STATISTICAL ANALYSIS PLAN

STUDY TITLE: SedAting With Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects On Ventilatory Parameters And Survival. A Multicentre open-label, pragmatic, randomized controlled trial and a parallel prospective (non-randomized) cohort study

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This document is part of the official trial documentation for the above references study and is maintained in accordance with Good Clinical Practice (ICH E6 R2) and institutional trial governance requirements.

ABSTRACT

Background. The Sedating with Volatile Anesthetics for COVID-19 and Non-COVID acute hypoxaemic respiratory failure patients in ICU (SAVE-ICU) is a randomised clinical trial comparing the effectiveness of inhaled versus intravenous sedation in ventilated adults with acute hypoxemic respiratory failure (AHRF).

Objective. To describe a pre-specified statistical analytical plan (SAP) for the SAVE-ICU trial that was developed during trial design and finalized prior to locking of the database, data analysis and un-blinding of treatment groups.

Methods The SAP outlines the trial study outcomes, planned interim and final analyses for the study outcomes. The SAP was developed by the SAVE-ICU investigators and statistician.
The primary outcome is hospital mortality. Secondary outcomes include ICU and ventilator-free days at day 30, oxygenation at day 3 (PaO_2/F_IO_2 ratio), need for adjunctive therapies for refractory hypoxaemia (prone positioning, inhaled nitric oxide, paralysis with a neuromuscular blocking agent and extra-corporeal life support) during ICU stay, days alive and free from delirium and coma at day 14, hospital-free days at day 60, disability score and health-related quality of life scores at 3- and 12-months after enrollment (12 month outcomes to be reported separately). Hospital mortality will be analyzed using generalized linear mixed model with log link and binomial distribution or modified Poisson regression and presented as risk ratios and 95% confidence intervals (CI). Secondary free-day outcomes will use Fine-Grey models. Linear mixed models will be used for continuous outcomes such as PaO_2/F_IO_2 ratio. Primary and several secondary outcomes will be adjusted for randomisation stratification variables (age, PaO_2/F_IO_2 ratio and random effect for site) and include pre-specified subgroup analyses based on age, sex, COVID-19 status and severity of AHRF. All analyses follow a frequentist approach.

Conclusion. The developed SAP will be used to support analysis of the SAVE-ICU trial. This trial will increase the body of evidence evaluating the effectiveness and safety of inhaled anesthetic utilisation in the ICU.

Strengths and limitations of this study

1. The statistical analysis plan was finalized prior to database locking and unblinding the data that limits the potential for outcome driven analytical decisions.
2. Pre-specified outcome appropriate statistical methods are used for analysis of primary and secondary outcomes.
3. Analyses adjust for randomisation stratification variables and account for site-level heterogeneity.
4. The inclusion of multiple secondary outcomes and pre-specified subgroup analyses supports interpretation of the findings.
5. Planned methods for handling missing data rely on modelling assumptions that may affect estimates.

INTRODUCTION

Acute hypoxaemic respiratory failure (AHRF) is a common cause of intensive care unit (ICU) admission, with approximately 10% of patients displaying features of acute respiratory distress syndrome (ARDS).[1] Management typically includes mechanical ventilation, where sedation is essential to improve comfort. Current guidelines recommend intravenous (IV) sedatives (i.e., propofol, dexmedetomidine) with opioid analgesia and delirium care.[2 3] However, IV sedation lacks continuous drug monitoring, may accumulate with impaired hepato-renal clearance, and is associated with delayed awakening, prolonged ventilation, and acute and longer-term cognitive dysfunction, resulting in longer ICU and hospital stays.[4] Inhaled anaesthetics such as isoflurane and sevoflurane are alternative ICU sedatives that are delivered via bedside vaporizers, monitored through gas analyzers, and undergo minimal hepatorenal metabolism that may be advantageous in multiorgan dysfunction.[5-7] Emerging evidence suggests comparable sedation depth to IV agents with potentially faster patient awakening, earlier ventilator liberation, reduced opioid exposure, and anti-inflammatory benefits.[7-10]

Despite these potential advantages, existing trial data remain limited and findings are inconsistent, particularly regarding the use of inhaled anaesthetics within contemporary, guideline-aligned sedation strategies. To address this evidence gap, we initiated the sedating with volatile anaesthetics for COVID-19 and non-COVID patients in ICU (SAVE-ICU) trial to evaluate the effectiveness of inhaled versus IV sedatives in mechanically ventilated adults with AHRF. Since the trial was conceived, additional randomised evidence has been published;[11] these studies were monitored by the SAVE-ICU investigators but did not influence the prespecified outcomes or statistical analysis plan, which was finalized prior to database locking.

