Cover Letter

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

NCT number: NCT02447692

Document: Statistical Analysis Plan

Date of document: 08 July 2024

Statistical Analysis Plan for PROMIZING study

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Version: 1.1
Revision Date: July 8, 2024
Final Sign-off Date:

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1 Study Design and Research Questions

1.1 Summary of Design

The Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation (PROMIZING) study is a multi-centre, open-label, randomized controlled trial designed to determine if, ventilation with proportional assist ventilation with load-adjustable gain factors (PAV+) will result in a shorter duration of time spent on mechanical ventilation compared to ventilation with pressure support ventilation (PSV) for patients with acute respiratory failure (ARF). Trial participants will include adult patients who are receiving invasive mechanical ventilation (IMV) for acute respiratory failure, are ventilated in Assist/Control (A/C) mode, and are ready to be maintained with partial ventilatory support but not yet ready for extubation.

1.2 Primary Research Question

The primary research question is whether 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 compared to ventilation with PSV for patients with acute respiratory failure.

1.3 Secondary Research Questions

The secondary research question is to determine whether other clinically important outcome measures are improved with PAV+ as compared to PSV. The primary and secondary research questions will be addressed using both frequentist and Bayesian methods.

1.4 Post-hoc pre-specified Research Questions

An additional pre-specified post-hoc research question that was developed after the protocol is to determine if there is heterogeneity of treatment effect within the study cohort. This will involve identifying clinically relevant subgroups of patients using cluster analysis techniques.

2 Outcomes

2.1 Primary Outcome

The primary outcome is the time from randomization to successful liberation from invasive mechanical ventilation. Successful liberation is reached the moment IMV is discontinued, provided the subject remains alive and free of IMV for at least 7 days subsequently. In other words, the date of successful liberation is the date of the extubation (or disconnection from ventilator for patients with tracheostomy) that was followed by at least 7 ventilator-free days.

2.2 Secondary Outcomes

The secondary outcomes are

1. Ventilator-free days at day 14, 21 and 28 post randomization

2. Time from randomization to live ICU discharge (up to day 90)

3. Time from randomization to live hospital discharge (up to day 90)

4. Mortality, measured as time to death, ICU mortality; hospital mortality; 21, 28, and 90 day mortality

5. Weaning Progress, measured as time from randomization to: first SBT; first successful SBT; first extubation or equivalent for tracheostomized patients.

6. Weaning Difficulties: Subjects will be classified in the 5 following groups according the WEAN Safe classification (calculated as time from first SBT/extubation):

(a) Successful liberation less than 24 hrs

(b) Successful liberation greater than 24 hrs but less than 7 days

(c) Successful liberation greater than 7 days

(d) Unsuccessful liberation – alive but remain ventilator dependent at day 90

(e) Died prior to successful liberation

7. Weaning Complications, measured as the number of patients

- used non-invasive ventilation post-extubation

- ventilated more than 7 days post randomization

- ventilated more than 21 days from time of 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)

8. Safety and Tolerance of modes

- Number of patients ever requiring A/C mode post randomization

- Number of patient-days requiring A/C mode post randomization

- Frequency and severity of reported serious adverse events across groups

9. Co-interventions are also monitored, including sedatives and anti-psychotic medications.

2.3 Exploratory outcomes

2.3.1 Status at 90 days

We will create a composite outcome to reflect status at 90 days. This outcome will be an ordinal outcome with the following categories listed from worse outcome to best outcome:

1. Died

2. Remaining on ventilation at any location

3. Not ventilated but remaining in hospital or ICU

4. Discharged from hospital not ventilated

3 Covariates of interest

The following were pre-specified as covariates are of particular interest

1. Duration of mechanical ventilation prior to randomization in 1) days and 2) as a binary indicator for greater than 5 days or not.

2. 2. Failed spontaneous breathing trial (SBT) vs. failed continuous positive airway pressure (CPAP) zero trial (CPAP trial of 0 cmH2O) vs. failed weaning criteria prior to randomization

3. Failed extubation prior to randomization (Failed extubation vs. No extubation attempt prior to randomization)

4. Mild, moderate, severe frailty assessed using the Clinical Frailty Scale (CFS) [1]. There should not be anyone with CFS 9 (Terminally ill) in the study based on the inclusion criteria

- Mild: CFS 1 to 3 (very fit to managing well)

- Moderate: CFS 4 to 6 (managing well to mildly frail)
- Severe: CFS 7 to 8 (severely frail to very severely frail)

In addition to the above pre-specified covariates, we will explore the effects of baseline cumulative fluid balance and baseline sedation category in adjusted analyses. In addition, baseline use of antipsychotics, neuromuscular blockers and steroids will be described.

4 Analysis Sets

4.1 Intention To Treat Sample

All analyses will use the intention to treat sample. The intention to treat sample will be comprised of all randomized patients who started the study intervention, irrespective of compliance to their randomized group. Patients will contribute outcome data to the analysis based on the randomized group.

4.2 Per Protocol Sample

The per-protocol sample will include only those randomized patients who stayed on the study protocol until successful liberation from IMV, 90 days, or death, whichever came first. The per-protocol sample will exclude subjects who were withdrawn from the study, or spent more than 48 hours in a non-protocolized mode of ventilation duringthe first 21 days (neither PAV, nor PSV, nor CPAP, nor AC). Note that use of assist-control mode in either volume or pressure control was allowed per protocol in each arm of the study. The per-protocol sample will also exclude patients who were transferred to another centre or ward prior to completing the study protocol, with the exception of patients who were transferred for palliation and died within 7 days of transfer; such patients will be considered to have completed the study protocol, and will be included in the per protocol sample.

5 Statistical Methods

5.1 Sample Size Justification

Sample size was calculated based on the primary outcome of time to first successful liberation from mechanical ventilation. The calculation treated death as a censoring event. Sample sizes assuming a hazard ratio ranging between 1.2 to 1.3 were calculated. We used 80% power and a 2-sided type I error of 5%. We also assumed a 5% rate of dropout.

As planned a priori, aggregate blinded data from the first 120 patients was used to re-estimate the sample size. Median time to successful liberation in the entire cohort was 6.8 days. The minimal clinically important difference was deemed to be 1 day. Assuming a hazard ratio of 1.3, to demonstrate a reduction in the median duration of ventilation by 1.78 days, we will require 529 patients or 558 patients if we assume a loss to follow-up of 5%. Assuming a hazard ratio of 1.25 will require 770 patients to demonstrate a difference of 1.5 days (Table xx). We expect to enroll a minimum of 558 patients within the planned 5 year of enrollment.

5.2 Handling of Incomplete Data

It is important to realize that the problem of incomplete data is distinct from ITT. The ITT philosophy is to attribute the available patient data to the group they were randomized to, irrespective of compliance to randomization. However, it is not possible to analyze data that you do not have. Therefore, we will begin with the complete case analysis. However, this analysis can be biased, although if missing data is minimal, less than 5% say, bias will be minimal and conclusions will not be affected by more sophisticated approaches.

There is controversy regarding the appropriateness of imputing outcome data in clinical trials. Therefore, even if loss to follow-up (i.e. missing outcome) exceeds 5% no imputation methods will be employed for post-randomization outcomes. The main value of imputation techniques is to enable an analysis to use all

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	1098	1157
7.60	6.08	1.52	1.25	630	731	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	6.76	1.54	1.25	630	733	772
7.70	5.92	1.78	1.30	456	529	557

complete data. Some unpublished simulations developed by the statistician demonstrate that if the outcome is the only thing missing, even if missing at random, multiple imputation has virtually no effect on bias or precision. Furthermore, post-randomization outcome data is frequently not missing at random and other simulations conducted by the statistician show multiple imputation may not correct the bias incurred by data not missing not at random. Also note that since the primary analysis is a time-to-event analysis, no subjects are dropped from the analysis, they are simply censored if necessary. Multiple imputation may be employed to handle missing covariate data in secondary, adjusted analyses.

5.3   Inverse Probability Weighted Analysis

In analyses that do not employ survival analysis methods where there is enough missing outcome data to cause concern for the complete case analysis, an inverse probability weighted analysis will be conducted. This is a two-step process.

First, a logistic regression model (or machine learning model) is fit to the complete ITT sample. The outcome for this model is 1 if the follow-up data (outcome) is present and 0 if missing. A list of baseline variables considered most likely to predict drop-out will be identified and used as covariates in the logistic regression model. The idea here is to obtain a model that predicts well who was complete and who was not. Once the model is fit, it will be used to generate predicted probabilities of "not being missing" for each patient.

The second stage proceeds on the complete case data as before, however the reciprocals of the predicted probabilities from the previous stage are used as regression weights. This weighted analysis attempts to correct for the selection bias that could exist in the complete case analysis.

