criteria" listed below.

B. Enrolment Inclusion Criteria:

B1.	Ability or potential ability to trigger ventilator breaths (i.e. not receiving neuromuscular blockade).
B2.	On Assist/Control volume-cycled ventilation: Technically satisfactory plateau pressure ≤ 30 cm H_2O (see Operations Manual) **OR** On Assist/Control pressure-controlled ventilation or similar mode: Pressure control plus PEEP ≤ 30 cm H_2O **OR** On Pressure Support ventilation: Pressure support plus PEEP ≤ 30 cm H_2O **OR** On Proportional Assist ventilation: PAV gain <85%
B3.	PaO_2 ≥ 60 mmHg or SpO_2 ≥ 90% on FiO_2 ≤ 0.60 and PEEP ≤ 15 cm H_2O
B4.	Metabolic disorders corrected: pH ≥7.32

B5.	Stable hemodynamic status: stable or decreasing doses of vasopressors for ≥6 hours
B6.	Anticipate ongoing need for ventilation >24 hours

B. Enrolment Deferral Criteria:

B11	Plan to extubate/discontinue mechanical ventilation within <24 hours (Reassess within 24 hours)
B12	Patient currently on ECMO (Reassess patient once off ECMO)
C9.	Plan for surgery or complex procedure that will require full ventilation to be done prior to attempting extubation (e.g. Procedure requiring neuromuscular blockade and/or heavy sedation, such that patient would be apneic, or not be able to trigger ventilator) (Reassess after surgery/procedure complete)

B. Enrolment Exclusion Criteria:

B7	Extubated
B8	Died
B9	Patient has met enrolment inclusion criteria B1-B5 AND has tolerated pressure support of 0-20 cm H_2O or proportional assist ventilation of 0-85% for ≥24 consecutive hours (including time on CPAP, t-piece, or tracheostomy mask). (Note (1):that it is acceptable to include a patient who has been tried on pressure support or proportional assist ventilation but has required pressures >20 cmH_2O or assistance >85% or has required return to A/C ventilation within the 24 hour time window; Note (2): B9 does not apply to patients on ECMO.)
B10	Patient transferred to a non-participating centre

For patients meeting all A. Screening and B. Enrolment Criteria, the treating ICU physician will be asked to provide verbal consent to (i) enroll the patient, (ii) proceed with standardized tests to determine eligibility for randomization, (iii) randomize the patient if eligibility criteria are met, and (iv) enable the research team to approach the patient/SDM for consent. The standardized tests are part of routine clinical care and include a trial of pressure support and screening for a trial of spontaneous breathing. **If the ICU physician plans to extubate the patient within 24 hours, enrolment may be deferred** until the next calendar day and the patient reassessed to determine if the patient has passed an SBT or is extubated. If the patient is not extubated by the following morning and/or fails an SBT, the patient should then be enrolled and proceed to randomization criteria. Patients on ECMO are not eligible for enrolment until off ECMO.

Eligible patients or their substitute decision makers (SDMs) will be approached for consent to participate in the clinical trial as soon as possible after the treating physician has provided verbal consent**.** The patient/SDM **will be provided a Letter of Information and asked to provide written informed consent** to proceed with (i) randomization if eligibility criteria are met during standardized tests and (ii) use of data collected from time of enrolment through to study termination. Obtaining informed consent prior to randomization is preferred; however, randomization of eligible patients may proceed with deferred consent if the patient is incapable and no SDM can be contacted despite at least two documented attempts. (See section 14.3 for further information on obtaining informed consent).

Physicians may institute pressure support at any time according to clinical discretion and usual care. The pressure support trial is intended for cases where the patient has not yet been placed on pressure support ≤20 cm H_2O (above PEEP) by the treating physician. The Pressure Support Trial (PST) is the first test in a series of

tests to determine if a patient is ready for randomization. Prior to initiating the PST, the treating physician must approve proceeding with the standardized tests and randomization if eligible.

C. Pressure Support Trial Inclusion Criteria:

C2.	Upon review of Screening and Enrolment criteria (A and B), the patient still passes.
C3.	Treating physician has provided verbal consent to proceed with standardized tests and randomization if eligibility criteria are met

C. Pressure Support Trial Deferral Criteria

C6.	High dose vasopressor requirements (i.e. epinephrine or norepinephrine >0.5 μg/kg/min or equivalent) OR patient requiring an increase in dose of vasopressor within 6 hrs
C7.	Active cardiac ischemia (dynamic ST changes on monitor or ECG within 6 hours)
C8.	Unstable arrhythmias (HR>140 or <50) with clinical signs of low cardiac output or or SBP<80 mmHg
C10.	Receiving a "strict lung protective" ventilation strategy for ARDS (eg. Order on chart to keep Vt ≤6 mL/kg PBW)

C. Pressure Support Trial Exclusion Criteria

C12.	Treating physician has declined consent

Patients already on pressure support of ≤20 cm H_2O (above PEEP) for >30 minutes will be considered to have passed the Pressure Support Trial and will move on to the next stage of enrolment.

Patients on A/C ventilation (or similar mode) or PAV or on pressure support >20 cmH_2O will be assessed daily and will undergo a daily Pressure Support Trial, provided none of the Pressure Support Deferral Criteria are present.

In the presence of any of the Pressure Support Trial Deferral Criteria, the pressure support trial may be deferred up to 24 hours. Patients should be reassessed at least daily and can proceed to the Pressure Support trial after discussion with the site PI, provided the patient still passes Criteria C and no deferral criteria are present. If deferral criteria remain present, the Pressure Support Trial may be deferred on a daily basis after daily reassessment.

Once no deferral criteria are present, patients proceed as follows:

- Patients already on pressure support of ≤20 cm H_2O for >30 minutes will be considered to have passed the Pressure Support Trial and will move on to the next stage of enrolment
- Patients on A/C mode or similar mode or PAV or on pressure support >20 cmH_2O will undergo the Pressure Support Trial

The Pressure Support Trial (PST) is conducted as follows: patients will be placed on PSV 5-20 cmH_2O (above PEEP) for at least 30 minutes under direct clinical observation, at the same PEEP and FiO_2 settings they were on prior to the PST. The maximum settings allowed for the PST are a pressure support of 20 cmH_2O or PS+PEEP=30 cmH_2O. The PST can be stopped at any time for prolonged apnea, Respiratory Distress or Clinical Instability (see definitions below). At the end of 30-120 minutes, an arterial blood gas will be drawn.

Patients fail the Pressure Support Trial if they develop prolonged apnea, Respiratory Distress, Clinical Instability (see definitions below), or require PS >20 cmH_2O, PS + PEEP > 30 cmH_2O, or require FiO_2>60% to maintain SpO_2>90%, or respiratory acidosis with pH <7.32 despite maximum PS of 20 cmH_2O. The PST is terminated immediately upon reaching any failure criteria. Patients who fail a PST are returned to their previous ventilator settings or settings that restore respiratory comfort. Patients who pass the PST may remain on pressure support 5-20 cmH_2O.

Definition of Respiratory Distress

At least 2 of the following:

1. SpO_2 <90%
2. Sustained (>5 min) respiratory rate >35 b/min
3. Heart rate >140 b/min or a sustained (>5 min) increase of 20% from baseline
4. Systolic blood pressure >180 or <80 mmHg and/or systolic BP changes >30% from baseline
5. Increased anxiety
6. Use of accessory muscles
7. Complaint of dyspnea
8. Diaphoresis

Definition of Clinical Instability

Any 1 of the following:

1. Unstable hemodynamic status (SBP<80 mmHg) with or without vasoactive drug
2. Vasopressor requirements >0.5 μg/kg/min epinephrine/norepinephrine or equivalent
3. Active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram
4. Unstable arrhythmias (HR >140 or <50) with clinical signs of low cardiac output or SBP<80 mmHg
5. Uncontrolled hypertension (SBP>180 mmHg)
6. Abrupt decrease in the level of consciousness (RASS -4 or -5 or SAS 1 or 2)
7. Dangerous agitation (RASS +4 or +3 or SAS 7)
8. Metabolic (or mixed) acidosis with pH <7.32
9. Emergency situation that merits return to full ventilation (A/C) according to best clinical judgement

Patients who fail the Pressure Support Trial will be re-evaluated daily, and, provided that they still pass Criteria C and no deferral criteria are present, will undergo a Pressure Support Trial at least once daily. Patients who pass the Pressure Support Trial will proceed to the next stage to be evaluated for (D**) Weaning Criteria.**

D. Weaning Criteria:

D1.	SpO_2≥ 90% on FiO_2 ≤0.40 and PEEP ≤8 cmH_2O
D2.	pH ≥7.32
D3.	Vasopressor requirements no higher than norepinephrine 0.1 μg/kg/min or equivalent.

Patients must meet all 3 of the Weaning Criteria to pass. Patients who do NOT meet all 3 of the Weaning Criteria FAIL the Weaning Criteria and proceed to the final stage, (E). Patients who meet all the Weaning Criteria PASS the Weaning Criteria and proceed to a screening test using a ZERO CPAP trial. .

The ZERO CPAP Trial screening test is performed as follows:

1. With patient's ETT connected to the ventilator circuit, change the ventilator mode to CPAP at 0 cmH_2O and FiO_2 0.40

2. Monitor patient for 2 min
3. On the ventilator, assess the f/Vt ratio after 1-2 minutes at 0 cmH_2O CPAP:
4. FAIL: If the f/Vt >100, or SpO2<90% or Clinical Instability, patient has failed the ZERO CPAP trial and will not proceed to SBT. Resume ventilation with the ventilator settings used immediately prior to the ZERO CPAP test
5. PASS: If the f/Vt is ≤100, and SpO2 ≥90%, proceed to SBT

Patients who fail the ZERO CPAP trial will proceed to the final stage (E). Patients who pass the ZERO CPAP trial will proceed to a Spontaneous Breathing Trial (SBT).

The SBT is performed as follows:

1. Disconnect endotracheal tube from ventilator circuit and place patients on T-piece* with FiO_2 0.40. (For patients with tracheostomy, place patients on tracheostomy mask trial with FiO_2 0.40)
2. Monitor patient for 30-120 minutes:
3. FAIL/ SBT Termination: Terminate the SBT and return patient to prior ventilator settings if at any time one of the following occur:
    a. Respiratory Distress
    b. Clinical Instability
    c. Increased somnolence with elevated pCO_2 and/or pH<7.32
    d. Desaturation with SpO_2 <90% on FiO_2 0.40

**for the purposes of this study, the Sponsor considers SBT performed with patients connected to ventilator on flow-by with CPAP of 0 cmH_2O and FiO_2 0.40 to be equivalent to SBT performed on T-piece with FiO_2 0.40.*

Following the SBT, proceed to the final stage (E).

In the final stage (E), patients will be considered eligible for randomization if the following criteria are met.

E. Randomization Inclusion Criteria

C1.	Patient/SDM has provided consent OR Plan to obtain deferred consent as Patient incapable and no SDM available to provide consent within the randomization window
E1.	Upon review of Criteria A, B, and C, the patient still passes and the patient has passed the PST.
E2.	Does not meet Weaning Criteria OR Fails the ZERO CPAP Trial OR Fails the SBT

E. Randomization Exclusion Criteria:

B9	Patient has met enrolment inclusion criteria B1-B5 AND has tolerated pressure support of 0-20 cm H_2O or proportional assist ventilation of 0-85% ≥24 consecutive hours (including time on CPAP, t-piece, or tracheostomy mask). Note (1): It is acceptable to include a patient who has been tried on pressure support or proportional assist ventilation but has required pressures >20 cmH_2O or assistance >85% or has required return to A/C ventilation within the 24 hour time window; Note (2): B9 does not apply to patients while on ECMO
C4.	Patient/SDM has declined consent
C5.	Patient incapable and no SDM available to provide consent (not applicable if plan to obtain deferred consent)

E3.	Passed SBT on t-piece, FiO_2 0.40 for 30-120 minutes
E4.	Approval withdrawn (by physician or patient/SDM)

Note: there may be patients who pass the SBT but remain intubated for other reasons (airway protection, pulmonary toilet). Such patients should be reassessed within 24 hrs and may be reconsidered for randomization if their ventilatory requirements increase and/or they fail subsequent SBTs, provided they are not excluded based on criteria B9, above.

Patients who pass the Randomization criteria will proceed to randomization according to the method described in section 10.3.1. Randomization should occur as soon as possible after meeting Randomization Criteria and must occur within the randomization window. The randomization window opens when the patient passes a Pressure Support Trial (tolerates 30-120 minutes of PSV ≤20 cmH_2O and closes once a patient tolerates 24 consecutive hours of PSV ≤20 cmH_2O while meeting inclusion criteria B1-B5.

Figures depicting the Enrolment and Randomization Algorithm and Eligibility Criteria are located in Appendix A and B, respectively.

8.0 Study Procedures

The Ventilator Algorithms for PAV+ and PSV are located in Appendices C and D, respectively.

8.1 Ventilation Strategy: Proportional Assist Ventilation (PAV+)

8.1.1 General Approach: PAV+

Patients randomized to the PAV+ group are treated with PAV+ on a PB840 or PB980 ventilator (Covidien LP, a Medtronic company). Only PAV+™ (Covidien LP, a Medtronic company) will be used. Proportional Pressure Support on the Draeger Evita 4 Ventilator may NOT be used. Patients will follow the PAV+ algorithm both day and night.

