

BMJ Open Sedating with volatile anaesthetics for COVID-19 and non-COVID-19 acute hypoxaemic respiratory failure patients in ICU (SAVE-ICU): protocol for a randomised clinical trial

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ABSTRACT

Introduction Inhaled anaesthetics can be used in mechanically ventilated critically ill patients to provide sedation. This approach to sedation potentially improves patient and health system outcomes, but further supportive evidence is needed. The objective of the SAVE-ICU clinical trial is to compare the effectiveness of inhaled versus intravenous sedation in ventilated adults with acute hypoxaemic respiratory failure.

Methods and analysis SAVE-ICU is a multicentre, open-label, pragmatic, randomised controlled trial conducted in 15 intensive care units (ICUs) in Canada and the USA. Eligible patients include mechanically ventilated and sedated adults with acute hypoxemic respiratory failure from COVID-19 or non-COVID causes with PaO₂/F_iO₂ ratio <300 mm Hg. Patients are excluded with a history of malignant hyperthermia, allergy to sedative agents, raised intracranial pressure, need for concomitant prostacyclin, low tidal volumes (<200 mL), one-lung ventilation or pneumonectomy, severe neuromuscular disorder (eg, amyotrophic lateral sclerosis, Guillain-Barré syndrome), pregnancy or moribund status (unlikely to survive >12 hour). A hierarchy of outcomes was identified at the time of trial design, as the trial was launched during the COVID-19 pandemic when study drug shortages, staffing challenges and healthcare system pressures were prevalent and there was a requirement for rapid evidence generation and implementation on this topic. The primary outcome and highest in the hierarchy is hospital mortality (requiring 758 participants). Secondary and lower hierarchical outcomes are ventilator-free days at day 30 (200 patients), quality of life at 3 months (144 participants) and ICU-free days at day 30 (128 participants). Additional secondary outcomes include median daily oxygenation at day 3 (PaO₂/F_iO₂ ratio), need for adjunctive acute respiratory distress syndrome therapies (prone positioning, inhaled nitric oxide, paralysis with a neuromuscular blocking agent and extracorporeal membrane oxygenation)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ SAVE-ICU is a multicentre randomised trial evaluating inhaled versus intravenous sedatives in ventilated adults with acute hypoxaemic respiratory failure to inform intensive care unit (ICU) sedation practices.
- ⇒ To reduce bias and generate high quality evidence on the effectiveness of inhaled anaesthetics for sedation in the critically ill, we will conduct an independent investigator-initiated randomised controlled trial free from industry influence.
- ⇒ A hierarchical approach allows powered evaluation of outcomes important to patients, clinicians and health system leaders and provides flexibility to adapt to uncertain circumstances encountered in a pandemic situation.
- ⇒ Differences between intravenous and inhaled sedative equipment and drug delivery routes precluded blinding of intervention delivery, but the data analyst remains blinded to treatment allocation.
- ⇒ As a novel practice for ICU providers, the clinical implementation of inhaled sedation presents logistical challenges and requires extensive interdisciplinary team training.

during ICU stay, days alive and free from delirium and coma at day 14, hospital-free days at day 60 and disability score at 3 months and 12 months after enrolment.

Ethics and dissemination The protocol was approved by all hospital ethics committees and by Health Canada. Informed consent will be obtained from substitute decision makers or deferred consent (as permitted by site ethics board). Trial findings will be shared at the end of the study using peer-review publications, conference presentations and social media as part of the trial knowledge translation plan.

INTRODUCTION

Acute hypoxemic respiratory failure (AHRF) is a leading cause of intensive care unit (ICU) admission, with approximately 10% of hypoxemic patients meeting the definition for acute respiratory distress syndrome (ARDS).¹ Patient management involves life supportive measures including invasive mechanical ventilation and adjunctive therapies to manage refractory hypoxaemia such as prone positioning and paralysis with neuromuscular blocking agents.

Sedation is provided to most mechanically ventilated patients to improve comfort and tolerance of this invasive therapy. Current guideline recommendations promote the use of intravenous sedatives (ie, propofol) along with opioid-based analgesia and delirium care.² However, these practices face several limitations, including lack of suitable drug monitoring techniques, the association with acute and longer-term cognitive dysfunction³ and drug accumulation from altered hepato-renal clearance slowing patient awakening and ventilator liberation; these factors all promote longer stays in the ICU.