5.4   Regarding P-Values and Statistical Significance

Controversy continues to exist around the use of p-values and significance testing. The problems are not so much the fault of p-values themselves but arise in the mechanical comparison to an arbitrary threshold of say 0.05 which categorizes results into, "statistically significant" or "not statistically significant." It is in this binary decision that the Type 1 error arises and the risk of making any Type 1 error among all tests increases with the number of tests. It is this problem that leads many to adjust p-values (or equivalently the threshold per test) in analysis.

However, the p-value as it stands simply represents a continuous measurement of the strength of the statistical evidence one has against some hypothesis (no difference between groups in this instance). It is thus best statistical practice to report for all outcomes analyzed, the estimated treatment effect, the 95% (or some other suitable level) confidence interval (CI) and the p-value. This is the practice that will be adopted in the analysis. This gives a reader all of the necessary information to put the results into proper context. Note that the policy of some journals to request only the CI does not solve the problem it is intended to solve. Specifically, a reader will still mentally make the "significance conclusion" entirely through the CI.

Finally, the ASA statement on p-values [2] recommends all computed p-values be reported to provide sufficient context to evaluate the evidence in totality.

5.5 Descriptive analysis

5.5.1 Baseline characteristics

Baseline data will be described using mean and standard deviation, median and interquartile range, counts and percentages as appropriate. Baseline characteristics will include but will not be limited to

- Diagnosis (operative vs. non-operative)
- Subdiagnosis for non-operative subjects (respiratory, cardiovascular, other)
- Charlson comorbidity index and components
- APACHE score
- SOFA score
- Cumulative fluid balance
- Neuromuscular blockade
- Steroid use
- Antipsychotic use
- Baseline sedation category

5.5.2 Co-interventions

Co-interventions occurring during the study will be described as well as other patient characteristics that were collected during follow-up such as SOFA score , daily fluid balance, cumulative dose of sedating medications, number of patients and patient-days receiving any antipsychotic medication.

Sedating Medications and Sedation, Agitation, and Delirium Scores:

Sedating medications are routinely administered as part of routine ICU care, and may influence duration of IMV (reference). As such, they are co-interventions. However, a patient's requirement for sedating medications may be influenced by many factors, including acuity of illness, presence of delirium, pain, and patient-ventilatory dyssynchrony. Since patient-ventilator dyssynchrony may differ between PAV+ and PSV, mode of ventilation may influence amount of sedating medications administered, and amount of sedating medications administered may in turn influence duration of IMV. We will take the following approach to analyzing sedating medications and sedation, agitation, and delirium scores:

Drug conversions

1. Opioids – daily total dose of all opioid medications will be converted to morphine IV equivalents (references)

2. Benzodiazepines – daily total dose of all benzodiazepine medications, propofol and dexmedetomidine will be converted to midazolam IV equivalents (reference)

3. Other sedative infusions – we had planned to analyze propofol, dexmedetomidine, and ketamine separately; however, a recent study by Waldrop et al. described a method for converting propofol and dexmedetomidine to midazolam equivalents based on "expert opinion and clinical practice;" we will use their conversion factor to convert propofol and dexmedetomidine to midazolam equivalents and include in the total daily dose of midazolam IV equivalents. Ketamine will be analyzed independently.

Drug doses will be compared across groups using mixed effects models adjusted for baseline and with a time by treatment interaction term.

The number of patients and number of patient-days receiving any antipsychotic medication will be compared between groups.

Sedation/agitation scores

Different scoring systems were used across institutions to assess the level of sedation or agitation and included the Richmond Agitation Sedation Score (RASS), the Riker Sedation-Agitation Scale (SAS) , or the Ventilator-Adjusted Motor Activity Assessment Scale (VA-MAAS). Sedation was scored twice daily (morning score and highest daily score) using whatever scale was in use at each participating centre. Each score will be analyzed separately, and scores will be converted to 4 categories using the following conversion table derived from Khan et al 2012[3], and analyzed descriptively.

Category	RASS	VAMASS	SAS
Moderate to deep sedation	**-3 to -5**	**0 to 1**	**1-2**
Light sedation	**-2 to -1**	**2**	**3**
Alert and calm	**0**	**3**	**4**
Restless/Agitated	**+1 to +4**	**4 to 6**	**5 to 7**

Delirium score

Delirium category will be assessed in a subset of patients where data is available using a combination of two scoring systems: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) values as follows:

1. Delirium not assessed: either missing data or marked as not assessed in database

2. Too sedated to assess = Coma

3. Delirious (CAM-ICU positive, ICDSC 4-8)

4. Not delirious (CAM-ICU negative, ICDSC 0-3)

The delirium category will be described over the study period for each group.

5.6 Primary Outcome

The primary outcome of time to successful liberation from mechanical ventilation will be summarized using cumulative incidence curves with death considered to be a competing risk. Cumulative incidence will be compared across groups using Gray's test.

5.6.1 Primary Analysis

Treatment effect will be reported as a hazard ratio with 95% confidence interval. The primary analysis will use a mutistate generalization of the Cox proportional hazard model. This approach simultaneously models the association between treatment and all transitions in the model. Missing outcome data will be treated as censored at the date of last contact.

Figure 1: State transition diagram
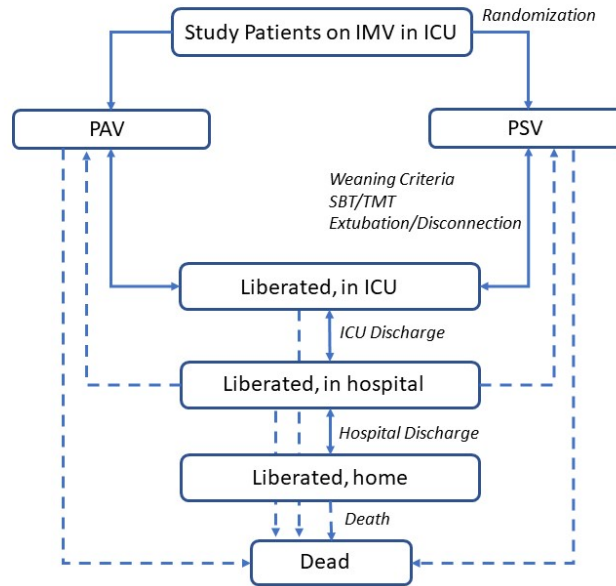
Figure 1: State transition diagram
IMV = invasive mechanical ventilation; SBT = spontaneous breathing trials; TMT =tracheostomy mask trials; ICU = intensive care unit

5.6.2 Secondary Analyses

A secondary analysis will be performed using a cause-specific Cox model to model the treatment effect on successful liberation with death prior to successful liberation treated as a censoring event.

5.7 Secondary Outcomes

The outcomes related to weaning progress and difficulties (listed below) also suffer from the competing risk of death and other improper subgroup issues. and will be looked at primarily descriptively.

- **Time to death:** will be analyzed using standard methods for survival data namely Kaplan-Meier curves and log-rank test. Treatment effects will be reported as hazard-ratios with 95% confidence intervals.

- **Time from randomization to live ICU discharge (up to day 90) and time from randomization to live hospital discharge (up to day 90):** Those two outcomes both have death as a competing risk. Cumulative incidence curves will be constructed to provide estimates of live ICU discharge and live hospital discharge that account for death. Cause-specific treatment effects on live ICU discharge and live hospital discharge will be reported as hazard ratios with 95% confidence intervals from Cox proportional hazard models.

- **Time from randomization to first SBT, first successful SBT, and first extubation:** These will be looked at primarily descriptively using cumulative incidence curves with death as a competing risk and compared across groups using the Gray's test.

- **Ventilator-free days:**

  Calculation of ventilator-free days

  "Ventilator-free days" (VFDs) are defined as the number of days alive and free of INVASIVE ventilation post SUCCESSFUL LIBERATION (successful extubation or successful termination of invasive MV for

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patients with tracheostomy). Non-invasive ventilation may be used post extubation, but is not counted as "invasive ventilation."

- If the patient dies before achieving successful liberation from invasive MV, that patient will have 0 VFDs.

- However, if a patient dies AFTER achieving successful liberation, 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 extubation, disconnection from invasive MV, ICU discharge, live hospital discharge, or death).

Ventilator-free days will be compared across groups using a Wilcoxon test. The treatment effect will be expressed as the difference in median ventilator-free days and its 95% confidence interval will be estimated using bootstrap methods. As per the calculation above, subjects might have 0 ventilator-free days because either they died before being liberated or they survived but remained ventilated. We will model this using a number of approaches. For the primary analysis, we will assign the value -1 ventilator free days to subjects who died prior to liberation.