When SAVE-ICU was designed during the COVID-19 pandemic, uncertainties regarding eligible patient volumes, site capacity, and implementation of a new inhaled-sedation pathway raised concerns about whether the trial could accrue the required number of participants. To mitigate these challenges, the trial was initially designed to utilize a hierarchy of independently powered outcomes, listed from highest to lowest priority: hospital mortality, ventilator-free days to day 30, quality of life at 3 months, and ICU-free days to day 30. This design allowed the study to pivot to the highest-ranking outcome with sufficient power if recruitment was curtailed. As recruitment remained strong without major safety concerns, the trial continued to full enrollment for the top hierarchical outcome, hospital mortality, which is analyzed as the primary outcome; the remaining hierarchical outcomes are analyzed as secondary outcomes. No study outcomes were unblinded at any time point before the final analysis.

The protocol for the SAVE-ICU trial has been previously described and involved a patient partner with lived experience.[12] This manuscript reports the pre-specified statistical analytical plan (SAP) according to the guidelines for the content of SAP in clinical trials.[13] This manuscript was prepared by the SAVE-ICU investigators (Supplemental eTable 1) on behalf of the Canadian Critical Care Trials Group (CCCTG).

OBJECTIVES

The primary objective of the SAVE-ICU RCT is to evaluate the effect of inhaled versus IV sedation on hospital mortality. We hypothesize that, compared with IV sedation, inhaled sedation will reduce the risk of in-hospital death among mechanically ventilated adults with AHRF. The secondary objectives are to evaluate the differences between inhaled and IV sedation with respect to quality of life at 3 months (assessed using EQ (EuroQoL)-5D-5L), ventilator-free days

and ICU-free days at day 30, hospital stay (hospital-free days at day 60), adjunctive therapies for refractory hypoxaemia (prone positioning, inhaled nitric oxide, paralysis with a neuromuscular blocking agent, extra-corporeal membrane oxygenation (ECMO) therapies during the index ICU admission), patient oxygenation (PaO_2/F_IO_2 ratio at 3 days after enrollment), delirium (days alive and free from delirium and coma while in ICU up to 14 days), and patient disability (World Health Organization Disability Assessment Score assessment at 3 and 12 months after enrollment).

METHODS

Design and Study Setting

SAVE-ICU is a multi-center, open-label, pragmatic, randomised controlled trial (RCT) designed to compare inhaled versus IV sedation in mechanically ventilated adults with AHRF, that was conducted in 14 adult ICUs across Canada. One site in the United States participated in the parallel prospective cohort arm. The trial was initiated during the COVID-19 pandemic, a period when staffing level, drug supplies and access to different sedatives varied across sites. These operational constraints informed the decision to use a hierarchy of independently powered outcomes (as outlined above). Eligible patients were randomised only when both study interventions and delivery equipment were available; otherwise, they were enrolled in a parallel prospective cohort study that followed the same treatment and will be analyzed and presented separately. Full details regarding the trial protocol are published separately.[14] This SAP describes analysis of the randomised trial only which forms the focus of the main manuscript accompanying the SAVE-ICU clinical trial.

Inclusion Criteria

Participant inclusion criteria are: (1) adult (≥ 18 years of age) ICU patient, (2) receiving invasive mechanical ventilation (+/- extracorporeal membrane oxygenation) and expected to remain mechanically ventilated at the end of the calendar day after the day of assessment for trial eligibility, (3) receiving IV sedation by infusion or bolus for ≤72 hours to facilitate mechanical ventilation and either (4) mechanical ventilation +/- extracorporeal membrane oxygenation support for (a) proven or suspected COVID-19 respiratory failure, or (b) non-COVID-19 respiratory failure with PaO_2/F_IO_2 ratio ≤300mmHg.

Exclusion Criteria

Participant exclusion criteria are: (1) contraindications to study sedatives, such as propofol infusion syndrome or malignant hyperthermia; (2) known allergy to any of the ingredients or components of the investigational products; sevoflurane or isoflurane; (3) suspicion or evidence of high intracranial pressure; (4) severe brain injury that is likely to lead to sustained very low conscious levels or vegetative state; (5) severe neuromuscular disorder (e.g., amyotrophic lateral sclerosis, Guillain-Barre Syndrome) that is the primary cause of ICU admission and respiratory failure requiring mechanical ventilation; (6) one-lung ventilation or pneumonectomy; (7) ideal estimated tidal volume too low for delivery of inhaled agents using the miniature vaporizer, i.e., target tidal volume (6ml/kg) < 200ml; (8) use of inhaled prostacyclin, which is contraindicated in the presence of a miniature vaporizer (i.e., Anaesthesia Conserving Device); (9) known pregnancy; (10) moribund patient not expected to survive >12 hours.