In the PAV+ strategy, the level of support (%Support or "gain") will be adjusted to target a respiratory muscle pressure within normal range, without evidence of respiratory distress. At a minimum, patients will be assessed at least every 8 hours (or according to standard practice in each ICU if patient assessments are routinely performed more frequently than every 8 hours) to determine if adjustments need to be made to maintain respiratory muscle pressure (Pmus) within the target range. The Pmus target range is 5-10 cmH_2O, the clinical targets are a RR <35 and Vte > 5mL/kg PBW, while maintaining a pH in the range of 7.32-7.47. FiO_2 and PEEP are titrated clinically to maintain a SpO_2 90-96%. Patients developing clinical instability or respiratory distress that cannot be alleviated on PAV+ will be changed to A/C mode and reassessed within 24 hours for criteria to resume PAV+.

8.1.2 Initiating PAV+

Ensure the patient's correct Body Weight is entered and displayed on the ventilator screen. Although the ventilator monitor uses the term "Ideal Body Weight" (IBW), enter the "Predicted Body Weight" (PBW) calculated as follows:

PBW (kg) Men = 50 +0.91(Height[cm] – 152.4)
PBW (kg) Women = 45.5 +0.91(Height[cm]-152.4)

(The ventilator "IBW" is preset at 50 kg, so if that is not the Predicted Body Weight of the patient, turn the ventilator off and restart as for a new patient, select "Invasive" and adjust IBW as needed). Set the correct type and size of tube, eg. Tube type=ET (endotracheal), Tube I.D. = diameter of endotracheal tube, in mm, and type of humidification.

Guidelines for the administration of sedation and analgesia are provided, (see section 8.4.1) with a strong recommendation for using the lowest possible dose of sedating drugs in both arms (or none at all) as required to keep the patient calm and cooperative, avoiding over-sedation whenever possible. Over-sedation during PAV+ may result in respiratory acidosis so patients emerging from heavy sedation must be closely monitored and light sedation or no sedation should be targeted.

Prior to initiating PAV+, record the patient's respiratory rate, heart rate, blood pressure, tidal volume (Vte) and minute ventilation (VE). The baseline vital signs will be needed to determine if the patient is developing signs of respiratory distress. The baseline Vt and VE required to maintain a normal pH (>7.32) will be used to monitor if the patient is developing a respiratory acidosis or respiratory alkalosis.

PAV+ is initiated at the following settings:

- PAV+ %Support (gain) : start at 70%
- Inspiratory trigger: per clinician
- Expiratory trigger (Esens): 3 L/min (default)
- PEEP: start at previous level patient was on prior to randomization
- FiO_2: at lowest level required to maintain SpO_2 90-96%

Alarm settings:

- Ppeak (Paw max): 40 cmH_2O
- RR max: 38 b/min
- Vte max: 12 mL/kg IBW
- Vte min: 0 mL
- VE max: 20 L/min
- VE min: 5 L/min
- Apnea setting: 20 s

8.1.3 Adjusting PAV+

Adjustments are made to the ventilator settings immediately (5 minutes) after initiating PAV+ and at a minimum every 8 hours thereafter (or according to standard practice in each ICU if patient assessments are routinely performed more frequently than every 8 hours). If pH on arterial blood gas (ABG) is outside of the target range of 7.32-7.47, serial adjustments should be made immediately post ABG and ABG's repeated every 30-60 minutes post ventilator adjustments until pH is back within the target range or patient meets criteria to switch to A/C.

The goal is to support patients' breathing while maintaining an adequate amount of respiratory muscle activity to avoid atrophy of the diaphragm, or help to rehabilitate an already weakened diaphragm. The target range for respiratory muscle pressure (Pmus) is 5-10 cmH_2O, while maintaining a pH of 7.32-7.47. Some patients may be able to be supported within this target range comfortably, while others may not be able to generate a Pmus of 5 cmH_2O without developing clinical signs of respiratory distress. Therefore, adjustments are made to the ventilator settings according to whether Respiratory Distress is present or absent. FiO_2 and PEEP are titrated clinically to maintain a SpO_2 90-96%. PEEP is set by the clinician according to clinical judgment at the bedside, but may be titrated taking into account clinically suspected intrinsic PEEP (PEEPi) and the ventilator automated

measurements of dynamic compliance (C_{PAV}) as described below. FiO_2 should be set and adjusted to the **lowest level required** to maintain SpO_2 90-96%. Patients developing prolonged apnea, respiratory distress or clinical instability will be changed to A/C mode and reassessed within 24 hours for criteria to resume PAV+.

The study protocol **defines Respiratory Distress as the presence of 2 or more** of the following signs:

Definition of Respiratory Distress

At least 2 of the following:

1. SpO_2 <90%
2. Sustained (>5 min) respiratory rate >35 b/min
3. Heart rate >140 b/min or a sustained (>5 min) increase of 20% from baseline
4. Systolic blood pressure >180 or <80 mmHg and/or systolic BP changes >30% from baseline
5. Increased anxiety
6. Use of accessory muscles
7. Complaint of dyspnea
8. Diaphoresis

Immediately after initiating PAV+, and at least every 8 hours (minimum, see above) while on PAV+, determine if adjustments need to be made to the ventilator settings. Adjustments are made according to whether Respiratory Distress is present or absent.

Adjusting PAV+ if Respiratory Distress is present:

If Respiratory Distress is present, complete the following steps:

1. Assess PAV+ Resistance (R) and Compliance (C) measurements. If R_{TOT} is high (> 10 $cmH_2O/L/s$), treat any apparent cause of high resistance (eg. Secretions, bronchospasm). If C_{PAV} is low (<35 mL/cmH_2O), treat any apparent cause of decreased compliance (e.g., Pulmonary edema). Treat any cause of metabolic acidosis, if present.
2. Increase PEEP in steps of 2 cmH_2O until compliance no longer increases.
3. Increase FiO_2 as needed to keep SpO_2 90-96%
4. Increase PAV+ %Support in steps of 10% until respiratory distress resolves and pH>7.32
5. Switch to A/C mode if one or more of the following occur during steps 1-4:
    a. PAV+ %Support >85%
    b. FiO_2 >60% required to maintain SpO_2 ≥90%
    c. Clinical Instability
    d. Requiring neuromuscular blockade and/or sedation such that patient is no longer able to trigger the ventilator

Definition of Clinical Instability

Any 1 of the following:

1. Unstable hemodynamic status (SBP<80 mmHg) with or without vasoactive drug
2. Vasopressor requirements >0.5 μg/kg/min epinephrine/norepinephrine or equivalent
3. Active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram)
4. Unstable arrhythmias (HR >140 or <50 with clinical signs of low cardiac output or SBP<80 mmHg)
5. Uncontrolled hypertension (SBP>180 mmHg)
6. Abrupt decrease in the level of consciousness (RASS -4 or -5 or SAS 1 or 2)
7. Dangerous agitation (RASS +4 or +3 or SAS 7)
8. Metabolic (or mixed) acidosis with pH <7.32

9. Emergency situation that merits return to full ventilation (A/C) according to best clinical judgement

Patients requiring A/C ventilation should be reassessed within 24 hours for Criteria for Switching from A/C to PAV.

Adjusting PAV+ if Respiratory Distress is Absent:

If respiratory distress is absent, complete the following steps for adjusting %Support, PEEP and FiO_2:

1. Adjust the PEEP according to clinical judgment at the bedside. When determining best PEEP level for the patient, consider the following:
   a. Does increasing/decreasing the extrinsic (set) PEEP reduce the intrinsic PEEP (PEEPi)?
   b. Does increasing/decreasing the extrinsic (set) PEEP improve compliance (C_{PAV})?
   c. Choose the set PEEP which results in the lowest PEEPi and highest C_{PAV}
2. Adjust the FiO_2 to the lowest level required to maintain SpO_2 >90% (and in the range 90-96%).
3. Using the Pmus Calculator card, calculate the Pmus, peak as follows:
   a. Observe the Peak airway pressure (Paw,peak) over 3-5 breaths and subtract the PEEP from the Paw, peak to obtain the Delta Paw (Delta Paw=Paw,peak – PEEP)
   b. Line up the Delta Paw number with the white arrow by sliding the inner card of the Pmus calculator
   c. The Pmus peak is the number displayed in the Pmus calculator window corresponding to the % Support set on the ventilator
4. Adjust the % Support according to the Pmus,peak as follows:
   a. Pmus,peak <5 cmH_2O: Decrease gain in steps of 5-10% until Pmus,peak is in the target range of 5-10 cmH_2O; If Respiratory Distress develops while decreasing the gain, follow the algorithm for Respiratory Distress
   b. Pmus, peak >10 cmH_2O: Increase the gain in steps of 5-10% until Pmus,peak is in the target range of 5-10 cmH_2O; If Respiratory Distress develops while increasing the gain, follow the algorithm for "Respiratory Distress"
   c. Pmus, peak 5-10 cmH_2O: Target range achieved: no adjustments required unless:
      i. RR <12 or >35 or Vte<5 or >10 mL/kg PBW, obtain arterial blood gas (ABG):
         1. If ABG demonstrates a respiratory alkalemia, treat any apparent cause of hyperventilation, (eg. pain, anxiety, metabolic acidosis), then decrease gain in steps of 5-10% until Vte <8 mL/kg PBW OR pH<7.47
         2. If ABG demonstrates a respiratory acidemia OR respiratory distress develops:
            a. Increase PEEP in steps of 2 cmH_2O until compliance no longer increases.
            b. Increase FiO2 as needed to keep SpO2>90%
            c. Increase PAV %Support in steps of 10% until pH>7.32 and respiratory distress resolves
            d. Switch to A/C mode if one or more of the following occur during steps a-c:
               i. PAV %Support >85%
               ii. FiO_2 >60% required to maintain SpO_2 ≥90%
               iii. **Clinical Instability** (see definition)
               iv. Requiring neuromuscular blockade and/or sedation such that patient is no longer able to trigger the ventilator

8.1.4 Resuming PAV+ after A/C ventilation

Patients switched to A/C ventilation as per study protocol should be reassessed within 24 hours, and at least once daily thereafter, for **Criteria for Switching from A/C to PAV+. These are the minimum criteria for switching from A/C back to PAV+.** If all of the criteria for switching from A/C to PAV are present, the patient **must** be tried on

PAV+: follow the Initiation of PAV+ protocol, with initial and subsequent adjustments made to PAV+ settings according to the Algorithm for Adjusting PAV+. After a trial of PAV+, patients may be switched back to A/C mode if they meet criteria according to the PAV+ ventilation strategy algorithm. The **Criteria for Switching from A/C to PAV+** are as follows:

Criteria for Switching from A/C to PAV+:

1. Able to trigger ventilator breaths
2. On assist/control with the following settings:
    a. AC/VC: Pplat≤30cmH_2O with Vt 6-8 ml/kg OR
    b. AC/PC: PC+PEEP≤30cmH_2O
3. PaO_2 ≥ 60 mmHg or SpO_2 ≥ 90% on FiO_2≤ 0.60 and PEEP ≤ 15 cm H_2O
4. Metabolic disorders corrected; pH >7.32
5. Stable hemodynamic status: stable or decreasing doses of vasopressors for ≥6 hours
6. Absence of **Clinical Instability** (see definition, above)

8.2 Ventilation Strategy: Pressure Support Ventilation (PSV)

8.2.1 General Approach: PSV

Patients randomized to the PSV group are treated with PSV on any ventilator capable of delivering standard pressure support mode. The make and model of the ventilator used to deliver PSV will be recorded as part of the data set. Patients will follow the PSV algorithm both day and night.

In the PSV strategy, the level of pressure support will be adjusted according to routine clinical parameters, targeting a comfortable respiratory rate and tidal volume. At a minimum, patients will be assessed at least every 8 hours (or according to standard practice in each ICU if patient assessments are routinely performed more frequently than every 8 hours) to determine if adjustments need to be made to maintain patient comfort, and ensure adequate ventilation and oxygenation. The clinical targets are a RR 12-35 and Vte 5-10 mL/kg PBW, while maintaining a pH in the range of 7.32-7.47. FiO_2 and PEEP are titrated clinically to maintain a SpO_2 90-96%. PEEP is set by the clinician according to clinical judgment at the bedside. FiO_2 should be set and adjusted to the **lowest level** required to maintain SpO_2 90-96%. Patients developing respiratory distress or clinical instability will be changed to A/C mode and reassessed within 24 hours for criteria to resume PSV.

8.2.2 Initiating PSV

Guidelines for the administration of sedation and analgesia are provided, (see section 8.4.1) with a strong recommendation for using the lowest possible dose of sedating drugs in both arms (or none at all) as required to keep the patient calm and cooperative, avoiding over-sedation whenever possible.

Prior to initiating PSV, record the patient's respiratory rate, heart rate, blood pressure, tidal volume (Vte) and minute ventilation (VE). The baseline vital signs will be needed to determine if the patient is developing signs of respiratory distress. The baseline Vt and VE required to maintain a normal pH (>7.32) will be used to monitor if the patient is developing a respiratory acidosis or respiratory alkalosis.