The following secondary analyses are also planned to help understand any observed treatment effect.

- Assigning the value of zero ventilator-free days to patients who died prior to being liberated from ventilation and performing a Wilcoxon test

- Poisson regression of the number of days on ventilator with the logarithm of the number of days observed as an offset

- Marginal structural model 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

- Invasively ventilated with tracheostomy and invasively ventilated with ETT

- **Number of patients successfully liberated in less than 24 hours since first SBT or first extubation attempt, number successfully liberated greater than 24 hours but less than 7 days, successfully liberated greater than 7 days, unsuccessful liberation (alive but remaining ventilator dependent at day 90), died prior to successful liberation.** These outcomes will be compared across groups using the Chi-Square or Fisher's exact test.

- **Delirium and sedation scores:** Daily sedation scores will be analyzed as described in Section 5.5.2.

- **Number of patients who received 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):** These outcomes will be compared across groups using the Chi-Square or Fisher's exact test.

- **Number of patients ever receiving A/C mode post randomization (Tolerance of modes):** This outcome will be compared across treatment groups using Chi-Square or Fisher's Exact test and treatment differences will be reported as an odds ratio with 95% confidence interval. Patients not receiving A/C will be assigned a value of zero days. The non-parametric Wilcoxon rank-sum test will be favoured over the parametric t-test for this analysis if there are many zero days entries.

5.8   Exploratory outcomes

Status at 90 days is an ordinal outcome defined in section 2.3.1 and it will be analyzed using ordinal logistic regression.

5.9 Subgroup analyses

There are 4 planned subgroup analyses testing whether the trajectory of baseline characteristics can influence the results. These will be based on:

1. Duration of MV prior to randomization as a continuous variable modeled with restricted cubic splines if necessary to account for potentially nonlinear effects.

2. Status of weaning attempts prior to randomization

   - Failed SBT prior to randomization

   - Failed CPAP (of zero cmH2O) trial prior to randomization

   - Failed weaning criteria prior to randomization

3. Failed extubation prior to randomization

4. Frailty (mild/ moderate/ severe)

In addition, we will explore the possibility of a subgroup analyis by covid status at randomization if there are enough COVID+ subjects. COVID+ will be defined as COVID+ and a respiratory diagnosis

1. COVID positivity at randomization (due to the onset of the pandemic)

2. tracheostomy prior to randomization

5.10 Sensitivity analyses

There are 2 planned sensitivity analyses based on:

1. Defining "successful extubation" as "48 hours without reintubation"

2. Assigning a value of 0 ventilator-free days to any participant who dies at any time during the study period.

6 Bayesian Analyses

The Bayesian analyses will be performed by Arlene Jiang, under the supervision of Drs. Anna Heath and Yongdong Ouyang. The goal of this analysis is to incorporate prior evidence into the analysis of the PROMIZING study. We will analyze the outcomes: time to liberation (in ICU) from mechanical ventilation and ventilator-free days. The analyses will be performed adjusted by the covariates of interest (section 3). Posterior mean, median, and 95% highest density credible intervals will be reported for all model parameters. The probability that the treatment reduces time on ventilation by the minimal clinically important difference (MCID) of 1 day will also be reported.

6.1 Informative Prior Treatment Distributions

Our analyses will incorporate prior information from a pragmatic meta-analysis [4]. Saunders et al. reported that compared to PSV, PAV+ reduced duration on ventilation by 1.53 days (95% confidence interval: 0.83 to 2.24). The meta-analysis estimate will be weighted to 100%, 50%, and 10% to calculate prior distributions, according to the approach in Goligher et al. [5]. Ventilator-free day data from the iCORE dataset were transformed to determine the priors for treatment effects specific to each outcome [6]. The iCORE dataset reports the number of days a patient is off ventilator within 28 days, in patients who have received PSV.

6.2 Bayesian Analysis of Primary Outcome

The primary outcome (time to successful liberation, in ICU from mechanical ventilation) will be analyzed using accelerated failure time (AFT) models. These differ from the proportional hazards models that will be used in the primary frequentist analysis (section 5.6.1) because they require distributional assumptions

for the hazards. AFT models are better suited to this context because Bayesian methods assume that all parameters have a distribution. These models will estimate time ratios, which can be interpreted as the multiplicative effect of a covariate on survival time.

As specified in the primary frequentist analysis, each transition in Figure 1 will be modelled. To maximize model flexibility, each transition will be fit to a separate AFT distribution [7]. For each transition, we will select the best model among exponential and Weibull AFT families. The model with the lowest AIC will then be modeled in INLA [8, 9].

Semi-Markov modelling will be implemented, based on clinical knowledge that the probability of transitioning would depend on the time spent in each state. For these models, time will reset to 0 when patients enter each new state.

6.2.1 Informative Prior Treatment Distribution for the Transition Between Invasive Ventilation to Liberated, In ICU

We will use an informative prior for the treatment effect on the transition between invasive ventilation to liberation, in ICU. To determine the prior, we assumed that the number of ventilator-free days in the baseline dataset would roughly correspond to the time that patients were freed from ventilation. Patients with 28 ventilator-free days were considered freed on day 0. These patients were assigned a time of 0.001, as only non-zero times could be included in AFT models. For patients with 1 to 27 ventilator-free days, the difference between 28 days and the number of ventilator-free days was considered the time to being freed from ventilation. Patients who died or started off-ventilator were excluded.

Each AFT family in the *survival* package was fit to the dataset [10]. The fitted estimates were used to generate 50000 observations from these distributions. Exponential and Weibull distributions were selected, with time ratios between the true and simulated datasets between 1 and 1.002. The AIC values, indicating the fit of these distributions to the baseline data, are presented below. The treatment effect was estimated by simulating data with incrementally decreasing location parameters within the location-scale parameterizations of the distributions. The coefficient value that generated a difference in means equal to the treatment effect in the meta-analysis (1.53 days) is reported in the table below. Standard deviations were derived by the same method with differences in means equal to estimates of the 95% confidence interval (0.83 or 2.24 days). As a conservative estimate, the standard deviation was calculated from the larger tail of the confidence interval, although estimates from either tail remained within 0.03 of each other. The MCID values were also estimated as log-time ratios using the method described above.

We will select the best fitting family, based on AIC, between exponential and Weibull distributions to model this transition with an informative prior. If there is a family that fits substantially better than exponential or Weibull, we will model this transition with a minimally informative prior for treatment in INLA.

Family	μ	σ_{100}	σ_{50}	σ_{10}	MCID	AIC
Exponential	-0.26	0.074	0.10	0.23	-0.16	10434.87
Weibull	-0.15	0.051	0.73	0.16	-0.098	8625.836

6.3 Bayesian Analysis of Secondary Outcome

The secondary outcome, ventilator-free days at 28 days, will be analyzed as ordinal data. This outcome is measured to the nearest tenth of a day in the trial, but will be rounded to the closest integer such that ventilator-free days can be analyzed as an ordinal variable. There are 30 levels for ventilator-free days at day 28, specifying a patient death (-1) and the number of days off ventilator (0 to 28). A cumulative logistic regression model will be used to analyze ventilator-free days with brms and stan [11, 12].

Log-odds ratios were estimated for the secondary ventilator-free day outcomes. We performed a grid search to find a difference in odds equivalent to reducing the mean time on ventilation by 1.53 days. The prior for this analysis is included below. Due to the composite nature of this endpoint, this prior assumes a different rate of mortality for those treated with PAV+. We assumed a mortality rate of 23.1% for PSV, based on

the iCORE dataset, and a mortality rate of 18.9% for PAV+. Based on the described grid search method, we found the MCID as a log-odds ratio reported below.

Outcome	μ	σ_{100}	σ_{50}	σ_{10}	MCID
Ventilator-Free Days at 28	0.25	0.060	0.085	0.19	0.17

7 Cluster analysis

The cluster analysis will be performed by Kaitlyn Wade under the supervision of Dr. Pingzhao Hu at the University of Western Ontario. Data quality will first be evaluated and unsupervised feature screening will be performed if necessary. Then, an estimation of the number of potential clusters in the data set will be performed. A consensus clustering approach will be used to identify the clusters in the data set as has been used before for breast cancer stratification [13]. The quality of the identified clusters will be evaluated using the internal metrics (e.g. Silhouette coefficient) and external metrics (depending on the clinical information available in the data set, e.g. survival) [14]. Other commonly used clustering approaches, such as k-means, hierarchical clustering, and advanced deep learning based approaches will be considered if necessary.

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Statistical Analysis Plan for the Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation (PROMIZING) Study

Principal Investigators:	Karen Bosma and Laurent Brochard
Version:	1.2
Revision Date:	July 26, 2024
Final Sign-off Date:	
Protocol Title:	Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation: The PROMIZING Study
Protocol Version:	5.0
Protocol Version Date:	December 1, 2019
Trial Registration:	ClinicalTrials.gov NCT 02447692. Prospectively registered on May 19, 2015.