Randomisation

Consented participants were randomised 1:1 to inhaled sedation or IV sedation using a central computerized randomization system. Randomisation is stratified by study site, age (<65 or ≥65y) and PaO_2/F_IO_2 ratio (<150 or ≥150mmHg) using permuted block sequences of undisclosed sizes.

Intervention

Sedation, analgesia, and delirium management followed a pragmatic protocol consistent with current clinical practice guidelines.[2] Participants in the intervention arm received isoflurane or sevoflurane titrated to target clinical sedation score prescribed by the clinical team. Inhaled agents were delivered through approved bedside vaporizing systems with continuous bedside gas concentration monitoring and appropriate scavenging. Use of IV sedatives was permitted if adequate sedation could not be achieved with inhaled agents. Full details of the sedation protocol are available in the published trial protocol.[12]

Control

Participants in the control arm received IV sedatives according to clinical practice guidelines.[2] Inhaled sedation was not permitted, and non-protocolized use was documented as protocol deviation.

Co-administered treatments

Both groups permitted use of neuromuscular blocking agents when clinically indicated. Sedation continued per randomised allocation until clinical team elected to stop sedation. All patients received usual care for AHRF, including lung protective ventilation i.e., 4-8 ml/kg tidal volumes, ≥5cmH_2O positive end-expiratory pressure (PEEP), and adjunctive refractory hypoxemia therapies (e.g., prone positioning, inhaled nitric oxide, paralysis with a

neuromuscular blocking agent, and extra-corporal life support), restrictive fluid strategy, vasoactive and renal replacement therapy as clinically indicated.

Primary outcome

The primary outcome for the trial is hospital mortality during index hospital stay assessed until last scheduled follow up at 365 days. For patients transferred from study hospital to another institution, all available data from the receiving site will be used.

Secondary outcomes

Secondary outcomes include:

1. ICU-free days at day-30 – defined as number of days the participant is alive and not in the ICU during the first 30-days after randomisation (day 1 is day of enrolment). Days spent in ICU within this period will be subtracted from 30. Participants who remain in the ICU for more than 30 days will have zero ICU-free days. To distinguish between participants who have prolonged ICU stays and death, participants who die within 30-days will be assigned a value of -1. For participants readmitted to the ICU within 30 days, both the ICU readmission days and intervening ward days will be subtracted from 30. This approach conservatively assumes that readmitted ICU patients remain critically ill during the time period spent on a ward. For patients transferred from study ICU to another hospital ICU within 30 days from randomization, all available data from the receiving site will be used.
2. Quality of life assessed at 3 and 12 months – assessed using EQ-5D-5L (Euroqol-5 dimension-5 level) questionnaire. The EQ-5D-5L questionnaire assesses 5 domains (personal care, pain/discomfort, anxiety/depression, mobility, and usual activities) using a 5-point scale (from 1=no problems to 5=extreme problems; total score ranging from 5 to 25 with higher score indicative of lower quality of life). The EQ-5D-5L health state will be converted to a

utility index value specific to Canada for analysis. The EQ-5D-5L includes an optional question where participants may provide a score of their health status on a visual analog scale between 0 and 100. Quality of life assessment is performed in-person, telephone or proxy (i.e., substitute decision maker) as most appropriate and will be combined for analysis.[15] [16]

3. Ventilator-free days at day-30 – defined as number of days the participant is alive and not receiving invasive mechanical ventilation during the first 30-days after randomisation. Calculation of ventilator-free days follows a similar approach to ICU-free days.
4. Day 3 PaO_2/F_IO_2 ratio – measured using lowest oxygen tension and associated fractional inspired oxygen concentration in patients with more than 1 arterial blood gas on the third day (timing of a single day defined as 07:00 to 07:00 the following day) after enrolment. For participants without an arterial line, the PaO_2 was imputed from the pulse oximeter saturation.[17] For patients receiving oxygen via a face mask or nasal prongs, the fraction inspired oxygen was estimated from the oxygen flow rate using established methods.[18] [19]
5. Use of adjunctive refractory hypoxaemia therapies (prone positioning, inhaled nitric oxide, paralysis, extra-corporal life support) during ICU stay – captured daily during ICU stay from day 2 after randomization up to 30 days.
6. Delirium and coma-free days within 14 days – defined as number of days the participant is alive and not comatose or suffering from delirium during the first 14-days after randomization. Delirium assessed daily using recommended tools including ICU-Confusion-Assessment Method (CAM-ICU) test (positive/negative) or Intensive Care Delirium Screening Checklist (ICDSC) (delirium present with score $\geq$ 4) on days that participants are not comatose.[20] [21] Coma is assessed clinically using bedside sedation scores and defined as

Richmond Agitation Sedation Scale (RASS) of -4/-5 or Motor Activity Assessment Score (MAAS) of 0/1.