PSV is initiated at the following settings:

- PS level: start at 10-20 cmH_2O (or start at level patient was on prior to randomization)
- Inspiratory trigger: per clinician
- Expiratory trigger: 25% of peak inspiratory flow (default)
- PEEP: start at previous level patient was on prior to randomization
- FiO_2: start at previous level patient was on prior to randomization

Alarm settings:

- Ppeak (Paw max): Per clinician
- RR max: 38 b/min
- Vte max: 12 mL/kg IBW
- Vte min: 0 mL
- VE max: 20 L/min
- VE min: 5 L/min
- Apnea setting: 20 s

8.2.3 Adjusting PSV

Adjustments are made to ventilator settings immediately (5 minutes) after initiating PSV and at a minimum every 8 hours thereafter (minimum, see above). If pH on arterial blood gas (ABG) is outside of the target range of 7.32-7.47, serial adjustments should be made immediately post ABG and ABG's repeated every 30-60 minutes post ventilator adjustments until pH is back within the target range or patient meets criteria to switch to A/C.

The algorithm to adjust pressure support is based on usual clinical parameters, keeping the RR ≤35 breaths/minute and Vte 5-10 mL/kg PBW, while maintaining a pH of 7.32-7.47. Some patients may be able to be supported within this target range comfortably on pressure support, while others may not be able to tolerate pressure support without developing clinical signs of respiratory distress. Therefore, adjustments are made to the ventilator settings according to whether Respiratory Distress is present or absent.

The study protocol **defines Respiratory Distress as the presence of 2 or more** of the following signs:

Definition of Respiratory Distress

At least 2 of the following:

1. SpO2 <90%
2. Sustained (>5 min) respiratory rate >35 b/min
3. Heart rate >140 b/min or a sustained (>5 min) increase of 20% from baseline
4. Systolic blood pressure >180 or <80 mmHg and/or systolic BP changes >30% from baseline
5. Increased anxiety
6. Use of accessory muscles
7. Complaint of dyspnea
8. Diaphoresis

Immediately after initiating PSV, and at least every 8 hours (minimum, see above) while on PSV, determine if adjustments need to be made to the ventilator settings.

Adjusting PSV if Respiratory Distress is present:

If Respiratory Distress is present, complete the following steps:

1. Treat any apparent cause of respiratory distress (eg. Secretions, bronchospasm, pulmonary edema, metabolic acidosis)
2. Increase pressure support in steps of 2-3 cmH_2O until respiratory distress resolves and pH>7.32
3. Increase PEEP and/or FiO_2 as needed to keep SpO_2 90-96%
4. Switch to A/C mode if one or more of the following occur during steps 1-3:
    a. Pressure support >20 cmH_2O
    b. Pressure support + PEEP > 30 cmH_2O

c. FiO_2 >60% required to maintain SpO_2 ≥90%
d. Clinical Instability
e. Requiring neuromuscular blockade and/or sedation such that patient is no longer able to trigger the ventilator

Definition of Clinical Instability
Any 1 of the following:

1. Unstable hemodynamic status (SBP<80 mmHg) with or without vasoactive drug
2. Vasopressor requirements >0.5 μg/kg/min epinephrine/norepinephrine or equivalent
3. Active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram)
4. Unstable arrhythmias (HR >140 or <50) with clinical signs of low cardiac output or SBP<80 mmHg)
5. Uncontrolled hypertension (SBP>180 mmHg)
6. Abrupt decrease in the level of consciousness (RASS -4 or -5 or SAS 1 or 2)
7. Dangerous agitation (RASS +4 or +3 or SAS 7)
8. Metabolic (or mixed) acidosis with pH <7.32
9. Emergency situation that merits return to full ventilation (A/C) according to best clinical judgement

Patients requiring A/C ventilation should be reassessed within 24 hours for **Criteria for Switching from A/C to PSV**.

Adjusting PSV if Respiratory Distress is Absent:

If respiratory distress is absent, adjust the level of pressure support, PEEP and FiO_2 as follows:

1. Adjust the PEEP according to clinical judgment at the bedside
2. Adjust the FiO_2 to the lowest level required to maintain SpO2>90% and in the range 90-96%.
3. If patient appears comfortable (RR 12-35 and Vt 5-10 mL/kg PBW): target range achieved.
   No adjustments required unless one of the following occurs:
   a. If RR <12 or >35 or Vte<5 or >10 mL/kg PBW, obtain arterial blood gas (ABG):
      i. If ABG demonstrates respiratory alkalemia, treat any apparent cause of hyperventilation (eg. pain, anxiety, metabolic acidosis), then decrease PS in steps of 2-3 cmH_2O until pH <7.47 OR Vte <8 mL/kg PBW
      ii. If ABG demonstrates respiratory acidemia OR respiratory distress develops:
         1. Increase PS in steps of 2-3 cmH_2O until pH>7.32 and respiratory distress resolves

         2. Switch to A/C mode if one or more of the following occur during above steps:
            a. PS > 20 cmH_2O
            b. PS + PEEP > 30 cmH_2O
            c. FiO_2 > 60% required to maintain SpO_2 ≥90%
            d. Clinical Instability
            e. Requiring neuromuscular blockade and/or sedation such that the patient is no longer able to trigger the ventilator

Patients requiring A/C ventilation should be reassessed within 24 hours for **Criteria for Switching from A/C to PSV**.

8.2.4 Resuming PSV after A/C ventilation

Patients switched to A/C ventilation as per study protocol should be reassessed within 24 hours, and at least once daily thereafter, for **Criteria for Switching from A/C to PSV.** If all of the criteria for switching from A/C to PSV are present, the patient **must** be tried on PSV: follow the Initiation of PSV protocol, with initial and subsequent adjustments made to PSV setting according to Algorithm for Adjusting PSV. After a trial of PSV, patients may be switched back to A/C mode if they meet criteria according to the PSV ventilation strategy algorithm. The **Criteria for Switching from A/C to PSV** are as follows:

Criteria for Switching from A/C to PSV:

1. Able to trigger ventilator breaths
2. On assist/control with the following settings:
    a. AC/VC: Pplat≤30cmH_2O with Vt 6-8 ml/kg OR
    b. AC/PC: PC+PEEP≤30cmH_2O
3. PaO_2 ≥ 60 mmHg or SpO_2 ≥ 90% on FiO_2≤ 0.60 and PEEP ≤ 15 cm H_2O
4. Metabolic disorders corrected; pH >7.32
5. Stable hemodynamic status: stable or decreasing doses of vasopressors for ≥6 hours
6. Absence of **Clinical Instability** (see definition, above)

8.3 Procedures Common to Both Groups

8.3.1 Weaning from Mechanical Ventilation

Weaning will be conducted in the same way in the two arms. The PSV level or the PAV+ %Support will **not** be used to assess readiness to wean. **At a minimum, patients in both arms will be assessed at least once daily for Criteria to Initiate Weaning, and will undergo the weaning trials at least once daily if criteria at each stage of weaning are met.** However, additional screening, additional pre-SBT readiness assessments, or additional SBTs may be performed at any time at the physician's discretion or as per institutional standard.

Criteria to Initiate Weaning:

1. SpO_2 ≥ 90%
2. FiO_2 ≤ 0.40
3. PEEP ≤ 8
4. pH ≥ 7.32
5. vasopressor requirements no higher than norepinephrine 0.1 μg/kg/min or equivalent and at a stable or decreasing dose ≥6 hours
6. No Respiratory Distress (see definition)
7. No Clinical Instability (see definition))

If all criteria are present except PEEP >8 cmH2O, decrease PEEP to ≤ 8 cmH2O and if all criteria still present after 30 min, proceed to next step, the pre-SBT readiness assessment.

Pre-SBT screening test (ZERO CPAP Trial)

Patients meeting above Criteria to Initiate Weaning will undergo a Pre-SBT readiness assessment to measure the Rapid Shallow Breathing Index (RSBI) as follows:

1. With patient's ETT connected to the ventilator circuit, change the ventilator mode to CPAP at 0 cmH_2O and FiO_2 0.40
2. Monitor patient for 2 min
3. On the ventilator, assess the f/Vt ratio after 1-2 minutes at 0 cmH_2O CPAP:

4. FAIL: If the f/Vt >100, or SpO2<90% or Clinical Instability, patient has failed the ZERO CPAP trial and will not proceed to SBT. Resume ventilation according to assigned ventilation algorithm at the ventilator settings used immediately prior to the CPAP test.
5. PASS: If the f/Vt is ≤100, and SpO_2 ≥90%, proceed to SBT

SBT

Patients who pass the Pre-SBT readiness assessment, will proceed to SBT as follows:

1. Disconnect endotracheal tube from ventilator circuit and place patients on T-piece* with FiO_2 0.40. (For patients with tracheostomy, place patients on tracheostomy mask trial with FiO_2 0.40)
2. Monitor patient for 30-120 minutes:
3. FAIL/ SBT Termination: Terminate the SBT and return patient to ventilator settings according to assigned algorithm if at any time one of the following occur:
    a. Respiratory Distress
    b. Clinical Instability
    c. Increased somnolence with elevated pCO_2 and/or pH<7.32
4. Pass: Patients will be considered to have passed the SBT if, after a minimum of 30 minutes and maximum of 120 minutes, none of the failure/SBT termination criteria have occurred. Proceed to evaluate patient for extubation criteria (or disconnection criteria for patients with tracheostomy, see below)

**for the purposes of this study, the Sponsor considers SBT performed with patients connected to ventilator on flow-by with CPAP of 0 cmH_2O and FiO_2 0.40 to be equivalent to SBT performed on T-piece with FiO_2 0.40.*

Extubation Criteria:

Patients are assessed for extubation criteria after successfully passing an SBT:

1. Criteria to initiate weaning still present
2. Passed SBT
3. A level of consciousness sufficient to ensure airway protection (as judged by the clinician)
4. A cough strong enough to clear secretions (as judged by the clinician) and not requiring suctioning more than every 2 hours

Note that Extubation Criteria do not need to be present prior to performing the pre-SBT assessment or the SBT . Patients who pass the SBT AND meet Extubation Criteria should be extubated immediately (within 2 hours). Extubation may be deferred (up to a maximum 24 hours after meeting all extubation criteria) if a procedure or surgery that will require intubation is planned within 24 hours or at the discretion of the treating physician (justification must be provided on the eCRF). In the event that extubation is deferred (beyond 2 hours from time of meeting extubation criteria), patients must be reassessed for extubation criteria within 24 hours and either extubated or justification provided on the eCRF on a daily basis for any further deferrals. Patients who pass the SBT but do NOT meet Extubation Criteria are returned to ventilator settings according to the assigned algorithm and reassessed for Extubation Criteria at least once daily. SBT will be repeated as needed, or as indicated by the clinician. If, upon reassessment, the Criteria to Initiate Weaning are no longer present, patients will continue on the assigned ventilation strategy and undergo daily assessments to restart the weaning process from the beginning.

In sites where Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) are routinely measured prior to extubation and recorded in the medical chart, these scores will be collected as part of the eCRF.

8.3.2 Ventilation on A/C mode

Patients meeting criteria to switch to A/C mode may be ventilated with pressure control (AC/PC) or volume control (AC/VC) according to standard practice in each ICU. Ventilator settings on A/C mode will be determined by the clinician/respiratory therapist. PEEP and FiO_2 will be titrated clinically. The FiO_2 should be weaned to the lowest level required to keep SpO_2 90-96% as soon as the clinical status of the patient is stable, as judged by the clinician. Once all the following criteria are reached, the patient must be tried on PAV+ or PSV, according to their randomization assignment.

Criteria for Switching from A/C to PAV+ or PSV:

1. Able to trigger ventilator breaths
2. On assist/control with the following settings:
    a. AC/VC: Pplat≤30cmH_2O with Vt 6-8 ml/kg OR
    b. AC/PC: PC+PEEP≤30cmH_2O
3. PaO_2 ≥ 60 mmHg or SpO_2 ≥ 90% on FiO_2≤ 0.60 and PEEP ≤ 15 cm H_2O
4. Metabolic disorders corrected; pH >7.32
5. Stable hemodynamic status: stable or decreasing doses of vasopressors for ≥6 hours
6. Absence of **Clinical Instability** (see definition, above)

8.3.3 Routine Ventilatory Care and Monitoring

Patients in both groups should be ventilated with the head of the bed elevated to 30^o unless otherwise contraindicated; in-line suction catheters and heated humidifiers are recommended.

Patients in both groups shall be monitored using continuous SpO_2 monitors and electrocardiography. Blood pressure may be monitored either intermittently with inflatable cuff or continuously with an arterial catheter. Arterial blood gases shall be performed at baseline after passing the pressure support trial, and after initiating the assigned ventilation strategy (30-60 minutes post initiation), with any significant changes in minute ventilation and as needed according to clinician assessment or to satisfy the ventilation algorithm requirements (eg. when Vte <5 or >10 mL/kg PBW, a blood gas should be done to assess for respiratory acidosis or alkalosis).

Patients will be assessed at minimum every 8 hours for adjusting ventilator settings or more frequently as per routine practice in each participating ICU. Frequency of assessments will be the SAME for patients in both study groups in each participating ICU.

8.3.4 Ventilation during Patient Transfers

The assigned ventilation strategy may be interrupted during patient transfers away from the ICU, and alternative means may be used (e.g. Manual ventilation, anaesthetic gas machines, transport ventilators, etc.) Upon return to the ICU, patients will immediately resume their assigned strategy, including the use of A/C ventilation as required until patients meet the Criteria for Switching from A/C to PAV+ or PSV.