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Document history:

Version	Reason for Change	Sign-off Date
Version 1.0	Original	April 30 2024
Version 1.1	Change the names of contributors to the Bayesian and Cluster analysis, and change Figure 1, the State transition diagram, with corresponding updates to the Bayesian analysis plan.	July 14 2024
Version 1.2	Addition of background information (from protocol manuscript, as published in Trials)	July 26 2024

The Statistical Analysis Plan (SAP) for the PROMIZING Study and subsequent revision was finalized prior to any statistical analysis of the data. There were no interim analyses.

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The following documents were reviewed when preparing this SAP:

1. Published Clinical Research Protocol for the PROMIZING Study [1]

2. Electronic case report forms (Version 2.0) and the Data Management Plan (Version 2.0) for the PROMIZING Study

3. The Operations Manual (Version 1.0) for the PROMIZING Study

4. Data Safety Monitoring Board (DSMB) Charter (March 8 2016) for the PROMIZING Study

5. ICH Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials [2]

6. ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials [3]

Contents

1 Introduction: Study Design and Research Questions

1.1 Background and rationale

Patients with acute respiratory failure (ARF) require invasive mechanical ventilation (MV) to support their work of breathing and provide adequate gas exchange until they recover from their acute illness. Although clinicians aim to wean and liberate patients from MV as soon as patients are capable of breathing unsupported, MV itself may induce respiratory muscle weakness, [4, 5, 6] patient-ventilator dyssynchrony [7, 8] and necessitate the administration of sedative drugs, all of which have been associated with a prolonged duration of dependence on MV. Since prolonged invasive ventilation is associated with increased morbidity and mortality [9, 10, 11], a major goal is to minimize the duration of weaning and aim for the highest proportion of patients successfully liberated from MV [12] . Avoidance of respiratory muscle atrophy, patient-ventilator dyssynchrony, and heavy sedation may enable clinicians to achieve this goal. Ideally, minimizing respiratory muscle atrophy and patient-ventilator dyssynchrony should theoretically occur if the level of ventilator assistance is adjusted to target normal or reasonable levels of respiratory effort [7, 8, 13] .

Proportional assist ventilation with load-adjustable gain factors is a mechanical ventilation mode (PAV+ mode) that delivers assistance to breathe in proportion to the patient's effort [14, 15] . 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. PAV+ mode is the only ventilation mode that allows measurement and targeting of a specific range of respiratory muscle activity by the patient [16] . Currently, pressure support ventilation (PSV) mechanical ventilation mode is the most common mode used after the acute phase of illness [17] and thus may be considered the standard of care for assisted breathing of patients during the recovery phase of acute respiratory failure [18]. Several small 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 [7, 12, 19, 20, 21, 22] . One randomized controlled trial (RCT) compared PAV+ mode to PSV over 48 hours and demonstrated it was better tolerated [23], but to date, there has been no large, multi-centre RCT comparing the two modes head-to-head to evaluate impact on clinically important, patient-centred outcomes. This study is poised to answer several research questions that have remained unanswered to date: (1) Does PAV+, set to maintain a workload of breathing within the normal range, decrease duration of MV and (2) improve other clinical outcomes compared to the current standard of care using PSV? (3) Do patients randomized to PAV+ receive fewer administered sedatives and/or antipsychotic medications than patients randomized to PSV, and (4) are pain/agitation/sedation/delirium scores different between patients on PAV+ vs. PSV? (5) In addition to mode of ventilation, do factors such as age, sex, frailty score, comorbidity index, severity of illness, prior duration of MV, prior SBT/extubation failure, work of breathing, sedation, or early mobilization, influence duration of weaning and weaning success?

1.2 Study Objectives and Hypothesis

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. A third objective of the study is to determine if, in addition to mode of ventilation, factors such as age, sex, frailty score, comorbidity index, severity of illness, prior duration of MV, prior SBT/extubation failure, work of breathing, sedation, or early mobilization, influence duration of weaning and weaning success differently in the two arms.

The hypothesis is that critically ill adult patients supported with PAV+ early in the recovery phase of acute respiratory failure will have a shorter duration of MV compared to PSV.

1.3 Research Questions

1.3.1 Primary Research Question

The primary research question is whether 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 compared to ventilation with PSV for patients with acute respiratory failure.

1.3.2 Secondary Research Questions

The secondary research question is to determine whether other clinically important outcome measures are improved with PAV+ as compared to PSV. The primary and secondary research questions will be addressed using both frequentist and Bayesian methods.

1.3.3 Post-hoc pre-specified Research Questions

An additional pre-specified post-hoc research question that was developed after the protocol is to determine if there is heterogeneity of treatment effect within the study cohort. This will involve identifying clinically relevant subgroups of patients using cluster analysis techniques.

2 Study Methods

2.1 Trial design

The PROMIZING study is a multi-centre, randomized, parallel assignment, open label clinical trial designed with a superiority framework. Neither the clinical team nor the study investigators will be blinded to the study intervention. The study statistician will be blind to the study arm. Allocation ratio is 1:1 to the two arms of the study. Patients randomized to the PAV+ intervention arm will follow a PAV+ ventilation protocol, where PAV+ is set to maintain respiratory muscle pressure within a target range of 5-10 cmH2O. Patients randomized to the PSV control arm will follow a PSV ventilation protocol, where PSV is set to maintain usual clinical parameters of respiratory rate and tidal volume. In both arms, patients who are not tolerating the assigned mode will be placed on assist/control ventilation, and in both arms, patients will undergo daily screening for readiness for liberation with protocolized spontaneous breathing trials.

2.2 Randomization

Each participant in this study will be randomized to either PSV or PAV+ in a 1:1 ratio in a centralized electronic data capture system called Medidata Rave (Medidata, USA). Participant allocation to treatment 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-generated sequence methodology, ensuring that the randomization methodology and the generated allocation sequence are concealed from the investigator and participants.

2.3 Sample Size

Sample size was calculated based on the primary outcome of time to first successful liberation from mechanical ventilation. The calculation treated death as a censoring event. Sample sizes assuming a hazard ratio ranging between 1.2 to 1.3 were calculated. We used 80% power and a 2-sided type I error of 5%. We also assumed a 5% rate of dropout.

As planned a priori, aggregate blinded data from the first 120 patients was used to re-estimate the sample size. Median time to successful liberation in the entire cohort was 6.8 days. The minimal clinically important difference was deemed to be 1 day. Assuming a hazard ratio of 1.3, to demonstrate a reduction in the median

duration of ventilation by 1.78 days, we will require 529 patients or 558 patients if we assume a loss to follow-up of 5%. Assuming a hazard ratio of 1.25 will require 770 patients to demonstrate a difference of 1.5 days (Table xx). We expect to enroll a minimum of 558 patients within the planned 5 year of enrollment.

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	1098	1157
7.60	6.08	1.52	1.25	630	731	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	6.76	1.54	1.25	630	733	772
7.70	5.92	1.78	1.30	456	529	557

2.4 Interim Analyses

No interim analyses of the outcomes will be conducted.

2.5 Timing of outcome assessments

The primary outcome is measured during the participant's initial ICU stay and hospital stay. Secondary outcomes are measured daily during the patients ICU stay, and at time of transfer between ICU and non-ICU hospital beds, at hospital discharge, and at 90 days post randomization.

2.6 Timing of final analysis

All outcomes will be analyzed collectively after the final 90-day follow-up has been completed on the last patient randomized, and the data verification and database locking is complete. Planned analyses identified in the trial protocol and this SAP will be performed only after the last patient has completed the 90 day follow-up assessment visit, the RAVE database has been cleaned and locked, and results from separate analysis for protocol violations and deviations have been completed and declared final. Blinded data review meetings will be held before locking the RAVE database and, again, before declaring final electronic copies of the data in Excel spreadsheets. There will be no un-blinded review and analyses will not commence until the SAP has been approved by the Lead Principal Investigators and Trial Statisticians. Any post-hoc exploratory analyses performed to provide support for planned analyses but not identified in this SAP will be clearly identified as unplanned analyses. All analyses and their interpretation will be conducted independently of the trial funders.

3 Statistical Principles

3.1 Regarding P-Values and Statistical Significance

Controversy continues to exist around the use of p-values and significance testing. The problems are not so much the fault of p-values themselves but arise in the mechanical comparison to an arbitrary threshold of say 0.05 which categorizes results into, "statistically significant" or "not statistically significant." It is in this binary decision that the Type 1 error arises and the risk of making any Type 1 error among all tests increases with the number of tests. It is this problem that leads many to adjust p-values (or equivalently the threshold per test) in analysis.