7. Hospital-free days at day 60 - Hospital-free days at day 60 - defined as number of days the participant is alive and not in hospital during the first 60-days after randomisation. Participants who died within 60-days will be assigned a value of -1. When patient is transferred to a different hospital before day-60, the discharge date at the transfer hospital will be used if available, otherwise data will be truncated to the participating site hospital discharge date. Information on hospital readmissions within 60 days was obtained at the 90-day follow up.
8. Disability at 3 and 12 months – assessed using World Health Organization Disability Assessment Schedule (WHODAS) 2.0. The WHODAS questionnaire was completed with the participant or proxy over the telephone or in-person, depending on most convenient option. This instrument assesses health and disability across 6 domains (cognition, mobility, self-care, getting along with people, life activities (domestic, school/work), and participation in society and community activities) using a score of 0 to 4 (from 0 = no limitation to 4 = extreme limitation/unable to complete). The total percentage score will be used for analysis, which ranges from 0 to 100 with higher scores indicating greater disability.

All outcomes were specified in version 1 or the protocol except for the assessment of delirium. The evaluation of delirium using days free from delirium and coma in 14-days from enrolment was added to trial protocol version 5 (27th November 2020). Additional sub-studies evaluating biological markers, cost assessment, and long-term neurocognitive outcomes will be performed in a subgroup of trial participants and will be analyzed separately from the main trial.

Adverse events

All adverse events were reported to the trial coordinating centre. Serious adverse events (SAE) were classified to have resulted in either a life-threatening reaction, death, hospitalization, or have caused a persistent or significant disability or congenital anomaly. Expected serious reactions included sedative drug allergic reaction, sedative drug associated hepatitis, malignant hyperthermia and propofol infusion syndrome. Serious adverse events were reported to sponsor and regulatory bodies. Adverse events of special interest included nausea/vomiting needing pharmacological treatment, accidental device removal (i.e., self-extubation, loss of invasive lines and other medical devices), technical equipment failure associated with IV and inhaled sedatives, removal of vaporizing device secondary to low tidal ventilation (<200ml). All events were reviewed by the data safety and monitoring board (DSMB).

Sample Size

The trial was originally designed during the COVID-19 pandemic with a hierarchical sequence of independently powered outcomes to ensure that informative results could be obtained if external factors necessitated early termination. Under this design, enrolment proceeded sequentially to the next outcome without unblinding any study results. In the event of early termination, the highest-ranking outcome for the which the target sample size had been achieved would be evaluated. Full details of the hierarchical design and sample size calculations for all outcomes are available in the published protocol.[14] Recruitment progressed without interruption or safety concerns, and no circumstances arose that required early cessation of the trial. As a result, the trial successfully accrued the full sample required for the top hierarchical outcome, hospital mortality, which is the definitive primary outcome for analysis. The primary outcome sample size was calculated assuming a control group mortality rate of 40% and an absolute risk

reduction of 10%, with 80% power and a two-sided alpha of 0.05. This required a sample of 758 participants allowing for an anticipated 5% withdrawal rate.[1] We chose to continue enrolment up to 800 patients to account for higher number of post-randomisation withdrawals than previously anticipated.

Lower hierarchical outcomes include quality of life at 3 months, ICU and ventilator-free days at day 30 form secondary outcomes in the analysis. Sample size calculations for these outcomes have been previously fully described.[12] In brief, (i) ICU-free days at day 30 requires 128 participants based on an expected median control group event rate of 10 ICU free days at 30 days (standard deviation 10 days) with a difference of 5 days [22], (ii) 3-month quality of life (measured using EQ-5D-5L) requires 144 participants based on an expected control group EQ-5D utility of 0.6 (standard deviation (SD) 0.1), minimum important difference 0.06 and anticipated patient loss from death (30%) up to 1 year after ICU discharge and loss to follow-up after discharge (10%)[23 24]; ventilator-free days at day 30 requires 200 participants based on a control group event rate of 16 days (SD 10 days) with target difference of 4 days.[25 26] At 200 patients, we can detect a hazard ratio (HR) of 1.65 or higher as well as to establish a non-inferiority margin of HR 0.85 if assuming the treatment is better than the control with a HR 1.4 or higher.