8.3.5 Post-extubation Ventilatory Care

8.3.5.1 Noninvasive Ventilation Guideline

Noninvasive ventilation (NIV) may be used post-extubation at the discretion of the treating clinician. We will collect data regarding use of NIV (refers to CPAP or Bilevel) and reason(s) for NIV initiation:

Reasons for Initiation of Noninvasive Ventilation post extubation:

1. To treat confirmed or suspected sleep-disordered breathing
2. To treat post-extubation respiratory distress or failure

3. To prevent post-extubation respiratory distress or failure

In both patient groups, NIV settings for IPAP/EPAP or CPAP and FiO_2 are prescribed and adjusted by the clinician according to clinical judgment. NIV should be delivered with the patient in a seated position with the upper body elevated to a minimum of 30 degrees and with a comfortable interface well fitted to the patient. Patients should be monitored closely for response to NIV therapy, with resolution of respiratory distress and improvement in arterial blood gases expected within 60 minutes of initiation. In the setting of post-extubation respiratory failure, **NIV should NOT be continued beyond 120 minutes** if, despite NIV, there is persistent or worsening signs of respiratory distress, persistent respiratory acidosis, or persistent hypoxemia, as defined above. In such cases, consideration should be given to reintubation.

NIV is relatively contraindicated if patient has:

1. High risk of aspiration due to recent vomiting (within 6 hours)
2. Decreased level of consciousness with impaired ability to protect the airway (as judged by clinician)
3. Weak cough required deep suctioning or cough assistance more frequently than every 2 hours
4. Severe Agitation (RASS ≥+3 or SAS 7)

NIV Failure is defined as any of the following occurring while on NIV:

1. Persistent or worsening signs of Respiratory Distress
2. Persistent respiratory acidosis (pH<7.32 with PaCO2>45) OR worsening PaCO2
3. Refractory hypoxemia (SpO_2 <90% or PaO_2<60mmHg with FiO_2 >0.60) OR worsening PaO_2
4. Abundant secretions that cannot be effectively cleared or are associated with lobar collapse, acidosis, hypoxemia, or change in mental status
5. Change in mental status (decrease in level of consciousness or severe agitation) rendering patient unable to tolerate NIV

8.3.5.2 Re-intubation Guideline

Reintubation is performed at the discretion of the treating clinician. Time of reintubation and reason(s) for reintubation will be recorded:

Reasons for Re-intubation:

1. Cardiac arrest
2. Respiratory arrest (respiratory pauses with loss of consciousness or gasping for air)
3. Respiratory distress (see definition) or respiratory failure and NIV relatively contraindicated
4. Respiratory distress (see definition) or respiratory failure and NIV Failure
5. Decreased level of consciousness impairing ability to protect airway
6. Hemoptysis or hematemesis impairing ability to protect airway
7. Abundant secretions that cannot be effectively cleared or are associated with lobar collapse, acidosis, hypoxemia, or change in mental status
8. Clinical instability (see definition)
9. Surgical/invasive procedure requiring sedation/anaesthesia +/- neuromuscular blockade such that patient will no longer be able to sustain unassisted breathing
10. Other (specify)

If a patient remains in ICU and requires reintubation within 7 days of extubation, that patient will remain in the study, and will resume ventilation according to the assigned ventilation strategy (i.e. using A/C and PAV+ only for patients in the PAV+ arm, and using A/C and PSV only for patients in the PSV arm). Patients initially supported with assist/control mode will be switched to PAV+ or PSV according to their assigned ventilation strategy upon

meeting Criteria for Switching from A/C to PAV+ or PSV. If a patient is discharged from ICU but readmitted to ICU within 48 hours of discharge, and requires reintubation within 7 days of extubation, that patient will remain in the study and will resume ventilation according to the assigned ventilation strategy, as per above.

8.3.6 Tracheostomy

Tracheostomy may be performed in either group when clinically indicated. Notwithstanding, there is no proven benefit to early tracheostomy and therefore we encourage clinicians to delay decisions regarding elective tracheostomy until day 10 post randomization.

Disconnection Procedure for Patients with Tracheostomy

For patients with tracheostomies, SBT will be performed on tracheostomy mask, with FiO_2 0.40. Tracheostomized patients who pass their initial SBT by completing 120 minutes of tracheostomy mask trial shall remain off the ventilator and on tracheostomy mask trial provided they do not develop any criteria for SBT termination. Tracheostomized patients who fail their initial SBT within 120 minutes may undergo gradual increments in tracheostomy mask trials according to local ICU site practice, provided local standards of care are applied equally to patients regardless of treatment group. When not undergoing tracheostomy mask trials, patients should be ventilated according to their assigned ventilation strategy, until successful termination of invasive MV is achieved. "Successful extubation/termination of invasive mechanical ventilation" will be defined as remaining off of invasive ventilation for 7 consecutive days, or discharge from hospital. Decanulation will be decided based on local practices.

8.4 Co-interventions

8.4.1 Sedation Guidelines

Each site will submit their clinical sedation procedures or preprinted orders to the CC and this procedure will be acknowledged by the sponsor prior to site activation. **Guidelines for the administration of sedation and analgesia are provided, with a strong recommendation for using the lowest possible dose of sedating drugs in both arms (or none at all) as required to keep the patient calm and cooperative, avoiding over-sedation whenever possible.** When sedation is necessary, we recommend assessing analgesia and intervening with appropriate pharmacological measures prior to administering sedatives. We will record the daily doses of sedatives, analgesics, and neuroleptic medications administered to the patient.

Guidelines for Sedation Administration

1. The critical care nurse should assess the patient (at least once per 8 or 12 hour shift) for pain, agitation, and delirium.
2. Pain should be assessed first, with attempts made to distinguish etiology of pain, and analgesia administered as needed to relieve pain. We recommend using a psychometrically validated self-report tool such as the Numeric Rating Scale (NRS). In patients unable to self-report, we recommend a validated behavioural pain scoring tool such as the Behavioral Pain Scale (BPS) or Critical-Care Pain Observation Tool (CPOT).
3. Level of alertness/sedation should be assessed after pain is adequately treated. We recommend using a validated sedation scale such as the Richmond Agitation-Sedation Scale (RASS) or Sedation-Agitation Scale (SAS) and targeting a RASS score of 0 or SAS score of 4 (equivalent). Some patients may need no sedation or only intermittent sedation as needed to maintain the target RASS or SAS score. If sedative medications are required, maintaining light levels of sedation is strongly recommended. If RASS or SAS score is below the target, attempts should be made to wean, withhold or discontinue sedating medication. If dangerous agitation is present, attempts should be made to distinguish etiology of agitation; anxiolytic or sedative medications may be administered as needed to relieve agitation and achieve target RASS/SAS score.

4. Patients should be assessed for the presence of delirium, with attempts made to distinguish and remove or treat contributing factors to delirium. We recommend using a validated delirium screening tool, such as the Intensive Care Delirium Screening Checklist (ICDSC) or the Confusion Assessment Method for the ICU (CAM-ICU).

In sites where validated pain, sedation, and delirium scoring systems are routinely used and recorded in the medical chart, these scores will be collected as part of the eCRF. In centres where a validated sedation score is not routinely recorded, a validated sedation scale (RASS or SAS) will be measured and recorded by research personnel at minimum once daily as required for completion of the relevant eCRF. See Appendix E and Appendix F for procedure for assessing RASS or SAS score respectively.

8.4.2 Nutrition Guidelines

Every attempt should be made to ensure patients are receiving adequate calories, protein and nutrients to meet their energy requirements. Nutrition may be administered enterally or parenterally. We strongly encourage consultation with a registered dietician with experience in critical care whenever possible.

8.4.3 Early Mobilization Guidelines

Patients should be assessed for ability to participate in passive and active exercises with the aim of mobilizing as early as possible, even while still on the ventilator, as per clinical practice protocols within each ICU. We strongly encourage consultation with a physiotherapist with experience in critical care whenever possible.

9.0 Data Management

9.1 Data Collection

We will collect the following demographic data on study participants: gender, birth month and year, race, height, and weight. We will collect data regarding reason for ICU admission, reason for intubation, comorbidities and severity of illness, including APACHE III score on admission, and code status. We will collect data regarding cumulative fluid balance and sedative medications administered pre-randomization. Pre and post randomization on selected days, we will collect data at a point in time each morning, including respiratory data (including ventilator mode and settings, respiratory rate, tidal volume, peak and mean airway pressure, blood pressure and heart rate, PAV resistance and PAV compliance, and arterial blood gas results if available), sedation score and SOFA score. In participating centres with technical capability, we will collect respiratory data continuously from the Puritan Bennett ventilators directly, which will also allow us to evaluate driving pressure on PAV+ as well as time on PAV+ mode. To ensure that differences in outcome are not due to differences in other therapies that may impact duration of mechanical ventilation, we will document daily fluid balance, and use of sedatives, narcotics, antipsychotics, corticosteroids and vasoactive drugs, attempts at enteral or parenteral feeding, and early mobilization. To document protocol adherence, we will collect daily information regarding screening for Criteria to Initiate Weaning, and results of the Pre-SBT readiness assessment and SBTs, as well as use of assist/control mode, PAV+ and PSV throughout the study period, and any deviations from protocol. We will collect data regarding interventions such as tracheostomy or use of non-invasive ventilation (NIV) post-extubation, and reintubation. Safety data will be collected using the serious adverse event form. Data used to calculate outcomes will include time and date of all SBTs, extubations, reintubations, tracheostomy mask trials, ICU discharge, hospital discharge, and vital status at ICU and hospital discharge. Vital status will also be determined at day 90 post randomization.

9.2 Outcome Measures and Duration of Follow-up

Liberation from invasive mechanical ventilation is achieved at the moment of "successful extubation" for patients with an endotracheal tube, or at the moment of "successful termination of invasive MV" for patients with a tracheostomy tube.

For patients with an endotracheal tube, "**successful extubation**" is defined as removal of the endotracheal tube AND remaining alive with no need for reintubation/reinstitution of invasive mechanical ventilation for 7 days post extubation, or until successful ICU discharge, or until live hospital discharge, whichever comes first.

For patients with a tracheostomy tube, "**successful termination of invasive MV**" is defined as having the tracheostomy tube disconnected from the ventilator AND remaining alive with no need for reinstitution of invasive MV for 7 consecutive days, or until successful discharge from ICU, or until live hospital discharge, whichever comes first.

"**Successful ICU discharge**" is defined as leaving the ICU where the patient was receiving invasive MV, AND remaining alive with no need for reinstitution of invasive MV AND no need for readmission to ICU within 48 hours of ICU discharge.

"**Ventilator-free days**" (VFDs) are defined as the number of days alive and free of INVASIVE ventilation post SUCCESSFUL EXTUBATION or post successful termination of invasive MV. Non-invasive ventilation may be used post extubation, but is not counted as "invasive ventilation." If the patient dies before achieving successful extubation or successful termination of invasive MV, that patient will have 0 VFDs. However, if a patient dies AFTER achieving successful extubation, successful termination of invasive MV, or successful ICU discharge, that patient will have the number of VFDs counted as the number of days alive and free of invasive MV occurring between time of successful extubation/successful termination and time of death.
All time intervals and durations will be measured in days (to the nearest 1/10 of a day) and calculated from the day and hour of randomization to the day and hour of the event (eg. day and hour of successful extubation, successful termination of invasive MV, successful ICU discharge, live hospital discharge, or death).

Patients will remain in the study and will continue on the assigned ventilation strategy until: successful extubation, successful ICU discharge, live hospital discharge, death, or 90 days post randomization, whichever comes first. All intubations and extubations (or for patients with tracheostomy, all disconnections lasting >48 hrs and reconnections following 48 hrs off ventilator) will be tracked from date of hospital admission to day 90 or date of death. Date of last follow-up will be 90 days post-randomization, when vital status will be assessed.

9.3 Confidentiality

Original records for each participant in the study will be maintained in separate files in a secure, limited access location at the study site for the duration of the study and after study completion for 15 years.

Copies of the de-identified documents may be made and supplied to the sponsor representative for the purposes of ongoing data monitoring and analysis of results.

Participants' identities will be kept confidential by assigning each participant a participant ID upon enrollment into the study.

The investigator must assure that participant confidentiality will be maintained and that participant identities shall be protected from unauthorized parties. On eCRFs or other documents submitted to the CC, participants should not be identified by their names, but by their participant identification code, which is assigned in the eCRF. The

investigator should keep a participant code log relating codes to the names of participants. The investigator should maintain study documents that are not for submission to the CC (e.g., participants' written consent forms), in strict confidence.

Information about study participants will be kept confidential and managed according to national and local requirements. Consistent with these regulations a signed authorization will be obtained that informs each participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

9.4 Source Documents

Source data are all original information (i.e. the first recorded instance of data), records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical charts, laboratory results, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, x-rays, and participant files.

All entries in the eCRF must be backed up by source data. Source data must be made available if requested by the Sponsor or CC. Study records should be kept in accordance with applicable national and local laws and regulations.

Sites will be provided with a printout of the eCRF which may be used as a **tool** for data collection. Whenever possible, source data should be transcribed directly into the eCRF from source. E.g. if a lab report is available, this is considered *source data* and these values should be entered to the eCRF, and not transcribed onto the paper copy of the CRF. However, the paper CRF will serve as the source document for any assessments that are completed only by the investigator and not otherwise documented in the patient's medical chart.

9.5 Case Report Forms

Medidata RAVE® will be used for this study for web-based randomization and data collection. All study data will be entered in electronic case report forms (eCRF) at the study site. Data collection will be completed by authorized study site personnel designated by the site Investigator. Appropriate security measures will be taken to authorize study site personnel using unique usernames and passwords prior to any data being entered into the system.

The study data will be housed on a secure in-house server at St. Michael's Hospital in Toronto throughout the duration of study, and up to 15 years after the study is complete.