However, the p-value as it stands simply represents a continuous measurement of the strength of the statistical evidence one has against some hypothesis (no difference between groups in this instance). It is thus best

statistical practice to report for all outcomes analyzed, the estimated treatment effect, the 95% (or some other suitable level) confidence interval (CI) and the p-value. This is the practice that will be adopted in the analysis. This gives a reader all of the necessary information to put the results into proper context. Note that the policy of some journals to request only the CI does not solve the problem it is intended to solve. Specifically, a reader will still mentally make the "significance conclusion" entirely through the CI.

Finally, the ASA statement on p-values [24] recommends all computed p-values be reported to provide sufficient context to evaluate the evidence in totality.

Treatment effect estimates will be reported with their 95% confidence intervals.

3.2 Handling of Incomplete Data

It is important to realize that the problem of incomplete data is distinct from ITT. The ITT philosophy is to attribute the available patient data to the group they were randomized to, irrespective of compliance to randomization. However, it is not possible to analyze data that you do not have. Therefore, we will begin with the complete case analysis. However, this analysis can be biased, although if missing data is minimal, less than 5% say, bias will be minimal and conclusions will not be affected by more sophisticated approaches.

There is controversy regarding the appropriateness of imputing outcome data in clinical trials. Therefore, even if loss to follow-up (i.e. missing outcome) exceeds 5% no imputation methods will be employed for post-randomization outcomes. The main value of imputation techniques is to enable an analysis to use all complete data. Some unpublished simulations developed by the statistician demonstrate that if the outcome is the only thing missing, even if missing at random, multiple imputation has virtually no effect on bias or precision. Furthermore, post-randomization outcome data is frequently not missing at random and other simulations conducted by the statistician show multiple imputation may not correct the bias incurred by data not missing not at random. Also note that since the primary analysis is a time-to-event analysis, no subjects are dropped from the analysis, they are simply censored if necessary. Multiple imputation may be employed to handle missing covariate data in secondary, adjusted analyses.

3.3 Inverse Probability Weighted Analysis

In analyses that do not employ survival analysis methods where there is enough missing outcome data to cause concern for the complete case analysis, an inverse probability weighted analysis will be conducted. This is a two-step process.

First, a logistic regression model (or machine learning model) is fit to the complete ITT sample. The outcome for this model is 1 if the follow-up data (outcome) is present and 0 if missing. A list of baseline variables considered most likely to predict drop-out will be identified and used as covariates in the logistic regression model. The idea here is to obtain a model that predicts well who was complete and who was not. Once the model is fit, it will be used to generate predicted probabilities of "not being missing" for each patient.

The second stage proceeds on the complete case data as before, however the reciprocals of the predicted probabilities from the previous stage are used as regression weights. This weighted analysis attempts to correct for the selection bias that could exist in the complete case analysis.

4 Trial population

The study population eligibility and selection criteria are detailed in the study protocol and summarized briefly below.

4.1 Eligibility Criteria

We will include critically ill adult patients (age $\geq$ 18 years) receiving invasive MV for ARF for at least 24 hours, and judged ready to commence, and be maintained with, partial ventilatory support (tolerating PSV

for at least 30 minutes) (20) but not yet ready for extubation (not yet ready for a spontaneous breathing trial (SBT) or having failed an SBT). The initial screening criteria will include critically ill patients who are:

- A1. Adult patients ≥18 years
- A2. Intubated, or tracheostomized, receiving invasive ventilation ≥ 24 hours

And will exclude patients who meet one or more of the following Screening Exclusion Criteria:

- A3. Anticipating withdrawal of life suport 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

4.2 Screening and Recruitment

We will use a staged recruitment process to identify which eligible patients are enrolled and subsequently randomized in the study if they are not found to be ready for extubation (21), as detailed in the study protocol . The five stages, which are performed to ensure that the patient is ready to tolerate PSV but not ready for extubation at the time of randomization, are as follows: A. Screening Criteria B. Enrolment Criteria and Obtaining Consent C. Pressure Support Criteria and the Pressure Support Tolerance Trial D. Weaning Criteria and the Zero CPAP Trial and the SBT E. Randomization Criteria

4.3 Screening and Recruitment Data

All participating sites are provided detailed screening log templates to track all patients who meet screening inclusion criteria, and record at which of the five stages of recruitment patients are excluded from progressing to the next stage. Screening logs devoid of patient identifiers are sent to the coordinating centre each month. All screening data will be compiled and reported in the CONSORT flow diagram to be included with the publication of the final results. The CONSORT flow diagram will depict (a) the flow of patients through the recruitment process, including the number of patients screened, eligible, enrolled and randomized, and the number of patients excluded and reason for exclusion at each stage; and (b) the flow of patients post randomization (see Figure 1).

Figure 1: CONSORT flow diagram pre-randomization

 # Screened

 # Excluded:
- # Anticipating palliation
- # Severe CNS disorder
- # Neuromuscular disorder
- # Severe COPD
- # Broncho-pleural fistula
- # Tracheostomy present at ICU admission for chronic IMV
- # Severe, end-stage, irreversible respiratory or cardiac disease
- # Enrolment in a confounding study
- # Previously randomized in PROMIZING
- # Unknown

 # Eligible

 # Excluded:
- # Outside 24h randomization window
- # Extubated
- # Passed SBT
- # Plan to extubate within 24hours
- # Died
- # Transferred to a non-participating centre
- # Treating Physician declined study
- # Patient/SDM declined consent
- # Unknown

 # Enrolled

 # Excluded (Enrolled Not Randomized):
- # Passed SBT / Extubated
- # Patient/SDM declined (after deferred consent)
- # Patient incapable/no SDM available (after deferred consent)
- # Approval withdrawn by physician
- # Died
- # Outside 24h randomization window
- # Transferred to another centre

 # Randomized

4.4 Retention, Withdrawal and Follow-up Data

Patients or their SDMs may withdraw consent for ongoing participation in the intervention, or from ongoing data collection, or both. At times, clinicians may choose to deviate from the study intervention or stop the study intervention for safety or other reasons. Finally, patients may be transferred to another hospital, and so may be withdrawn from study intervention for that reason. Part two of the CONSORT diagram will depict the flow of patients post randomization, including number of patients in each arm who started the study intervention, completed the study intervention, were withdrawn from study intervention (and reasons for early withdrawal), the number of patients with complete follow-up data collection to Day 90 or death (and reasons for incomplete follow-up); and number of patients included in the intention-to-treat and per-protocol analyses (see Figure 2).

Figure 2: CONSORT flow diagram post-randomization
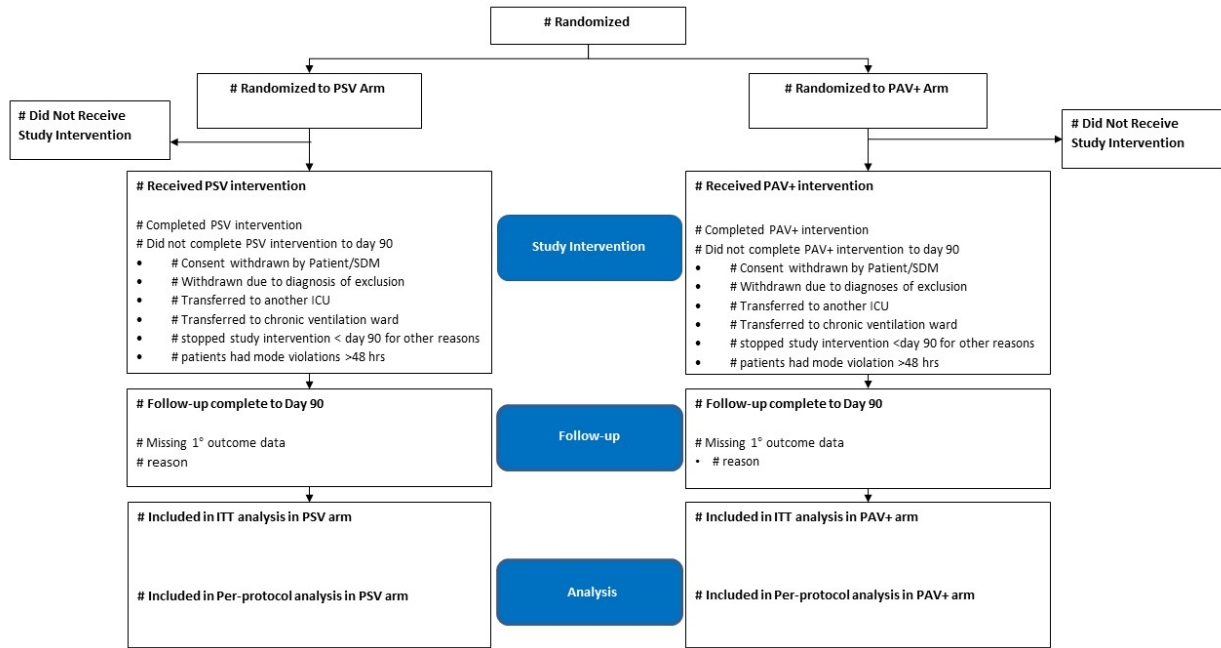
4.5 Adherence and protocol deviations