STATISTICAL ANALYSIS

Interim Analyses

The Data and Safety Monitoring Board (DSMB) monitored trial conduct, recruitment rate and safety aspects of the trial. Interim safety analyses at 64 and interim superiority ICU free days at 128 and ventilator free days at 200 participants. Safety analyses include review of adverse events

only with any suggestions incorporated into staff training and operating procedure documents. Stopping rules allowed the DSMB to recommend stopping the trial in the event of any safety concerns and harm analysis for mortality at the half-way point of the trial. At 379 patients, the half-way point for hospital mortality, the DSMB reviewed the blinded analysis to assess for harm and excess mortality using a 1-sided test, O'Brien-Fleming (criterion $p<0.0026$). This data was only shared with the DSMB with no information shared with the study team to ensure blinding of the trial groups were maintained. After all interim reviews, the DSMB notified the lead investigators to recommend continuing study enrolment as planned to meet participant target for hospital mortality.

Final Analysis

Analysis and reporting principles

The first trial paper will report primary and secondary trial outcomes except quality of life and disability assessment at 12 months for randomised participants only and will not include any sub-study information. Secondary outcome analyses will be considered exploratory.

Descriptive analyses for continuous variables will use median (interquartile range) or mean (SD) depending on the data distribution and categorical variables will be summarized as frequency and percentage. All analyses will use a frequentist approach and will be conducted using SAS v9.4 (Cary, US) and R (version 4.5.2; R Foundation for Statistical Computing, Vienna).

Intention-to-treat principle

Analyses will be performed at end of study after data cleaning and queries are completed. The main trial analysis will use intention-to-treat for all randomised participants. This will analyze participants according to their allocation group irrespective of protocol adherence. We will

exclude patients from this analysis if consented participant were randomised in error from review of eligibility criteria.