All eCRF corrections are to be made by an Investigator or other authorized study site personnel. The site Investigator must confirm by his/her electronic signature in a specific section of the eCRF to confirm that he/she has reviewed the data, and that the data is complete and accurate.

Data validation procedures will be described in detail in the Data Validation and Management Plans.

9.6 Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigator study file (ISF), commonly referred to as the regulatory binder, will contain the study's Essential Documents as noted by local regulatory guidelines.

Should the investigator wish to assign the study records to another party or move them to another location, the investigator must notify the CC and the CC must provide acknowledgment in advance. Study records at each site should be stored as per local requirements. If there are no local requirements they should be retained for 15 years after the completion of the trial.

10.0 Study Schedule of Events

The Ventilator Algorithms for PAV+ and PSV are located in Appendices C and D, respectively. The Enrolment Algorithm is located in Appendix A.

10.1 Run-In Phase

To assess for feasibility and compliance a run-in phase will be implemented at each site prior to randomizing patients in the trial. Each site will have a contract and ethics approval in place, and will have received training as needed on use of the ventilation algorithms for PSV and PAV+ and use of the data capturing system prior to beginning the run-in phase. During the run-in phase, each site will follow the screening and enrolling procedure as outlined in the protocol. After obtaining consent (a priori or deferred) to participate, the first eligible patient in participating ICUs will be assigned to the PAV+ algorithm, and the second eligible patient will be assigned to the PSV algorithm. The PAV+ run-in patient will receive the study intervention and follow-up until day 7, or until completing the study, as defined in the study protocol, whichever comes first, and the PSV run-in patient will receive the study intervention and follow-up until day 3, or until completing the study, as defined in the study protocol, whichever comes first. After patients exit the run-in phase, no further safety assessments or data collection will occur. After exiting the run-in phase, all treatment decisions, including ventilation strategy, will be at the discretion of the treating physician. Upon completion of the first and second run-in patients, the completed CRFs will be evaluated by the CC to assess (i) the ability of the participating centre to screen and enroll patients, (ii) compliance with study procedures, (iii) data completeness and timeliness of data collection. Should the CC or the participating site identify problems in any of these 3 areas of assessment, further run-in patients will be enrolled and the process will be re-evaluated. Once the approval is granted from the CC, the run-in phase is concluded and sites will be able to enroll and randomize patients in the PROMIZING trial.

The initial start-up fee is inclusive of the run-in phase. No per-patient fees are allotted to sites for patients in the run-in phase. Patients in the run-in phase will not be included in the final data set.

10.2 Screening and Eligibility Assessment

All patients admitted to a participating site ICU during the study period meeting the screening inclusion criteria will be entered into a screening log and followed daily until they satisfy all inclusion criteria, are enrolled and randomized, or meet one of the exclusion criteria and exit the screening/enrolment process. A participant will be ineligible for participation in this study and will be counted as a "screen failure" if he or she satisfies any one or more of the exclusion criteria. A staged enrolment process will be used to identify patients eligible to be enrolled and randomized in the study. The five stages of enrolment are:

A. Screening Criteria
B. Consenting Criteria and Obtaining Consent
C. Pressure Support Trial Criteria and the Pressure Support Trial
D. Weaning Criteria and the ZERO CPAP Trial and the Spontaneous Breathing Trial (SBT)
E. Randomization Criteria

See section 7.0: Participant Identification and Appendix B for additional information on screening and eligibility assessment.

Informed consent will be administered prior to any study procedures and will be compliant with local institutional/REB requirements. See sec. 15.3 for additional information on consent.

10.3 Randomization & Blinding

10.3.1 Randomization

Participants will be randomized once eligibility is determined, by having satisfied all of the inclusion criteria and none of the exclusion criteria, have passed the Pressure Support Trial and either not meeting Weaning Criteria or failing the ZERO CPAP Trial or failing the SBT. Each participant in this study will be randomized to either PSV or PAV+ in a 1:1 ratio in Medidata RAVE.

Participant allocation to procedure group will be via variable block randomization with varying block sizes and stratified by site to minimize the likelihood of predicting the next procedure assignment. Randomization will be attained using computer generation sequence methodology, ensuring that the randomization methodology and the generated allocation sequence are concealed from the investigator and participants.

10.3.2 Blinding

Neither the clinical team nor the study investigators will be blind to the study intervention. The study statistician will be blind to the study arm.

10.4 Baseline Assessment

A Pre-Randomization assessment will be recorded immediately prior to implementing PSV or PAV+ to provide a baseline measure for evaluation. The Pre-Randomization assessment will include:

- Ventilator settings and most recent arterial blood gas (ABG) results prior to the Pressure Support Test (PST)
- Ventilator settings used for the PST, and respiratory parameters, vital signs, and arterial blood gas results at the end of the PST

A Randomization form will be completed to document:

- Weaning Criteria
- ZERO CPAP Trial result (RR and Vt or RSBI)
- SBT result: failure criteria
- Randomization assignment

10.5 Administration of Intervention

Switching ventilator mode to PSV or PAV+ with adjustment of the settings according to the assigned PSV or PAV+ Ventilation Strategy will indicate administering the intervention. The intervention (the PSV or PAV+ Ventilation Strategy) is administered continuously from time of randomization until study completion (study completion occurs at time of successful extubation/successful termination of invasive MV, successful ICU discharge, hospital discharge, death or 90 days post randomization, whichever comes first.

10.6 Follow up assessments and Final Study Visit

A Post-Randomization assessment will be recorded 1 hour post-randomization and will include:

- Make and model of ventilator, ventilator settings, respiratory parameters and vital signs

Day of randomization is considered Day 1, until 0700 a.m. Each subsequent study day is from 0700 a.m. to 0700 a.m. Daily follow-up "snapshot" assessments are completed daily (or on selected days) between 0800 a.m. -1200 p.m. and will include daily assessment for Criteria to Initiate Weaning and results of Pre-SBT readiness assessments and SBTs.
Daily follow-up "cumulative" assessments are completed based on the 0700 – 0700 hrs time frame and will include data on co-interventions administered in each 24 hour interval.

Event-based assessments are conducted at the time of the following events: extubation, use of NIV post-extubation, reintubation, tracheostomy, protocol deviation, or serious adverse events.

An outcome assessment will be recorded to document time of successful extubation, time of successful ICU discharge, time of hospital discharge, or death.

A final study visit will occur on Day 90 to document vital status and outcome assessment if not previously completed.

10.7 Protocol Amendments and Deviations

Investigators must read, understand and follow the study protocol.

Amendments are changes to the protocol (or protocol procedures) that are planned and that are approved by the REB prior to implementation. Changes to the protocol shall only be made by the EC in the form of protocol amendments. The CC is responsible for the distribution of any protocol amendments to site Investigators. Site Investigators are responsible for the distribution of an amendment to all staff involved in the study and for obtaining approval for the amendment from the local REB as required by local institutional guidelines.

Deviations differ from amendments in that they generally apply to a single occurrence or participant, and are not intended at the time to modify the entire protocol. Examples of protocol deviations that must be recorded and reported to the CC and may be reported to the REB per local institutional requirements include the following:

- Implementation of additional procedures for monitoring participants, beyond the standard of care;
- Suspension of enrollment of new participants;
- Suspension of research procedures in currently enrolled participants

In the event that a patient is randomized in error (e.g. incorrect eligibility assessment) the site should notify the CC immediately, and make a note in the patient's source documents. Patients randomized in error will be withdrawn from the study. The site will be required to document and implement a preventative action plan to avoid future errors.

If an unanticipated deviation or divergence from the approved research protocol, consent document(s) or study addenda **jeopardizes participants, study efficacy or data integrity,** it must be promptly reported to the CC and

may be reported to the local REB per local institutional requirements, if it has not otherwise been reported through an amendment to the protocol or consent form. Specific examples of reportable deviations (i.e., if they place participants at a greater risk) include the following:

- Informed consent improperly obtained or not obtained;
- Participant enrolment without meeting the eligibility criteria and without prior sponsor approval;
- Eligibility Waiver: participant enrolment without the eligibility criteria with prior sponsor approval;
- Assigned ventilation strategy not administered per protocol with increased risk of harm to participant;
- Major, non-emergent deviations without prior approval;
- Emergency deviations to the research protocol initiated by the investigator prior to obtaining REB approval to (e.g., eliminate apparent immediate hazards to participants).

Emergency deviations to the research protocol (e.g. to eliminate apparent immediate hazards to participants) will also be reported to funding agencies according to contract stipulations, no later than five (5) working days after the emergency situation occurred. Protocol Deviations that lead to an SAE must be reported according to guidelines set forth in section 11.3.

11.0 Safety Assessments

11.1 General Comments

The ventilation algorithms and study protocol provide a variety of measures to ensure the safety of enrolled patients, including instructions to use assist/control ventilation in case of clinical instability , or in the event that respiratory distress or impaired gas exchange does not resolve with optimizing ventilator settings on PAV+ or PSV. Based on the 2 pilot studies performed by the co-primary investigators, we anticipate no increase in risk to participants in this trial. Nonetheless, the target population for this trial is critically ill patients with a high baseline risk of complications and death. We expect that some patients may die during the course of their enrolment in the study. If the patient expires the site investigator is required to complete a SAE assessment in their source documents. A death due to a decision to withdraw life support, or a decision to not re-intubate post extubation, or a change in the goals of care, does not constitute a serious adverse event and does not need to be reported as such. We are interested in reviewing Serious Adverse Events that *may* be related to the study interventions, rather than adverse events that occurred due to the underlying critical illness. An independent Data Safety Monitoring Board (DSMB) will review each Serious Adverse Event for which a possible, probable, or definite relationship to the study intervention exists.

Notwithstanding the safety measures provided within the ventilation algorithm, in the event of an emergency situation, the site PI and/or attending physician will ensure that best medical judgment is used to protect the life or well-being of the participant, which may include deviations from the Protocol. The safety and welfare of participants in the study takes absolute precedence over the evaluation goals and objectives of the study, in any emergency situation. Reporting of protocol deviations is described in section 10.7, and reporting of serious adverse events is described below in section 11.3.

A Serious Adverse Event (SAE) in the PROMIZING Study is defined as:

Any adverse event that results in 1 of the following:

- Results in unanticipated/non-palliative death
- Life-threatening
- Results in persistent or significant disability/incapacity:

- Requires medical or surgical intervention to prevent one of the above outcomes

Examples of reportable SAEs:

Criteria for SAE	Definition
Results in unanticipated/ non-palliative death	An adverse event which directly results in the patient's death, excluding one-way extubations, withdrawal of life support, or expected deaths occurring in patients who have been made palliative (eg. Cardiac arrest with unsuccessful attempt at resuscitation)
Life-threatening	An event in which the subject was at risk of death at the time of the event (eg. respiratory or circulatory arrest with return of spontaneous circulation)
Results in persistent or significant disability/incapacity	An event which results in significant, persistent disability AFTER the event has resolved/ been treated (eg. hypotension leading to stroke with resulting hemiplegia)
Requires medical or surgical intervention to prevent one of the above outcomes	An important medical event that may not result in death or be life-threatening but may jeopardize the subject and requires medical or surgical intervention to prevent one of the above outcomes, based on appropriate medical judgment. (e.g. a patient has an episode of major agitation leading to self-extubation, requiring re-intubation)

11.2 Assessment and Reporting of a Serious Adverse Event (SAE)

An SAE may be due to the participant's underlying critical illness, or may be directly related to enrolment in the study (i.e. it is unlikely to have occurred if the patient were not enrolled in the study).

It is the responsibility of the site PI to ensure all SAE's are assessed to determine causality, that is, to determine the likelihood that the SAE was caused by a study intervention.

The site PI should ask the attending physician caring for the patient at the time the SAE occurred to assist with assessment of causality. An SAE may be assessed as being unrelated, unlikely related, possibly related, probably related, or definitely related to the study intervention, according to the definitions provided below. In cases where causality is "unknown" or the site PI and attending physician have disagreement or doubt regarding whether an SAE has "unlikely" relation vs. "possible"relation to the study intervention, the site PI must contact one of the study co-PIs/sponsors (Dr. Bosma or Dr. Brochard) to discuss and adjudicate the SAE.

Causality	
Unrelated	A definitive alternative etiology for the AE must exist
Unlikely	Must have 2: • No temporal relationship to the intervention • Could readily have been produced by the patient's clinical state or have been due to environmental or other interventions • Does not follow a known pattern of response to intervention • Does not reappear or worsen upon intervention re-exposure
Possible	Must have 2: • Reasonable temporal relationship to the intervention

	• Could not have readily been produced by the patient's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with replacement of intervention with standard of care procedures and recurs with re-exposure
Probable	Must have 3: • Reasonable temporal relationship to the intervention • Could not have readily been produced by the patient's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with replacement of intervention with standard of care procedures and recurs with re-exposure
Definite	Must have all 4: • Reasonable temporal relationship to the intervention • Could not have readily been produced by the patient's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with replacement of intervention with standard of care procedures and recurs with re-exposure

It is the responsibility of the site investigator to identify and report SAEs occurring between patient enrolment and study completion (enrolment occurs once patient or SDM has provided consent and study completion occurs once patient achieves successful extubation, successful ICU discharge, hospital discharge, dies, or day 90 post randomization, whichever comes first).