Protocol deviations are defined and categorized as minor or major as follows:

Type of Deviation	Category
Patient met criteria for switching from A/C to PAV+, A/C to PSV but not switched	Minor
Patient met extubation criteria but not extubated	Minor
Study timelines not followed	Minor
SBT performed with different respiratory parameters than specified	Minor
Weaning/screening algorithm not followed when patient met weaning criteria	Major
Use of non-protocolized mode	Major

To improve adherence to study interventions, the bedside clinician responsible for adjusting the ventilator (e.g., respiratory therapist, physiotherapist, physician) will complete a daily checklist which will be recorded in the RAVE database. The checklist serves as a reminder to the clinician to follow the study protocol, and also allows us to document protocol adherence. Additionally, use of any non-protocolized mode of ventilation, duration of exposure to non-protocolized mode, and reason for non-protocolized mode is recorded in the database.

Protocol deviation summary reports are presented to the DSMB at regular intervals and include:

(a) number of deviations of each type that occurred and the category (minor, major)

(b) number of patients with each type of deviation

(c) total number of major and minor deviations

(d) total number of study days

(e) rate of occurrence, calculated as the number of deviations divided by the total number of study days, expressed as a percentage of the total number of study days, for each type of deviation and in total.

(f) Mode deviations – number of patients who used non-protocolized mode and number of hours spent on non-protocolized mode

Descriptive statistics on use of non-protocolized modes as well as intolerance of PAV+ and PSV (duration in days and percentage of time in study spent on assist/control mode) will be provided

4.6 Analysis Sets

Statistical analysis will be based on intention-to-treat, per protocol analysis. Patients with missing outcome data will be censored at last contact.

4.6.1 Intention To Treat Sample

All analyses will use the intention to treat sample. The intention to treat sample will be comprised of all randomized patients who started the study intervention, irrespective of compliance to their randomized group. Patients will contribute outcome data to the analysis based on the randomized group.

4.6.2 Per Protocol Sample

The per-protocol sample will include only those randomized patients who stayed on the study protocol until successful liberation from IMV, 90 days, or death, whichever came first. The per-protocol sample will exclude subjects who were withdrawn from the study, or spent more than 48 hours in a non-protocolized mode of ventilation duringthe first 21 days (neither PAV, nor PSV, nor CPAP, nor AC). Note that use of assist-control mode in either volume or pressure control was allowed per protocol in each arm of the study. The per-protocol sample will also exclude patients who were transferred to another centre or ward prior to completing the study protocol, with the exception of patients who were transferred for palliation and died within 7 days of transfer; such patients will be considered to have completed the study protocol, and will be included in the per protocol sample.

4.6.3 Safety Sample

Safety analysis will include all randomized patients.

4.7 Baseline patient characteristics

Baseline data will be described using mean and standard deviation, median and interquartile range, counts and percentages as appropriate. Baseline characteristics will include but will not be limited to

- Diagnosis (operative vs. non-operative)
- Subdiagnosis for non-operative subjects (respiratory, cardiovascular, other)
- Charlson comorbidity index and components
- APACHE score
- SOFA score
- Cumulative fluid balance
- Neuromuscular blockade
- Steroid use
- Antipsychotic use
- Baseline sedation category

5 Outcomes

5.1 Primary Outcome

The primary outcome is the time from randomization to successful liberation from invasive mechanical ventilation. Successful liberation is reached the moment IMV is discontinued, provided the subject remains alive and free of IMV for at least 7 days subsequently. In other words, the date of successful liberation is the date of the extubation (or disconnection from ventilator for patients with tracheostomy) that was followed by at least 7 ventilator-free days.

5.2 Secondary Outcomes

The secondary outcomes are

1. Ventilator-free days at day 14, 21 and 28 post randomization

2. Time from randomization to live ICU discharge (up to day 90)

3. Time from randomization to live hospital discharge (up to day 90)

4. Mortality, measured as time to death, ICU mortality; hospital mortality; 21, 28, and 90 day mortality

5. Weaning Progress, measured as time from randomization to: first SBT; first successful SBT; first extubation or equivalent for tracheostomized patients.

6. Weaning Difficulties: Subjects will be classified in the 5 following groups according the WEAN Safe classification (calculated as time from first SBT/extubation):

    (a) Successful liberation less than 24 hrs

    (b) Successful liberation greater than 24 hrs but less than 7 days

    (c) Successful liberation greater than 7 days

    (d) Unsuccessful liberation – alive but remain ventilator dependent at day 90

    (e) Died prior to successful liberation

7. Weaning Complications, measured as the number of patients

    - used non-invasive ventilation post-extubation

    - ventilated more than 7 days post randomization

    - ventilated more than 21 days from time of 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)

8. Safety and Tolerance of modes

    - Number of patients ever requiring A/C mode post randomization

    - Number of patient-days requiring A/C mode post randomization

    - Frequency and severity of reported serious adverse events across groups

9. Co-interventions are also monitored, including sedatives and anti-psychotic medications.

5.3 Exploratory Outcomes

5.3.1 Status at 90 days

We will create a composite outcome to reflect status at 90 days. This outcome will be an ordinal outcome with the following categories listed from worse outcome to best outcome:

1. Died

2. Remaining on ventilation at any location

3. Not ventilated but remaining in hospital or ICU

4. Discharged from hospital not ventilated

5.4 Measurement and Units of Outcomes

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 extubation, disconnection from invasive MV, ICU discharge, live hospital discharge, or death).

5.5 Calculation of ventilator-free days

"Ventilator-free days" (VFDs) are defined as the number of days alive and free of INVASIVE ventilation post SUCCESSFUL LIBERATION (successful extubation or successful termination of invasive MV for patients with tracheostomy). Non-invasive ventilation may be used post extubation, but is not counted as "invasive ventilation."

- If the patient dies before achieving successful liberation from invasive MV, that patient will have 0 VFDs.

- However, if a patient dies AFTER achieving successful liberation, 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.

5.5.1 Assessment of Co-interventions

Co-interventions occurring during the study will be described as well as other patient characteristics that were collected during follow-up such as SOFA score , daily fluid balance, cumulative dose of sedating medications, number of patients and patient-days receiving any antipsychotic medication.

5.5.2 Sedating Medications and Sedation, Agitation, and Delirium Scores:

Sedating medications are routinely administered as part of routine ICU care, and may influence duration of IMV (reference). As such, they are co-interventions. However, a patient's requirement for sedating medications may be influenced by many factors, including acuity of illness, presence of delirium, pain, and patient-ventilatory dyssynchrony. Since patient-ventilator dyssynchrony may differ between PAV+ and PSV, mode of ventilation may influence amount of sedating medications administered, and amount of sedating medications administered may in turn influence duration of IMV. We will take the following approach to analyzing sedating medications and sedation, agitation, and delirium scores:

Drug conversions

1. Opioids – daily total dose of all opioid medications will be converted to morphine IV equivalents [25, 26, 27]

2. Benzodiazepines – daily total dose of all benzodiazepine medications, propofol and dexmedetomidine will be converted to midazolam IV equivalents [28] [26]

3. Other sedative infusions – we had planned to analyze propofol, dexmedetomidine, and ketamine separately; however, a recent study [28] described a method for converting propofol and dexmedetomidine to midazolam equivalents based on "expert opinion and clinical practice;" we will use their conversion factor to convert propofol and dexmedetomidine to midazolam equivalents and include in the total daily dose of midazolam IV equivalents. Ketamine will be analyzed independently.

Drug doses will be compared across groups using mixed effects models adjusted for baseline and with a time by treatment interaction term.

The number of patients and number of patient-days receiving any antipsychotic medication will be compared between groups.

Sedation/agitation scores

Different scoring systems were used across institutions to assess the level of sedation or agitation and included the Richmond Agitation Sedation Score (RASS), the Riker Sedation-Agitation Scale (SAS) , or the Ventilator-Adjusted Motor Activity Assessment Scale (VA-MAAS). Sedation was scored twice daily (morning score and highest daily score) using whatever scale was in use at each participating centre. Each score will be analyzed separately, and scores will be converted to 4 categories using the following conversion table derived from Khan et al 2012[29], and analyzed descriptively.