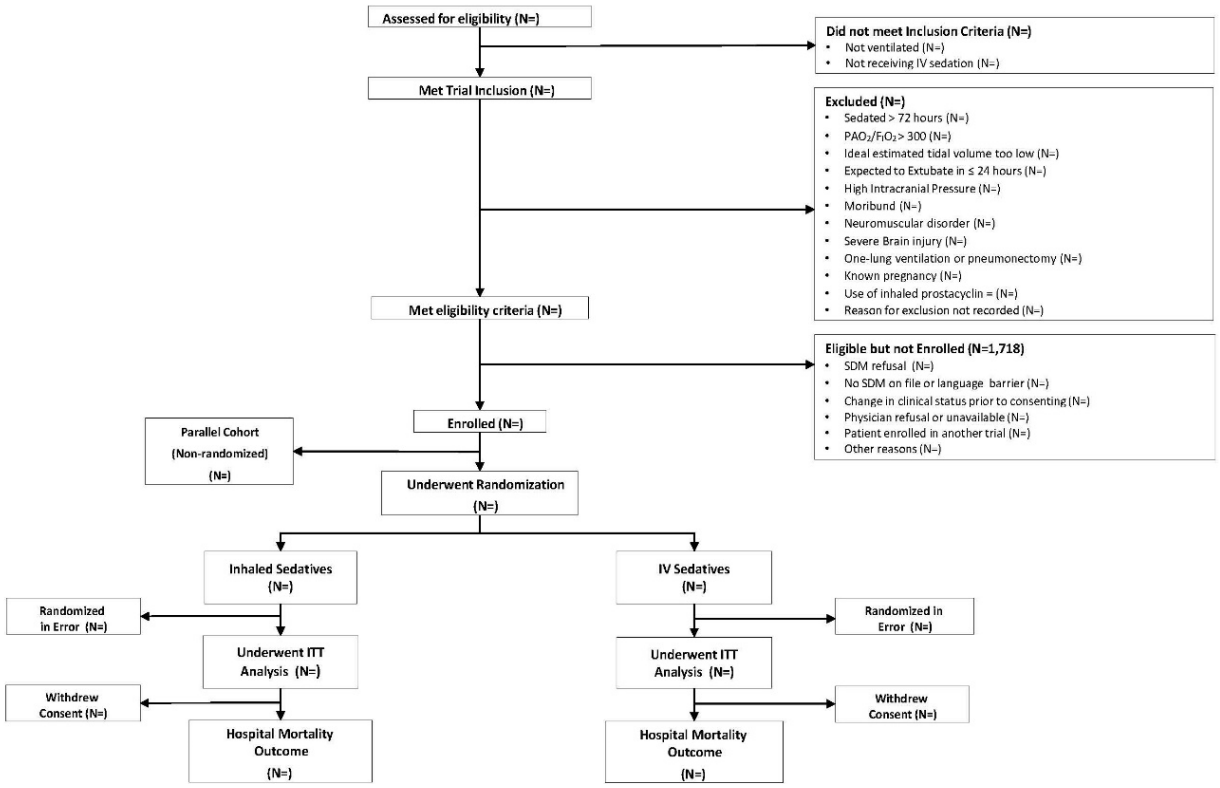
Per-protocol analysis

The per-protocol population will include participants who received the randomised intervention for a minimum of two days (based on prior data)[27] of the assigned treatment, or for the entire duration of mechanical ventilation if ventilation lasted fewer than two days.

Trial description

A Consolidated Standards of Reporting Trials (CONSORT) diagram will describe trial patient flow. This figure will describe number of participants screened and meeting eligibility, number of patients randomised and included in the primary intention-to-treat analysis, Figure 1. The diagram will include number and reasons for participants not fulfilling study eligibility, number of withdrawals and losses to follow up.

Figure 1. Draft figure of participant trial flow



Participant characteristics

Baseline patient-level characteristics will be described for randomised participants based on group allocation, Table 1. This table will capture patient demographics, comorbidities, severity of illness, baseline PaO_2/F_IO_2 ratio, ICU admission diagnosis, baseline sedative agents and use of

adjunctive refractory hypoxaemia therapies to manage AHFR (for e.g., prone positioning, inhaled nitric oxide etc.).

Analysis of primary outcome

The primary analysis will evaluate hospital death during index hospital admission. Analyses will use generalized linear mixed model with log link and binomial distribution or modified Poisson regression and results presented as risk ratios and 95% confidence intervals (CI). We will use Kaplan-Meier curves to display the survival per group. Model will adjust for stratification variables at randomisation i.e., age and PaO_2/F_IO_2 ratio and site as random effect. The analysis of hospital mortality will be considered significant if 2-sided test are significant with $p < 0.048$ (to account for the interim analysis).

Analysis of secondary outcomes

Analysis of ICU, ventilator and hospital-free days will use time-to-event analysis using marginal Fine and Gray models with robust standard error (recommended model[28]) with death as competing risk. EQ-5D-5L and WHODAS disability scores at 3 months will be described as between group mean difference and 95% confidence interval and day 3 PaO_2/F_IO_2 ratio will be analyzed using linear mixed regression model.[29] The models will adjust for stratification variables at randomization (i.e., age, PaO_2/F_IO_2 ratio and clustering for site) for ICU-, ventilator- and hospital-free days and day 3 PaO_2/F_IO_2 ratio outcomes. ICU-, ventilator- and hospital- free days data will also be presented at medians and interquartile ranges (IQR) with sub-distribution hazard ratios and 95% CI.

For participants with missing data for hospital mortality (primary outcome) and secondary outcomes, the analyses will be performed with participants with outcome data. We will perform sensitivity analysis using worst-best case of imputation for all patients with missing

mortality data who are in the inhaled group and will assume they did not have the outcome, whereas those in the IV sedative group did (best case), and the opposite scenario for worst case. For participants with missing day 3 PaO_2/F_IO_2 ratio remaining in the ICU we will use the treatment group mean PaO_2/F_IO_2 ratio for ICU patients at day 3. For participants discharged alive from ICU before day 3, we will use the treatment group mean PaO_2/F_IO_2 ratio for participants with available data on day 7. For participants who died before day 3, the lowest PaO_2 value from our conversion tables with an F_IO_2 of 1.0 (100%) will be assigned.