SAEs are to be documented in source and in the Serious Adverse Events eCRF. Whenever possible, if a unifying diagnosis can be made, all associated complications should be grouped together and reported as one SAE. If the patient expires the site investigator is required to complete a SAE assessment in their source documents. Sites can refer to the Data Entry Guidelines for instructions on how to access the eCRF. The eCRF system (Medidata RAVE) will notify the study PI, CC and Medical Monitor of the SAE so that it may be immediately assessed for further action in any applicable local or federal requirements.

The investigator or his/her designate will promptly report SAEs with probable or definite relation to study intervention within 24 hours of becoming aware of the event, and update as additional information becomes known. Each site will also need to report SAEs with probable or definite relation to a study intervention to the local REB according to local institutional requirements.

The site may be asked for additional information to assist with the assessment, and a narrative with appropriate clinical context should be included in each SAE reported.

11.3 Definition and Reporting of an Adverse Device Effect

Subject to section 59 of the Medical Device Regulations, any incident that comes to the attention of the investigator which meets the following conditions must be reported to the coordinating centre within 24 hours of becoming aware of the incident:

(1) Incident is related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or in its directions for use;

AND

(2) Has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur.

In such a situation, the investigator must complete the study Incident Report and submit the report to the coordinating centre within 1 business day of becoming aware of the incident. The following information will be required: date of the incident, details of the incident, course of action taken, and other relevant details.

Follow-up reports must be provided to the coordinating centre as any new information becomes available. The device manufacturer will report these incidents to the Medical Devices Bureau of Health Canada within the timelines specified in section 60 of the regulations.

(http://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/page-13.html#h-42)

11.4 Data Safety Monitoring Board (DSMB)

The DSMB will review safety reports biannually. The DSMB will have the ability to request additionally safety analyses and make recommendations about the safe conduct of the trial. The DSMB Chair will review all serious adverse events classified as probably or definitely related to enrolment in the trial within 7 days and communicate directly with the co-principal investigators, who in turn will communicate back to the Steering Committee.

12.0 Statistical Plan

12.1 Sample Size Determination

Primary and secondary outcomes will be analyzed at the conclusion of the trial.

A table of sample sizes for time from randomization to first successful extubation/liberation is shown below. These calculations incorporate death by treating death as censoring. The current hazard rate for death is used in this calculation. The final column is obtained by dividing the "Total N" column by 0.95 to account for the 5% dropout. Assuming this increase is sufficient to observe the required number of events in the presence of the drop-out, it should be a reasonable target.

All calculations are using 80% power and 2-sided Type I error of 5%. Exponential survival is assumed for the purposes of hazard calculations. The expected median time to extubation in PAV is determined from the PSV value by converting to the hazard scale, multiplying by the hazard ratio and converting back to time.

Median Time (PSV)	Median Time (PAV)	Difference	Hazard Ratio	Required Events	Total N	Total N (5% lost)
7.40	6.17	1.23	1.20	944	1095	1153
7.40	5.92	1.48	1.25	630	729	768
7.40	5.69	1.71	1.30	456	526	554
7.50	6.25	1.25	1.20	944	1097	1155
7.50	6.00	1.50	1.25	630	731	770
7.50	5.77	1.73	1.30	456	527	555
7.55	6.29	1.26	1.20	944	1098	1156
7.55	6.04	1.51	1.25	630	731	770

7.55	5.81	1.74	1.30	456	528	556
7.60	6.33	1.27	1.20	944	1099	1157
7.60	6.08	1.52	1.25	630	732	771
7.60	5.85	1.75	1.30	456	528	556
7.70	6.42	1.28	1.20	944	1101	1159
7.70	6.16	1.54	1.25	630	733	772
7.70	**5.92**	**1.78**	**1.30**	**456**	**529**	**557**

As planned a priori, we used aggregate, blinded data from the first 120 patients to re-estimate our sample size. Using a time to event analysis, median time to successful liberation in the entire cohort was 6.8 days. The minimum clinically important difference in time to successful liberation is deemed to be 1.0 day. Using a hazard ratio of 1.30, to demonstrate a reduction in the median duration of ventilation by 1.78 days (assuming 7.70 days versus 5.92), alpha of 0.05 (two-sided) and a power of 80%, requires 529 patients. Anticipating a maximum loss to follow-up (e.g. consent withdrawn) rate of 5%, 558 patients (279 per group) should be randomized in the study. Using a hazard ratio of 1.25, to demonstrate a reduction in the median duration of ventilation by 1.51 days would require770 patients (385 per group) to be randomized in the study.

We anticipate being able to enroll a minimum of 558 patients within the planned 5 year enrolment period. If enrolment exceeds expectations, we will be powered to show a smaller difference between the 2 groups, which will still be clinically important. The enrolment period will continue until we have complete data on randomized participants and have attained the minimum number of required events in our study cohort.

12.2 Statistical Methods Analysis

Analysis will follow the intention-to-treat principle. Baseline data will be analyzed descriptively (e.g. mean and standard deviation, median and interquartile range, counts and percentages as appropriate). Time to extubation will be summarized by cumulative incidence curves with death treated as a competing risk and compared between groups with the Gray test. The treatment effect will be expressed as a hazard ratio with 95% confidence interval from a multistate generalization of the Cox model. Additionally, a cause-specific Cox model where death is treated as a censoring event will be fit for comparison. Patients with missing outcome data will be censored at last contact. The secondary outcomes of ventilator-free days will be compared between the groups by means of a Wilcoxon test. The treatment effect will be expressed as the difference in median ventilator free days along with a 95% confidence interval obtained by bootstrap methods. The time-to-event outcomes ICU discharge and hospital discharge present the same special challenge as the primary outcome because death is a competing risk. Furthermore, "survivor-only" analyses are an improper subgroup which further complicates interpretation. To mitigate these problems, cumulative incidence curves will be constructed that provide estimates of the outcome of interest, accounting for death. Cause-specific treatment effects will be given as hazard ratios with 95% confidence intervals from Cox models. Time-to-death will be analyzed using standard methods for survival data (Kaplan-Meier curve, log-rank test) and the treatment effect will be expressed as a hazard ration with 95% confidence interval. Four of the secondary outcomes describe weaning difficulties in various ways. These also suffer from the competing risk of death and other improper subgroup issues. These outcomes will be looked at primarily from a descriptive perspective. The outcome, "requiring A/C" will be compared by a chi-square test (or Fisher's Exact Test) and treatment difference will be expressed as an odds ratio with 95% confidence interval.

For days requiring A/C, patients not receiving A/C will be assigned a value of zero. Although a t-test is the appropriate parametric approach, the non-parametric Wilcoxon rank-sum will be favoured if there are many 'null' (zeros) entries. Total medication dose, pain, agitation, and delirium scores will be compared by a t-test between study arms. Ordinal regression analyses will be used to assess factors associated with weaning group classification (short/difficult/prolonged weaning groups). Exploratory analyses using multiple regressions will be used to identify factors associated with duration of MV.

The secondary outcome of Ventilator-Free Days (VFD) has a number of difficulties, one of which is that death is indistinguishable from someone alive at day 21 but still ventilated. Analysis of survivors only results in an improper sub-group and potentially loses the benefits of balanced confounders due to randomization. Therefore a number of secondary and supplemental analyses are planned to fully understand any observed treatment effect. One analysis will assign -1 to deaths (instead of zero) to make that distinction. We will also examine time on ventilator in a number of ways (some of which subsume secondary outcomes). A Poisson regression model can be used which considers number of days on ventilator as the outcome and uses the logarithm of the number of days observed (up to 21) as an offset. Another analysis will consider time to extubation as the outcome with death treated as a competing risk. Cumulative incidence curves will be produced and suitable competing risks survival model will be used to estimate a treatment effect. Finally, a marginal structural model will be employed where first the probability of surviving will be modeled and then the weighted analysis of the survivors will be carried out using the inverse of the survival probability as the weight.

There are 4 planned subgroup analyses based on: (a) duration of MV prior to randomization greater than 5 days, which is associated with prolonged weaning; (b) failed SBT prior to randomization, depicting a subgroup classified as difficult weaning vs. failed CPAP 0 trial vs. failed weaning criteria prior to randomization; (c) failed extubation prior to randomization, depicting a subgroup classified as difficult weaning; and (d) mild vs. moderate vs. severe frailty.

There are 2 planned sensitivity analyses of primary and secondary outcomes, based on: (a) defining "successful extubation" as "48 hours without reintubation"; and (b) assigning a value of 0 ventilator-free days to any participant who dies at any time during the study period.

The secondary VFD outcomes will be analyzed similarly to the primary outcome. Similar methods will also be applied to ICU free days as these outcomes suffer from the same limitations as VFD. The time-to-event outcomes (except mortality) present special challenge because death is a competing risk. Furthermore, as stated above "survivor-only" analyses are an improper sub-group which further complicates interpretation. To mitigate these problems, cumulative incidence curves will be constructed that provide estimates of the outcome of interest, accounting for death. Cause-specific treatment effects will be given as hazard ratios with 95% confidence intervals from Cox models. Time to death will be analyzed using standard methods for survival data (Kaplan-Meier curve, log-rank test) and the treatment effect will be expressed as a HR with 95% confidence interval. Four of the secondary outcomes describe weaning difficulties in various ways. These also suffer from the competing risk of death and other improper sub-group issues. These outcomes will be looked at primarily from a descriptive perspective. The complication outcome, "ever requiring A/C" will be compared by a chi-square test (or Fisher's Exact Test if needed) and treatment difference will be expressed as an odds ratio with 95% confidence interval. For days requiring A/C, patients not receiving A/C will be assigned a value of zero. Although a t-test is the appropriate parametric approach here, it may be preferable to use the non-parametric Wilcoxon rank-sum if there are many zeros. Finally, total medication dose will be compared by a t-test.

13.0 Trial Management

13.1 Study Oversight

Lawson Health Research Institute (Lawson) in London, Ontario, Canada will oversee all contracts, trial insurance and financial disbursements.

The Applied Health Research Centre (AHRC) in Toronto, Ontario, Canada will serve as the Coordinating Centre (CC) for the study.

The Executive Steering Committee (EC) will consist of the lead investigators (KJB, LB, KEAB, CM, JM, YS) with support from the study statistician (KT) and the AHRC coordination centre. The executive committee will oversee all aspects of the study including implementation of all policies and the daily operations. The EC will meet weekly during the planning phase of the trial and bimonthly thereafter. Regular meetings with Site Investigators by region (eg. Europe, Canada, Argentina, Saudi Arabia) will occur before enrollment begins, and monthly or bi-monthly to discuss enrollment rates and non-adherence and at the completion of the study.

13.2 Study Monitoring

Participating sites will be contacted by the coordinating centre during the study to follow the recruitment and the return of study documents (e.g. copy of screening/enrollment log forms), and to address any issues that the site may have or any questions related to the study.

In addition, on-site monitoring visits will be planned by the coordinating centre. A risk-based approach will govern the monitoring activities for this study. A combination of centralized and on-site monitoring activities will be used to ensure the quality of the data captured, the study operations, and the safety of patients.

Source data verification on critical data elements will be performed on a selection of the participants by comparing the data in the patient's files (source documents) with data in the CRF, and will be conducted as per the Sponsor-approved Monitoring and Quality Plan. Electronic CRF will not constitute source documentation and data entered in the CRF must be traceable to an original source record (electronic or paper) either as part of the electronic database or in the patient's file. For selected patients, the presence of a signed written informed consent as well as compliance with inclusion and exclusion criteria will be checked.

The Investigators must agree to monitoring visits at the site, providing direct access to source/data verification and cooperation with the monitors. Key study personnel must be available to assist the monitor during these visits.

The purpose of monitoring visits is, but is not limited to, the following:

- Evaluate study progress;
- Check compliance with the study protocol;
- Discuss safety issues; and
- Assure continuous good clinical practice (GCP) compliance of the site.

A monitoring report will be provided to the Sponsor for each visit in which the progress of the study is documented and all issues will be described. The monitor has the right to compare entries in the CRFs with original data in the patient's files and must treat patient data as confidential. Patients must have consented to data inspection. The Investigator(s) must maintain source documents for each patient in the study, consisting of case and visit notes containing demographic and medical information, relevant laboratory data, and the results of any other tests or assessments. The Investigator(s) must also keep the original copy of the signed ICF. No information in source

documents about the identity of the patients will leave the study site. If it is necessary to provide any personal information of the patients, all data will be sent without personal health identifiers.

13.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the REB, the Sponsor, the CC and government regulatory bodies, of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. intensive care units, etc.).

14.0 Ethical Considerations

14.1 Declaration of Helsinki / ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and with the ICH Guidelines for Good Clinical Practice.

14.2 Research Ethics Board Approval

According to local laws and regulations, the study protocol and the participant informed consent form (in the local language) must be approved by an REB for each participating centre.

14.3 Informed Consent

It is an obligation of the participating site to administer informed consent with the participant or Substitute Decision Maker (SDM) by means of a dated and signed informed consent form. Consent should be obtained prior to randomization whenever possible; however, if the participant is incapable of providing informed consent and no SDM is available within the randomization window, consent must be sought as soon as possible after randomization (provided that the local Research Ethics Board has provided approval for deferred consent). The informed consent form must be written in the local language in accordance with local laws and regulations.

'Informed consent' also implies individual discussion with the participant/SDM about the nature of study treatment and examinations to be conducted in a language that is easy to comprehend. The participant/SDM should fully understand that his/her refusal to participate in the study will not affect the quality of medical care. In addition, the participant/SDM must be informed that, without disclosing his/her name, relevant medical data will be disclosed to the Coordinating Centre (CC), that his/her medical records will be inspected during on-site monitoring, and may be inspected again by auditors and/or regulatory authorities.