Category	RASS	VAMASS	SAS
Moderate to deep sedation	**-3 to -5**	**0 to 1**	**1-2**
Light sedation	**-2 to -1**	**2**	**3**
Alert and calm	**0**	**3**	**4**
Restless/Agitated	**+1 to +4**	**4 to 6**	**5 to 7**

Delirium score

Delirium category will be assessed in a subset of patients where data is available using a combination of two scoring systems: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) values as follows:

1. Delirium not assessed: either missing data or marked as not assessed in database

2. Too sedated to assess = Coma

3. Delirious (CAM-ICU positive, ICDSC 4-8)

4. Not delirious (CAM-ICU negative, ICDSC 0-3)

The delirium category will be described over the study period for each group.

6 Analysis methods: Frequentist Analysis

6.1 Primary Outcome

The primary outcome of time to successful liberation from mechanical ventilation will be summarized using cumulative incidence curves with death considered to be a competing risk. Cumulative incidence will be compared across groups using Gray's test.

6.1.1 Primary Analysis

Treatment effect will be reported as a hazard ratio with 95% confidence interval. The primary analysis will use a mutistate generalization of the Cox proportional hazard model. This approach simultaneously models the association between treatment and all transitions in the model. Missing outcome data will be treated as censored at the date of last contact.
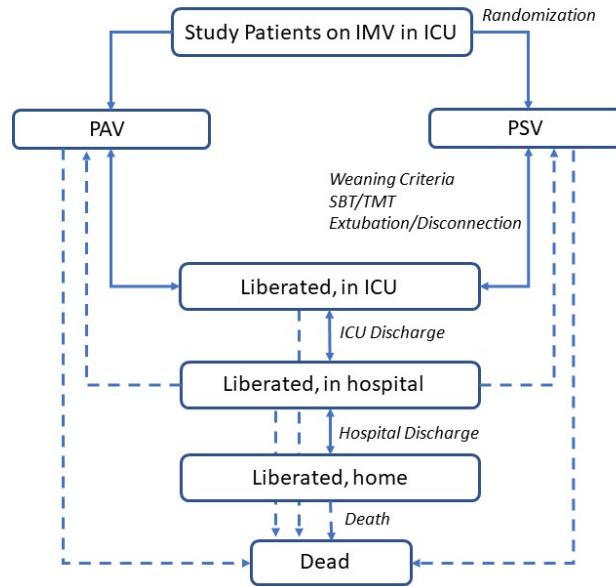
Figure 3: State transition diagram

Figure 3: State transition diagram
IMV = invasive mechanical ventilation; SBT = spontaneous breathing trials; TMT =tracheostomy mask trials; ICU = intensive care unit

6.1.2 Secondary Analyses

A secondary analysis will be performed using a cause-specific Cox model to model the treatment effect on successful liberation with death prior to successful liberation treated as a censoring event.

6.2 Secondary Outcomes

The outcomes related to weaning progress and difficulties (listed below) also suffer from the competing risk of death and other improper subgroup issues. and will be looked at primarily descriptively.

- **Time to death:** will be analyzed using standard methods for survival data namely Kaplan-Meier curves and log-rank test. Treatment effects will be reported as hazard-ratios with 95% confidence intervals.

- **Time from randomization to live ICU discharge (up to day 90) and time from randomization to live hospital discharge (up to day 90):** Those two outcomes both have death as a competing risk. Cumulative incidence curves will be constructed to provide estimates of live ICU discharge and live hospital discharge that account for death. Cause-specific treatment effects on live ICU discharge and live hospital discharge will be reported as hazard ratios with 95% confidence intervals from Cox proportional hazard models.

- **Time from randomization to first SBT, first successful SBT, and first extubation:** These will be looked at primarily descriptively using cumulative incidence curves with death as a competing risk and compared across groups using the Gray's test.

- **Ventilator-free days:**

  Ventilator-free days will be compared across groups using a Wilcoxon test. The treatment effect will be expressed as the difference in median ventilator-free days and its 95% confidence interval will be estimated using bootstrap methods. As per the calculation above, subjects might have 0 ventilator-free days because either they died before being liberated or they survived but remained ventilated. We

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will model this using a number of approaches. For the primary analysis, we will assign the value -1 ventilator free days to subjects who died prior to liberation.

The following secondary analyses are also planned to help understand any observed treatment effect.

- Assigning the value of zero ventilator-free days to patients who died prior to being liberated from ventilation and performing a Wilcoxon test

- Poisson regression of the number of days on ventilator with the logarithm of the number of days observed as an offset

- Marginal structural model 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

- Invasively ventilated with tracheostomy and invasively ventilated with ETT

- **Number of patients successfully liberated in less than 24 hours since first SBT or first extubation attempt, number successfully liberated greater than 24 hours but less than 7 days, successfully liberated greater than 7 days, unsuccessful liberation (alive but remaining ventilator dependent at day 90), died prior to successful liberation.** These outcomes will be compared across groups using the Chi-Square or Fisher's exact test.

- **Delirium and sedation scores:** Daily sedation scores will be analyzed as described in Section 5.5.2.

- **Number of patients who received 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):** These outcomes will be compared across groups using the Chi-Square or Fisher's exact test.

- **Number of patients ever receiving A/C mode post randomization (Tolerance of modes):** This outcome will be compared across treatment groups using Chi-Square or Fisher's Exact test and treatment differences will be reported as an odds ratio with 95% confidence interval. Patients not receiving A/C will be assigned a value of zero days. The non-parametric Wilcoxon rank-sum test will be favoured over the parametric t-test for this analysis if there are many zero days entries.

6.3 Exploratory Outcomes

Status at 90 days is an ordinal outcome defined in section 2.3.1 and it will be analyzed using ordinal logistic regression.

Exploratory analyses will include regression analyses to assess factors potentially associated with weaning group classification (short/difficult/prolonged weaning groups) and with duration of mechanical ventilation.

6.4 Covariates of Interest

The following were pre-specified as covariates are of particular interest

1. Duration of mechanical ventilation prior to randomization in 1) days and 2) as a binary indicator for greater than 5 days or not.

2. 2. Failed spontaneous breathing trial (SBT) vs. failed continuous positive airway pressure (CPAP) zero trial (CPAP trial of 0 cmH2O) vs. failed weaning criteria prior to randomization

3. Failed extubation prior to randomization (Failed extubation vs. No extubation attempt prior to randomization)

4. Mild, moderate, severe frailty assessed using the Clinical Frailty Scale (CFS) [30]. There should not be anyone with CFS 9 (Terminally ill) in the study based on the inclusion criteria

- Mild: CFS 1 to 3 (very fit to managing well)
- Moderate: CFS 4 to 6 (managing well to mildly frail)
- Severe: CFS 7 to 8 (severely frail to very severely frail)

In addition to the above pre-specified covariates, we will explore the effects of baseline cumulative fluid balance and baseline sedation category in adjusted analyses. In addition, baseline use of antipsychotics, neuromuscular blockers and steroids will be described.

6.5   Subgroup Analyses

There are 4 planned subgroup analyses testing whether the trajectory of baseline characteristics can influence the results. These will be based on:

1. Duration of MV prior to randomization as a continuous variable modeled with restricted cubic splines if necessary to account for potentially nonlinear effects.

2. Status of weaning attempts prior to randomization

   - Failed SBT prior to randomization
   - Failed CPAP (of zero cmH2O) trial prior to randomization
   - Failed weaning criteria prior to randomization

3. Failed extubation prior to randomization

4. Frailty (mild/ moderate/ severe)

In addition, we will explore the possibility of a subgroup analyis by covid status at randomization if there are enough COVID+ subjects. COVID+ will be defined as COVID+ and a respiratory diagnosis

1. COVID positivity at randomization (due to the onset of the pandemic)

2. tracheostomy prior to randomization

6.6   Sensitivity Analyses

There are 2 planned sensitivity analyses based on:

1. Defining "successful extubation" as "48 hours without reintubation"

2. Assigning a value of 0 ventilator-free days to any participant who dies at any time during the study period.

7   Bayesian Analyses

The Bayesian analyses will be performed by Arlene Jiang, under the supervision of Drs. Anna Heath and Yongdong Ouyang. The goal of this analysis is to incorporate prior evidence into the analysis of the PROMIZING study. We will analyze the outcomes: time to liberation (in ICU) from mechanical ventilation and ventilator-free days. The analyses will be performed adjusted by the covariates of interest (section 3). Posterior mean, median, and 95% highest density credible intervals will be reported for all model parameters. The probability that the treatment reduces time on ventilation by the minimal clinically important difference (MCID) of 1 day will also be reported.