For alive participants with missing 3-month quality of life (EQ-5D) or disability (WHODAS) scores due to loss to follow-up or inability to contact the participant or proxy, we will impute values using multiple imputation with the following predictive variables: age, sex, site, randomization group, MODS, ICU length of stay, hospital length of stay, COVID-19 status, consistent with methods used in prior studies.[29 30]

The number (%) of participants affected by delirium and coma within 14 days will be described. For alive participants, the median (inter-quartile range) number of delirium- and coma-free days within 14 days will be described for both treatment groups and compared using quantile regression for difference in medians (95% confidence interval) The distribution of delirium- and coma-free days will be summarized at the patient level. For alive participants with missing coma and delirium status, coma will be assumed if the participant is receiving paralytic agents otherwise coma status will be carried forward from the prior day. If paralytic agents were not used or coma status on prior day is unavailable, coma will be assumed to be absent. For alive participants with missing delirium data and no coma, we will use a multiple imputation strategy with predictive variables (age, sex, MODS, site, number of sedative agents, use of anti-psychotic

agents on day of or prior to missing day (if unavailable on missing day), receiving invasive mechanical ventilation) consistent with prior delirium trials.[31]

The adjunctive refractory hypoxaemia therapies will be summarized by difference in proportions and 95% CI. Primary and secondary outcomes will be summarized in Table 2 and key figures including Kaplan-Meier curves. Event free days will be displayed using cumulative distribution function for each group.

Subgroup analyses

All subgroup analyses were prespecified and selected based on biological plausibility and clinical relevance. We will analyze the effect of inhaled sedation versus IV sedation in randomised participants on hospital mortality in subgroups based on patient characteristics of age (<65y and ≥65y), sex (male vs. female), COVID-19 status (COVID-19 positive vs. non-COVID respiratory failure), and severity of hypoxic respiratory failure defined on baseline PaO_2/F_IO_2 ratio (<150 vs. ≥150 mmHg).[32] Treatment effect heterogeneity will be tested using an interaction term between treatment group and each of the subgroups. Subgroup specific treatment effect estimates will be reported with 95% confidence interval and depicted using Forest plot. No adjustments will be made for multiple comparisons. All subgroup patient characteristics are available at time of randomization. The cut-off for age subgroups of <65y and ≥65y was based on prior inhalation sedation trials where median participant age was 65 years.[8 11] The cut-off for PaO_2/F_IO_2 ratio was chosen to evaluate participants with moderate-severe (<150 mmHg) and mild (≥150 mmHg) respiratory disease.[11] We hypothesize that inhaled sedation is associated with lower hospital mortality in participants aged ≥65 years, female sex, PaO_2/F_IO_2 ratio < 150 mmHg and admitted with non-COVID respiratory failure based on prior ICU sedation and respiratory failure studies.[1 11 33-35]

Sensitivity analyses

Several sensitivity analyses will be conducted. This includes evaluating hospital mortality with risk adjustment by adding pre-specified patient-level characteristics (sex, COVID-19, multiple organ dysfunction score categorized at the median, Charlson comorbidity index score categorized at the median) to the primary analysis model. ICU-free days at day-30 will also be evaluated for readmitted patients that only subtracts the number of ICU days within the 30-day period. Ventilation-free days at day 30 will also be calculated by subtracting only mechanical ventilation days in those patients with two or more ventilation episodes.

Safety outcomes

We will present the number of patients with each specific serious adverse event and safety event of interest (for e.g., sedative drug associated hepatitis, malignant hyperthermia, propofol infusion syndrome, accidental device removal, hypotension etc.) for both treatment groups and compare using risk ratios (95% confidence interval). We will also compare the number of patients with any serious adverse event or safety events of interest.

Table 1. Draft table summarising baseline patient characteristics.

Characteristic	**Inhaled Sedation (N=)**	**Intravenous Sedation (N=)**
Age - year		
Female sex - no. (%)		
Multi organ dysfunction syndrome score		
PaO_2/FiO_2 ratio		

Charlson comorbidity index score - no. (%)		
Delirium - no. (%)		
Coma - no. (%)[1]		
Aetiology of AHRF - no. (%)		
COVID 19		
Non-COVID 19		
Reason for ICU admission - no. (%)		
COVID-19 pneumonia		
Non-COVID pneumonia		
Trauma		
Extrapulmonary sepsis		
Surgery		
Cardiovascular		
Cancer		
Gastrourinary/metabolic		
Neurologic		
Time from ICU admission to randomisation - days		
Time from sedation to randomisation - days		
Sedatives and opioids on day of randomisation - no. (%)		
Propofol		
Benzodiazepine		
Ketamine		
Dexmedetomidine		
Barbiturates		
Opioid		
Treatments – no. (%)		
Prone positioning		
Inhaled vasodilator therapies		
Extra-corporal life support		
Neuromuscular blocker		
Steroids		
Antibiotics		
Antiviral		
Vasoactive medication		
Antipsychotics		

AHRF acute hypoxaemic respiratory failure; COVID 19 coronavirus disease 2019; FIO_2 fractional inspired oxygen concentration; ICU intensive care unit; PaO_2 arterial oxygen tension