The participant/SDM should be informed in writing that his/her medical data relevant to this study will be stored and analyzed while maintaining confidentiality in accordance with local data protection laws. All data transferred to the eCRF and any process derived from the eCRF will be de-identified. In cases where the participant dies prior to being capable of providing informed consent, and there is no SDM available, the de-identified data will be included in the eCRF in centres where the Research Ethics Board permits waived consent under such circumstances.

Should a protocol amendment be made, the informed consent form may be revised to reflect the changes in the protocol. It is the responsibility of the investigator to ensure that an amended informed consent form is reviewed and approved by the local REB, and that it is signed by all participants/SDMs subsequently entered in the study and those currently in the study, if affected by the amendment.

15.0 Study Finances

15.1 Funding Source

This study is funded by a Canadian Institutes of Health Research (CIHR) Operating Grant: Industry-partnered Collaborative Research Grant, with Covidien LP, a Medtronic company as the industry partner, and by a CIHR Project Grant. Funding from Covidien LP, a Medtronic company, is provided through the Covidien Investigator Sponsored Research (ISR) Program and subsequently the Medtronic External Research Program (ERP).

15.2 Conflict of Interest

Any investigator who has a conflict of interest with this study must disclose it to the CC or sponsor/principal investigator immediately upon becoming aware of the conflict. The conflict will be reviewed by the sponsor/principal investigator and a decision will be made regarding how to proceed with the affected investigator's involvement in the study.

16.0 Publication Plan

Since the PROMIZING study is a multicenter study, it is the intention of the co-Principal Investigators that the first publication or presentation of the results and data of this study will be made to our collaborators in the two scientific networks supporting this study: the Canadian Critical Care Trials Group (CCCTG) and the Réseau Européen de Recherche en Ventilation Artificielle (REVA), and in conjunction with presentation of the study results and data with the investigators and the institutions from all appropriate sites contributing data, analyses and comments. Site principal investigators will be invited to contribute to writing and reviewing the primary manuscripts and abstracts. The primary manuscript and abstracts will undergo review by the steering committee and internal peer review by the CCCTG.

For the main results, we plan to submit an abstract for presentation at an international critical care meeting and possibly to national meetings, and we plan to submit a manuscript for publication in an international medical journal.

Additional secondary analyses, using the database, can be proposed by investigators and will be discussed with the steering committee.

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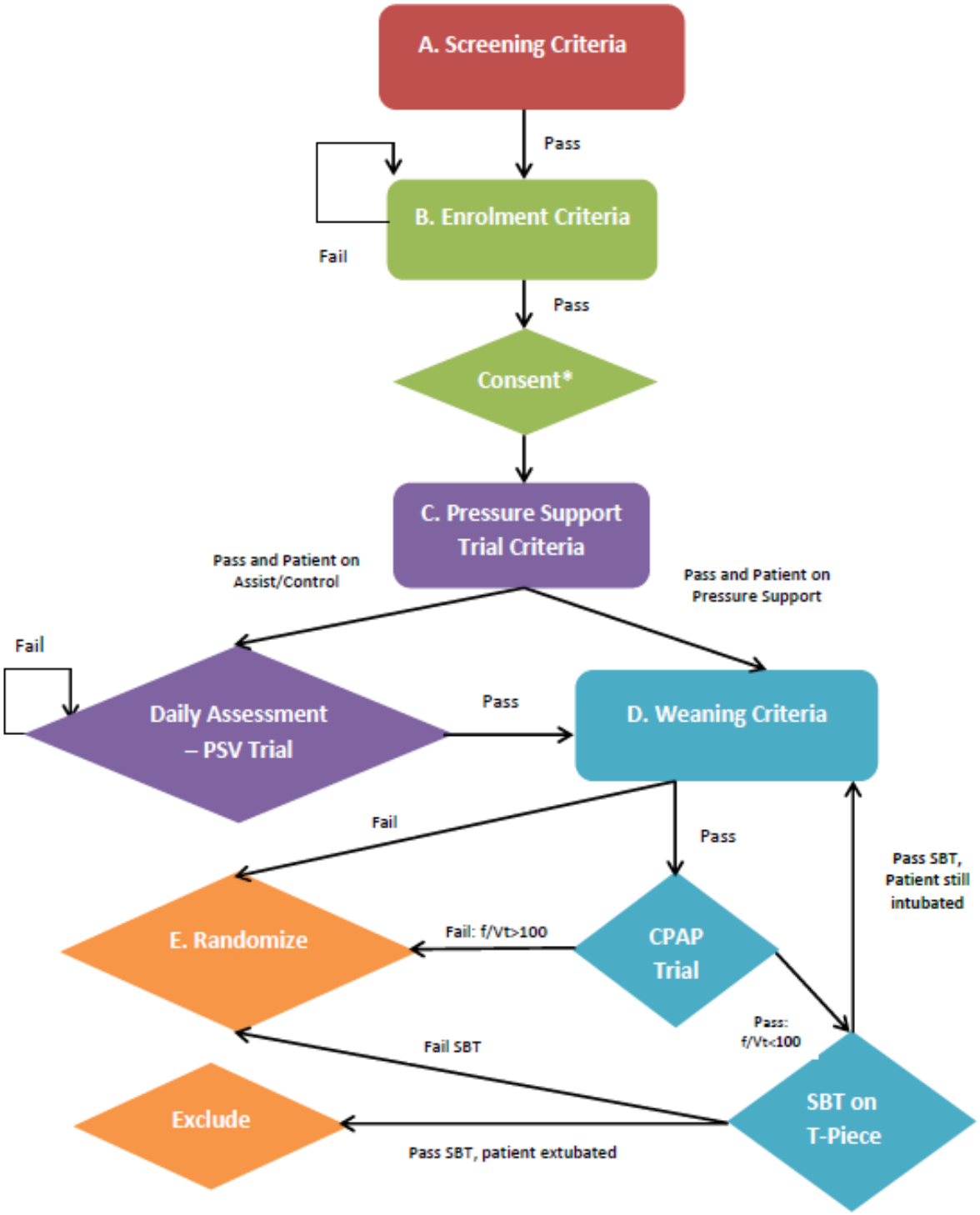
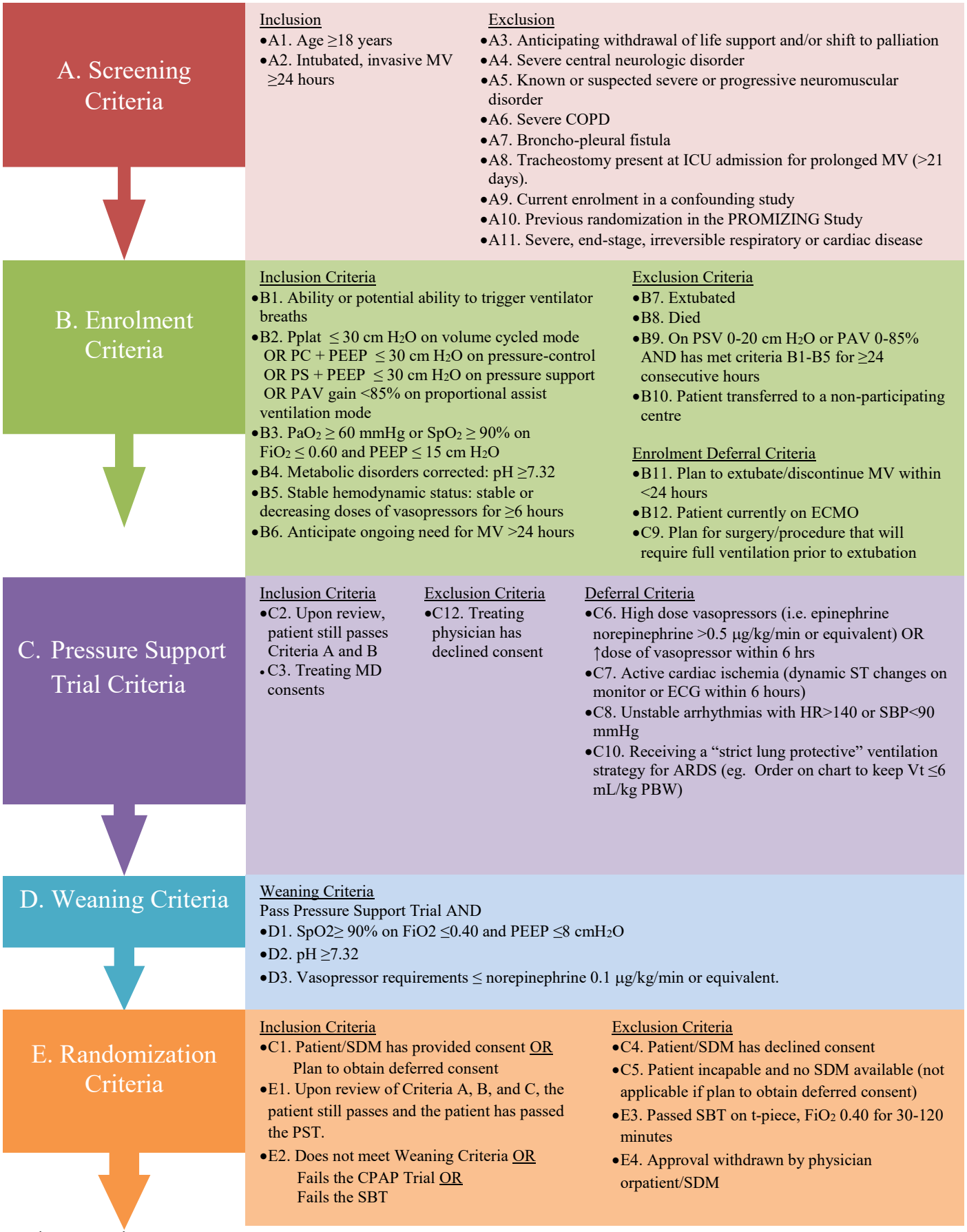
Appendices

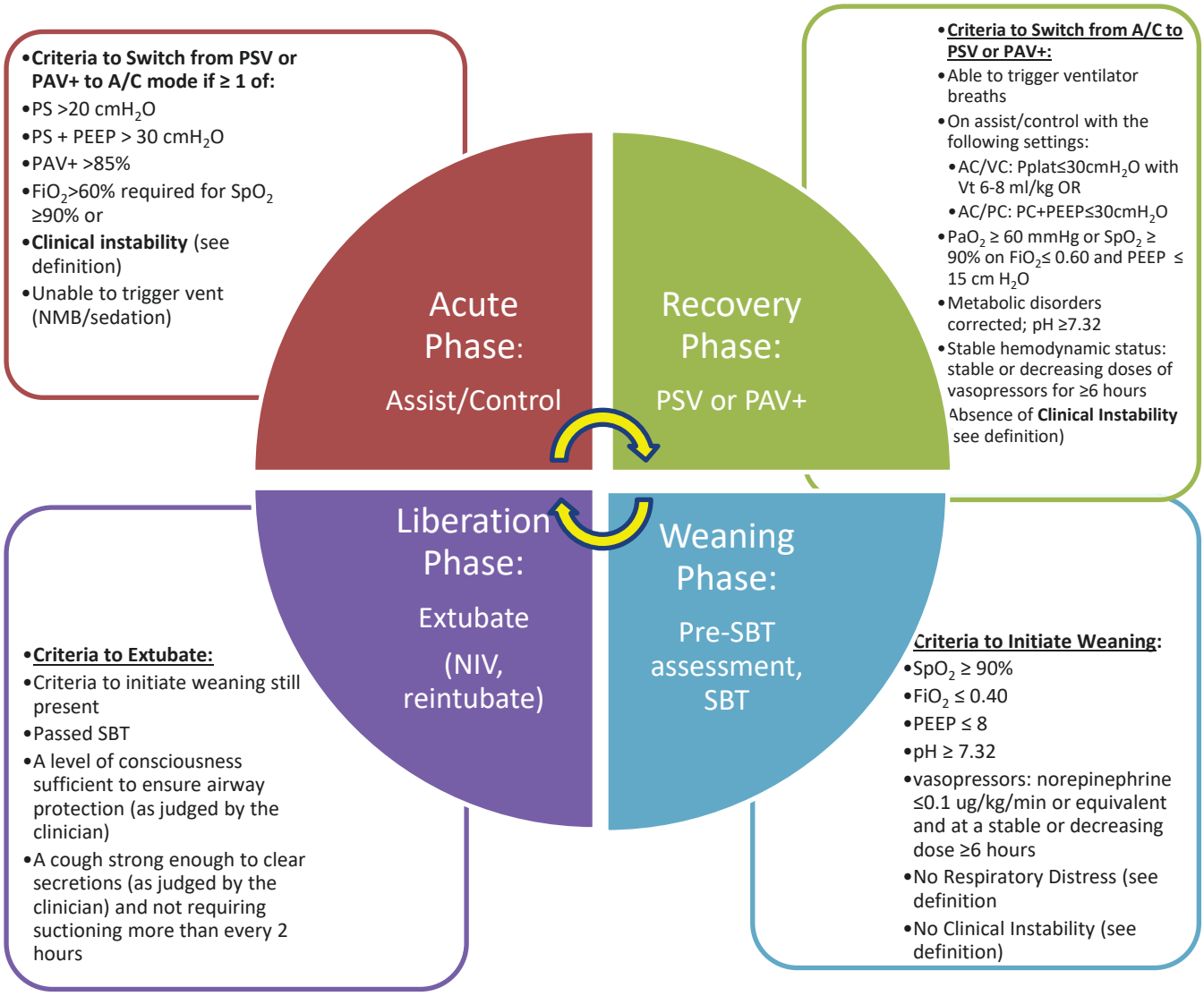
Appendix A: Enrolment Algorithm



* Obtaining consent prior to randomization is preferred; however, randomization of eligible patients may proceed with deferred consent if the patient is incapable and no SDM can be contacted despite at least two attempts.