7.1   Informative Prior Treatment Distributions

Our analyses will incorporate prior information from a pragmatic meta-analysis [31]. Saunders et al. reported that compared to PSV, PAV+ reduced duration on ventilation by 1.53 days (95% confidence interval: 0.83 to 2.24). The meta-analysis estimate will be weighted to 100%, 50%, and 10% to calculate prior distributions,

according to the approach in Goligher et al. [32]. Ventilator-free day data from the iCORE dataset were transformed to determine the priors for treatment effects specific to each outcome [33]. The iCORE dataset reports the number of days a patient is off ventilator within 28 days, in patients who have received PSV.

7.2 Bayesian Analysis of Primary Outcome

The primary outcome (time to successful liberation, in ICU from mechanical ventilation) will be analyzed using accelerated failure time (AFT) models. These differ from the proportional hazards models that will be used in the primary frequentist analysis (section 5.6.1) because they require distributional assumptions for the hazards. AFT models are better suited to this context because Bayesian methods assume that all parameters have a distribution. These models will estimate time ratios, which can be interpreted as the multiplicative effect of a covariate on survival time.

As specified in the primary frequentist analysis, each transition in Figure 3 will be modelled. To maximize model flexibility, each transition will be fit to a separate AFT distribution [34]. For each transition, we will select the best model among exponential and Weibull AFT families. The model with the lowest AIC will then be modeled in INLA [35, 36].

Semi-Markov modelling will be implemented, based on clinical knowledge that the probability of transitioning would depend on the time spent in each state. For these models, time will reset to 0 when patients enter each new state.

7.2.1 Informative Prior Treatment Distribution for the Transition Between Invasive Ventilation to Liberated, In ICU

We will use an informative prior for the treatment effect on the transition between invasive ventilation to liberation, in ICU. To determine the prior, we assumed that the number of ventilator-free days in the baseline dataset would roughly correspond to the time that patients were freed from ventilation. Patients with 28 ventilator-free days were considered freed on day 0. These patients were assigned a time of 0.001, as only non-zero times could be included in AFT models. For patients with 1 to 27 ventilator-free days, the difference between 28 days and the number of ventilator-free days was considered the time to being freed from ventilation. Patients who died or started off-ventilator were excluded.

Each AFT family in the *survival* package was fit to the dataset [37]. The fitted estimates were used to generate 50000 observations from these distributions. Exponential and Weibull distributions were selected, with time ratios between the true and simulated datasets between 1 and 1.002. The AIC values, indicating the fit of these distributions to the baseline data, are presented below. The treatment effect was estimated by simulating data with incrementally decreasing location parameters within the location-scale parameterizations of the distributions. The coefficient value that generated a difference in means equal to the treatment effect in the meta-analysis (1.53 days) is reported in the table below. Standard deviations were derived by the same method with differences in means equal to estimates of the 95% confidence interval (0.83 or 2.24 days). As a conservative estimate, the standard deviation was calculated from the larger tail of the confidence interval, although estimates from either tail remained within 0.03 of each other. The MCID values were also estimated as log-time ratios using the method described above.

We will select the best fitting family, based on AIC, between exponential and Weibull distributions to model this transition with an informative prior. If there is a family that fits substantially better than exponential or Weibull, we will model this transition with a minimally informative prior for treatment in INLA.

Family	μ	σ_{100}	σ_{50}	σ_{10}	MCID	AIC
Exponential	-0.26	0.074	0.10	0.23	-0.16	10434.87
Weibull	-0.15	0.051	0.73	0.16	-0.098	8625.836

7.3 Bayesian Analysis of Secondary Outcome

The secondary outcome, ventilator-free days at 28 days, will be analyzed as ordinal data. This outcome is measured to the nearest tenth of a day in the trial, but will be rounded to the closest integer such that

ventilator-free days can be analyzed as an ordinal variable. There are 30 levels for ventilator-free days at day 28, specifying a patient death (-1) and the number of days off ventilator (0 to 28). A cumulative logistic regression model will be used to analyze ventilator-free days with brms and stan [38, 39].

Log-odds ratios were estimated for the secondary ventilator-free day outcomes. We performed a grid search to find a difference in odds equivalent to reducing the mean time on ventilation by 1.53 days. The prior for this analysis is included below. Due to the composite nature of this endpoint, this prior assumes a different rate of mortality for those treated with PAV+. We assumed a mortality rate of 23.1% for PSV, based on the iCORE dataset, and a mortality rate of 18.9% for PAV+. Based on the described grid search method, we found the MCID as a log-odds ratio reported below.

Outcome	μ	σ_{100}	σ_{50}	σ_{10}	MCID
Ventilator-Free Days at 28	0.25	0.060	0.085	0.19	0.17

8   Cluster analysis

The cluster analysis will be performed by Kaitlyn Wade under the supervision of Dr. Pingzhao Hu at the University of Western Ontario. Data quality will first be evaluated and unsupervised feature screening will be performed if necessary. Then, an estimation of the number of potential clusters in the data set will be performed. A consensus clustering approach will be used to identify the clusters in the data set as has been used before for breast cancer stratification [40]. The quality of the identified clusters will be evaluated using the internal metrics (e.g. Silhouette coefficient) and external metrics (depending on the clinical information available in the data set, e.g. survival) [41]. Other commonly used clustering approaches, such as k-means, hierarchical clustering, and advanced deep learning based approaches will be considered if necessary.

9   Safety Reviews

9.1   Serious Adverse Events

Any SAE is defined as:

(a) any event that results in unanticipated/non-palliative death, is life threatening, results in persistent or significant disability/incapacity, or requires prolonged inpatient hospitalization, or

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

All SAEs will be reported to the DSMB in aggregate form at least 7 days prior to the scheduled meeting. However, those SAEs which the attending physician perceives are probably or definitely directly related to the mode of ventilation or the ventilator shall be reported to the DSMB chair in an expedited fashion as per the procedures described below. An SAE will be considered to be "probably" study-related if the event meets 3 of the following 4 criteria: (1) has a reasonable temporal relationship to the intervention, (2) could not have readily been produced by the patient's clinical state or have been due to environmental or other interventions, (3) follows a known pattern of response to intervention, or (4) disappears or decreases with replacement of intervention with standard of care procedures and recurs with re-exposure. An SAE will be considered to be "definitely" study-related if the event meets all 4 of the above criteria. Adverse events are not study-related if they are related primarily to the underlying disease or its sequelae.

9.2   Procedures for Reporting SAE

Each site research coordinator will liaise with the clinical team and review the medical records of study participants during the period of trial participation to identify potential SAEs. The site research coordinator (RC) will notify the site investigator and the local REB (according to local requirements) about each local SAE. Bedside clinicians will treat the study patient at their discretion. The site investigator has primary responsibility for the safety of individual study patients at his/her study site. Upon recognition of a probably or definitely related SAE, the site research coordinator or site investigator will notify the AHRC

Methods Centre within 24 hours of becoming aware of the SAE, in accordance with standard SAE reporting requirements of regulatory authorities (e.g., Health Canada). The site RC will complete the SAE form (or any outstanding case report form if the CRF is not available) for that patient within 24h. In addition, a copy of all relevant clinical notes will be forwarded to the AHRC Methods Centre on their request, including all physicians' and nurses' notes, relevant diagnostic test results, and surgical and other intervention reports, within 3 business days of becoming aware of the SAE. These notes will be previewed at the Methods Centre to ensure that they do not contain sensitive or confidential patient information, in accordance with PHIPA requirements. If the SAE is thought to be probably or definitely study-related and requires expedited reporting to the DSMB, the Data Manager will contact the co-PIs (Dr. Karen Bosma, Dr Laurent Brochard) and the DSMB Chair (Dr. Taylor Thompson) to alert them of forthcoming documentation regarding the SAE. Upon receiving all relevant clinical notes and case report forms from the site, research personnel at the Methods Centre will collate this material into a detailed report for distribution to the co-PIs and the DSMB Chair within 10 business days of the original notification to the Methods Centre. The DSMB Chair will review all SAEs classified as probably or definitely related to enrolment in the trial within 7 business days. After reviewing the clinical notes and CRFs, the DSMB chair will determine whether immediate input from other DSMB members is required and will contact them as needed. The DSMB will send their determinations to the PIs. Final determinations of the DSMB will be entered onto the relevant case report form, and into the database.

The DSMB will also review aggregate SAEs at approximately 6-month intervals. At this time, the DSMB will recommend to the SC whether to (a) continue patient enrolment, (b) suspend enrolment until careful review by the SC, or (c) request additional information before making a recommendation.

9.3 Reporting of Safety Data

Frequency and severity of reported serious adverse events across groups will be presented and analyzed descriptively.

10 Statistical Software

All analyses will be performed using R unless otherwise specified.

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