[1]*Richmond Agitation Sedation Scale score -5/-4 or Motor Activity Assessment Score of 0/1.*

Table 2. Draft table summarising primary and secondary outcomes

Outcome	Inhaled Sedation	Intravenous Sedation	Measure of association (95% CI)
Primary outcome			
Hospital mortality - no. (%)			
Secondary outcomes			
Median no. of ICU-free days at 30 days (IQR)			
Median no. ventilation-free days at 30 days (IQR)			
Median no. hospital-free days at 60 days (IQR)			
PaO_2/FiO_2 at day 3			
AHRF adjunctive therapies - no. (%)[a]			
Neuromuscular blocker			
Inhaled vasodilator			
Prone positioning			
Extra-corporeal life support			
Median no. delirium and coma free-days at day 14 (IQR)			
EQ-5D-5L score at 3 months			
Mobility			
Self-care			
Usual activities			
Pain or discomfort			
Anxiety or depression			
Score on visual analogue scale[b]			
EQ-5D-5L utility			
WHODAS score at 3 months			
Cognition			
Mobility			
Self-care			
Getting along			
Participation			
Life activities - domestic			
Life activities - school/work			
Serious adverse event, no. (%)			

[a]Adjunctive therapies were defined as use of one or more adjuncts to manage hypoxic respiratory failure within 30 days including neuromuscular blocker, inhaled vasodilator, prone ventilation or extra-corporeal life support
[b]For available patients

AHRF acute hypoxaemic respiratory failure; COVID 19 coronavirus disease 2019; EQ-5D-5L Euroqol-5 dimension-5 level; FIO_2 fractional inspired oxygen concentration; ICU intensive care unit; no. number; PaO_2 arterial oxygen tension; WHODAS World Health Organization Disability Assessment Schedule

Additional Tables and Figures

Additional tables and figures will be developed to summarise participant baseline characteristics in parallel cohort arm, treatment received analyses, summary of sensitivity and subgroup analyses, summary of safety events, incidence and duration of delirium, and daily sedative drug use.

REGULATORY APPROVAL AND FUNDING

SAVE-ICU protocol was approved by the research ethics board approval (2149) and Health Canada approval (240138). SAVE-ICU is an investigator-initiated trial funded by Alternate Funding Plan, Canadian Institute for Health Research and Government of Ontario and was first registered with clinical.trials.gov (NCT04415060) on 4th June 2020 with first patient recruited on September 10th, 2020. All protocol updates were documented by a dated new version, approved by our regulatory board and shared with participating sites. We used a priori ongoing consent model, with initial consent obtained from substitute decision maker in incompetent patients via telephone or in-person interviews, with final consent obtained in surviving patients when they regained competency.

RESULTS

Enrolment for the SAVE-ICU trial has been completed with ongoing assessment of 12-month quality of life and disability for select participants. Currently, data continues to be extracted for all participants, cleaned and remains fully blinded to research team and statistician. Sharing of main trial results is estimated to occur in 2026.

DISCUSSION

SAVE-ICU is an investigator-initiated clinical trial evaluating the effectiveness of inhaled versus intravenous sedation for adult ventilated patients with AHRF using a pragmatic protocol and innovative trial design. Findings from this trial will have implications for sedation practices and utilization of inhaled sedatives in the ICU. This SAP outlines the prespecified analyses that will be conducted following completion of all data activities and locking of the trial database.

An important feature of SAVE-ICU is its hierarchical outcome structure, which was designed during the COVID-19 pandemic to ensure that meaningful results could still be generated if the trial was disrupted. By powering each outcome independently and ordering them by clinical priority, the design allowed the study to pivot to the highest-ranking outcome with adequate power if recruitment was curtailed by supply chain interruptions, staffing challenges, or difficulties implementing a new complex intervention and sedation pathway. This flexibility was particularly valuable for a complex intervention delivered during a period of global pandemic. Ultimately, recruitment proceeded successfully, allowing the trial to reach the full sample size for hospital mortality (top hierarchical outcome) which serves as the definitive primary outcome. Although the hierarchical approach was not required for the final analysis, its inclusion highlights a pragmatic and resilient trial design strategy that may be important for future studies of emerging or resource-dependent critical care interventions, or during future pandemics. Such designs can safeguard trial integrity when external pressures threaten continuity, while maintaining the ability to generate robust and clinically relevant evidence.

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FIGURES AND TABLES

Figure 1. Draft figure of participant trial flow

Table 1. Draft table summarising baseline patient characteristics.

Table 2. Draft table summarising primary and secondary outcomes.