A. Screening Criteria
Inclusion
•A1. Age ≥18 years
•A2. Intubated, invasive MV ≥24 hours
Exclusion
•A3. Anticipating withdrawal of life support and/or shift to palliation
•A4. Severe central neurologic disorder
•A5. Known or suspected severe or progressive neuromuscular disorder
•A6. Severe COPD
•A7. Broncho-pleural fistula
•A8. Tracheostomy present at ICU admission for prolonged MV (>21 days).
•A9. Current enrolment in a confounding study
•A10. Previous randomization in the PROMIZING Study
•A11. Severe, end-stage, irreversible respiratory or cardiac disease
B. Enrolment Criteria
Inclusion Criteria
•B1. Ability or potential ability to trigger ventilator breaths
•B2. Pplat ≤ 30 cm H2O on volume cycled mode OR PC + PEEP ≤ 30 cm H2O on pressure-control OR PS + PEEP ≤ 30 cm H2O on pressure support OR PAV gain <85% on proportional assist ventilation mode
•B3. PaO2 ≥ 60 mmHg or SpO2 ≥ 90% on FiO2 ≤ 0.60 and PEEP ≤ 15 cm H2O
•B4. Metabolic disorders corrected: pH ≥7.32
•B5. Stable hemodynamic status: stable or decreasing doses of vasopressors for ≥6 hours
•B6. Anticipate ongoing need for MV >24 hours
Exclusion Criteria
•B7. Extubated
•B8. Died
•B9. On PSV 0-20 cm H2O or PAV 0-85% AND has met criteria B1-B5 for ≥24 consecutive hours
•B10. Patient transferred to a non-participating centre
Enrolment Deferral Criteria
•B11. Plan to extubate/discontinue MV within <24 hours
•B12. Patient currently on ECMO
•C9. Plan for surgery/procedure that will require full ventilation prior to extubation
C. Pressure Support Trial Criteria
Inclusion Criteria
•C2. Upon review, patient still passes Criteria A and B
•C3. Treating MD consents
Exclusion Criteria
•C12. Treating physician has declined consent
Deferral Criteria
•C6. High dose vasopressors (i.e. epinephrine norepinephrine >0.5 µg/kg/min or equivalent) OR ↑dose of vasopressor within 6 hrs
•C7. Active cardiac ischemia (dynamic ST changes on monitor or ECG within 6 hours)
•C8. Unstable arrhythmias with HR>140 or SBP<90 mmHg
•C10. Receiving a "strict lung protective" ventilation strategy for ARDS (eg. Order on chart to keep Vt ≤6 mL/kg PBW)
D. Weaning Criteria
Weaning Criteria
Pass Pressure Support Trial AND
•D1. SpO2≥ 90% on FiO2 ≤0.40 and PEEP ≤8 cmH2O
•D2. pH ≥7.32
•D3. Vasopressor requirements ≤ norepinephrine 0.1 µg/kg/min or equivalent.
E. Randomization Criteria
Inclusion Criteria
•C1. Patient/SDM has provided consent OR Plan to obtain deferred consent
•E1. Upon review of Criteria A, B, and C, the patient still passes and the patient has passed the PST.
•E2. Does not meet Weaning Criteria OR Fails the CPAP Trial OR Fails the SBT
Exclusion Criteria
•C4. Patient/SDM has declined consent
•C5. Patient incapable and no SDM available (not applicable if plan to obtain deferred consent)
•E3. Passed SBT on t-piece, FiO2 0.40 for 30-120 minutes
•E4. Approval withdrawn by physician orpatient/SDM

Appendix B: Criteria to Change Mode of Ventilation



Definition of Clinical Instability

Any 1 of the following:

1. Unstable hemodynamic status (SBP<80 mmHg) with or without vasoactive drug
2. Vasopressor requirements >0.5 μg/kg/min epinephrine/norepinephrine or equivalent
3. Active cardiac ischemia (dynamic ST changes on cardiac monitor or electrocardiogram)
4. Unstable arrhythmias (HR >140 or <50) with clinical signs of low cardiac output or SBP<80 mmHg)
5. Uncontrolled hypertension (SBP>180 mmHg)
6. Abrupt decrease in the level of consciousness (RASS -4 or -5 or SAS 1 or 2)
7. Dangerous agitation (RASS ≥+3 or SAS ≥6)
8. Metabolic (or mixed) acidosis with pH <7.32
9. Emergency situation that merits return to full ventilation (A/C) according to best clinical judgement

Appendix C: PAV+ Ventilation Strategy

Assess at least once daily *while on A/C for Criteria for Switching from A/C to PAV*

INITIATION OF PAV

Ventilator Settings:
IBW (Ideal Body Weight): Correct PBW (Predicted Body Weight
Tube Type: ET or Trach
PAV %support/gain:70%
Inspiratory trigger: per clinician
Expiratory trigger (Esens): 3 L/min
PEEP: at previous level
FiO_2: at lowest level required to keep SpO_2 90-96%

Alarm Settings:
Paw max: 40 cmH_2O
RR max: 38 b/min
Vte max: 12 mL/kg of PBW
Vte min: 0 mL
VE max: 20 L/min
VE min: 5 L/min
Apnea setting: 20 s

Assess at least every 8 hours *while on PAV to determine if adjustments are needed to maintain Target Range*

**Repeat blood gas q 30 min as needed to confirm pH 7.32-7.47*

†Best clinical judgement should always prevail in setting of deterioration, with frequent reassessment until stable

ALGORITHM TO ADJUST PAV BASED ON PHYSIOLOGIC AND CLINICAL PARAMETERS

No Respiratory Distress:
Calculate $P_{mus,Peak}$

- $P_{mus,Peak}$ <5 cmH_2O → Decrease gain in steps of 10% until $P_{mus,Peak}$ 5-10 cmH_2O
- $P_{mus,Peak}$ 5-10 cmH_2O → **Target range achieved:** No adjustments required unless:
- $P_{mus,Peak}$ >10 cmH_2O → Increase the gain in steps of 10% until $P_{mus,Peak}$ 5-10 cmH_2O

RR <12 or >35 or Vte <5 or >10 mL/kg PBW:
Obtain arterial blood gas.
No adjustments required unless:

- Respiratory alkalemia → Treat any apparent cause of hyperventilation (eg. Pain, anxiety, metabolic acidosis) → Decrease gain in steps of 10% until Vte <8 mL/kg PBW and/or pH≤7.47
- Respiratory acidemia or **Respiratory Distress** (see definition) → **Increase PEEP in steps of 2 cmH_2O** until Compliance no longer increases → Increase FiO_2 as needed to keep SpO_2>90% → Increase PAV %support/gain in steps of 10% until respiratory distress resolves and pH ≥7.32 (confirm on blood gas*) → Switch to A/C mode if ≥ 1 of:
  PAV gain>85%
  FiO_2>60% required for SpO_2 ≥90%
  Clinical instability (see definition)†
  Unable to trigger vent (NMB/sedation)
  → *Reassess within 24 hours for Criteria for Switching from A/C to PAV*

Respiratory Distress with ≥2 signs:
See definition → Assess PAV+ Resistance (R) and Compliance (C) measurements. Treat any apparent cause of increased R (eg. secretions, bronchospasm) or decreased C (eg. pulmonary edema)

Assess at least once daily *while on PAV for Criteria to Initiate Weaning; Attempt to wean FiO_2 to 0.40 and PEEP to ≤8 cmH_2O*

ALGORITHM FOR WEANING

Criteria to Initiate Weaning:
SpO_2 ≥90%
FiO_2 ≤0.40
PEEP ≤8 cmH_2O
pH ≥ 7.32
vasopressors no higher than norepinephrine 0.1 µg/kg/min

→ Pre-SBT readiness assessment:
CPAP 0 cmH_2O and FiO_2 0.40 for 2 min; assess f/Vt

- f/Vt<100 → SBT: t-piece, FiO_2 0.40 for 30 min → Pass SBT: assess for extubation
- f/Vt ≥100 → Return to PAV *Reassess within 24 hr*

Fail SBT → Return to PAV *Reassess within 24 hr*

Appendix D: PSV Ventilation Strategy

Assess at least once daily *while on A/C for Criteria for Switching from A/C to PSV*

INITIATION OF PSV

Ventilator Settings:
PS level: 10-20 cmH_2O or at previous level
Inspiratory trigger: per clinician
Expiratory trigger: 25% of peak $flow_i$
PEEP: at previous level
FiO_2:at lowest level required to keep SpO_2 90-96%

Alarm Settings:
Paw max: per clinician
RR max: 38 b/min
Vte max: 12 mL/kg of PBW
Vte min: 0 mL
VE max: 20 L/min
VE min: 5 L/min
Apnea setting: 20 s

Assess at least every 8 hours *while on PSV to determine if adjustments are needed to maintain Target Range*

**Repeat blood gas q 30 min as needed to confirm pH 7.32-7.47*

†Best clinical judgement should always prevail in setting of deterioration, with frequent reassessment until stable

ALGORITHM TO ADJUST PSV BASED ON CLINICAL PARAMETERS

No Respiratory Distress:
Patient appears comfortable
RR 12-35 and Vte 5-10 mL/kg PBW

Target range achieved.
No adjustments required unless one of the following occurs:

RR <12 or >35 or Vte <5 or >10 mL/kg PBW:
Obtain arterial blood gas.
No adjustments required unless:

- Respiratory alkalemia → Treat any apparent cause of hyperventilation (eg. Pain, anxiety, metabolic acidosis) → Decrease PS in steps of 2-3 cmH_2O until Vte <8 mL/kg PBW and/or pH≤7.47
- Respiratoryacidemia or **Respiratory Distress** (see definition) → Increase PS in steps of 2-3 cmH_2O until respiratory distress resolves and pH ≥7.32 (confirm with repeat blood gas*)

Respiratory Distress with ≥2 signs:
See definition

Treat any apparent cause of respiratory distress (eg. secretions, bronchospasm, pulmonary edema)

Increase FiO_2 and/or PEEP as needed to keep SpO_2>90%

Increase PS in steps of 2-3 cmH_2O until respiratory distress resolves and pH ≥7.32 (confirm with repeat blood gas*)

Switch to A/C mode if ≥ 1 of:
PS >20 cmH_2O
PS + PEEP > 30 cmH_2O
FiO_2>60% required for SpO_2 ≥90%
Clinical instability (see definition)†
Unable to trigger vent (NMB/sedation)

Reassess within 24 hours for Criteria for Switching from A/C to PSV

Assess at least once daily *while on PSV for Criteria to Initiate Weaning; Attempt to wean FiO_2 to 0.40 and PEEP to ≤8 cmH_2O*

ALGORITHM FOR WEANING

Criteria to Initiate Weaning:
SpO_2 ≥90%
FiO_2 ≤0.40
PEEP ≤8 cmH_2O
pH ≥ 7.32
vasopressors no higher than norepinephrine 0.1 μg/kg/min

Pre-SBT readiness assessment:
CPAP 0 cmH_2O and FiO_2 0.40 for 2 min; assess f/Vt

- f/Vt<100 → SBT: t-piece, FiO_2 0.40 for 30 min → Pass SBT: assess for extubation
- f/Vt ≥100 → Return to PSV *Reassess within 24 hr* ← Fail SBT

Appendix E: Richmond Agitation Sedation Scale (RASS)

C. Sessler,M. Gosnell, M. Grap , G. Brophy, P. O'Neal , K. Keane, E. Tesoro, R. Elswick. "The Richmond Agitation–Sedation Scale", *Am. J. Respir. Crit Care Med*, vol. 166, no. 10 (2002), pp. 1338-1344.

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained (> 10 seconds) awakening, with eye contact, to voice
-2	Light Sedation	Any movement (but no eye contact) to voice
-3	Moderate Sedation	Movement or eye opening to *voice* **(but no eye contact)**
-4	Deep Sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under description)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
Patient has any movement to physical stimulation (score −4).
Patient has no response to voice or physical stimulation (score −5).

Appendix F: Sedation Agitation Scale (SAS)

Riker Sedation-Agitation Scale (SAS)*[Need to Verify/reconcile citation, likely Prospective evaluation of the sedation-agitation scale in adult ICU patients. Crit Care Med 1999;27:1325-1329.]*

Score	Term	Description
7	Dangerous Agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and Cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Procedure for SAS Assessment

1. Agitated patients are scored by their most severe degree of agitation as described
2. If patient is awake or awakens easily to voice ("awaken" means responds with voice or head shaking to a question or follows commands), that's a SAS 4 (same as calm and appropriate – might even be napping).
3. If more stimuli such as shaking is required but patient eventually does awaken, that's SAS 3.
4. If patient arouses to stronger physical stimuli (may be noxious) but never awakens to the point of responding yes/no or following commands, that's a SAS 2.
5. Little or no response to noxious physical stimuli represents a SAS 1.

This helps separate sedated patients into those you can eventually wake up (SAS 3), those who can't awaken but can arouse (SAS 2), and those you can't arouse (SAS 1).