During the COVID-19 pandemic, many countries faced major drug supply chain disruptions leading to insufficient supply of intravenous sedatives and paralytic agents.⁴ An alternative option for providing ICU sedation uses inhaled anaesthetic-based agents such as isoflurane or sevoflurane.⁵ Inhaled anaesthetics can be delivered at the bedside using miniature vaporising and ICU scavenging systems. They are easy to titrate, with dosing continuously monitored through a bedside gas analyser. In contrast to intravenous agents, inhalational anaesthetics possess unique clearance properties relying on pulmonary exhalation with minimal end-organ metabolism, making them less likely to accumulate in patients with liver or kidney dysfunction, which is common in critically ill patients receiving intravenous sedation.

Existing data

In addition to providing an alternative ICU sedation pathway, emerging evidence suggests that inhaled anaesthetics may offer important sedative and non-sedative benefits over traditional intravenous agents for ventilated patients with AHRF.^{6–8} First, several studies have shown that inhalational anaesthetics are able to achieve sedation targets with similar effect to intravenous agents.^{8,9} Second, studies have also shown that use of inhaled anaesthetics may promote faster patient awakening, spontaneous breathing trials and extubation.^{7,8,10,11} Third, inhalational agents reduce bronchial smooth muscle tone through blockade of the calcium channel on the airway smooth muscle and therefore act as a powerful bronchodilator, which may improve gas exchange and oxygen levels by altering ventilation-perfusion matching.^{10,12} Fourth, animal and human data have also shown inhaled anaesthetics may possess anti-inflammatory properties that

lower levels of proinflammatory cytokines (eg, α -tumor necrosis factor (TNF), interleukin (IL)-1 β , IL-6, IL-8).^{6,13} Reducing inflammation has been shown to be associated with less histological evidence of acute lung injury and lung oedema that could explain potential improvements in patient oxygenation.^{14,15} Porcine ARDS models showed that inhaled therapy significantly lowered TNF- α (112 vs 141 pg/mL; $p=0.02$), IL-6 (101 vs 580; $p=0.03$) and IL-1 β (127 vs 174; $p=0.04$) with better oxygenation compared with intravenous propofol.¹¹ Similar findings were identified in a small human trial of ARDS patients ($n=50$), where 72 hours of inhaled sevoflurane therapy improved patient oxygenation by 20% and lowered systemic inflammatory markers compared with midazolam-based sedation.⁶ Fifth, inhalational agents may be particularly useful in managing patients with high and complex sedation needs (eg, COVID-19 patients, burns, drug misuse) and reduced requirements for adjunctive intravenous agents.¹² Although a retrospective study ($n=200$) showed that inhaled sedation using isoflurane was associated with a lower adjusted in-hospital mortality (OR 0.35, 95% CI 0.18 to 0.68; $p=0.002$), a recent trial ($n=687$) comparing sevoflurane to propofol in moderate-severe ARDS patients ($\text{PaO}_2/\text{F}_1\text{O}_2$ ratio <150 mm Hg and positive end-expiratory pressure ≥ 8 cm H₂O) found that use of sevoflurane in a deep sedation protocol with concurrent neuromuscular blockade was associated with fewer ventilator-free days at day 28 (median difference -2.1 , 95% CI -3.6 to -0.7 ; standardised HR 0.76, 95% CI 0.50 to 0.97) and higher 3-month mortality (HR 1.31, 95% CI 1.05 to 1.62).^{16,17}

Aims and objectives

The primary objective of SAVE-ICU is to evaluate the effect of inhaled versus intravenous sedation on patient and health system outcomes (ie, hospital mortality, quality of life at 3 months, ventilator-free days and ICU-free days at day 30). The secondary objectives are to evaluate the differences between inhaled and intravenous sedation with respect to hospital stay (hospital-free days at day 60), adjunctive therapies for refractory hypoxemia (prone positioning, inhaled nitric oxide, paralysis with a neuromuscular blocking agent, extracorporeal membrane oxygenation (ECMO) therapies during the index ICU admission), patient oxygenation ($\text{PaO}_2/\text{F}_1\text{O}_2$ ratio at 3 days after enrolment), delirium (days alive and free from delirium and coma while in ICU up to 14 days) and patient disability (WHO Disability Assessment Score assessment at 3 months and 12 months after enrolment).

METHODS AND ANALYSIS

SAVE-ICU is a multicentre, open-label, pragmatic, hierarchical-outcome, randomised controlled trial (RCT) that aims to investigate the effectiveness of inhaled versus intravenous sedation in mechanically ventilated adults with AHRF (figure 1). A hierarchical outcome design was chosen due to resource constraints during the COVID-19 pandemic, including variations in staffing level, drug and

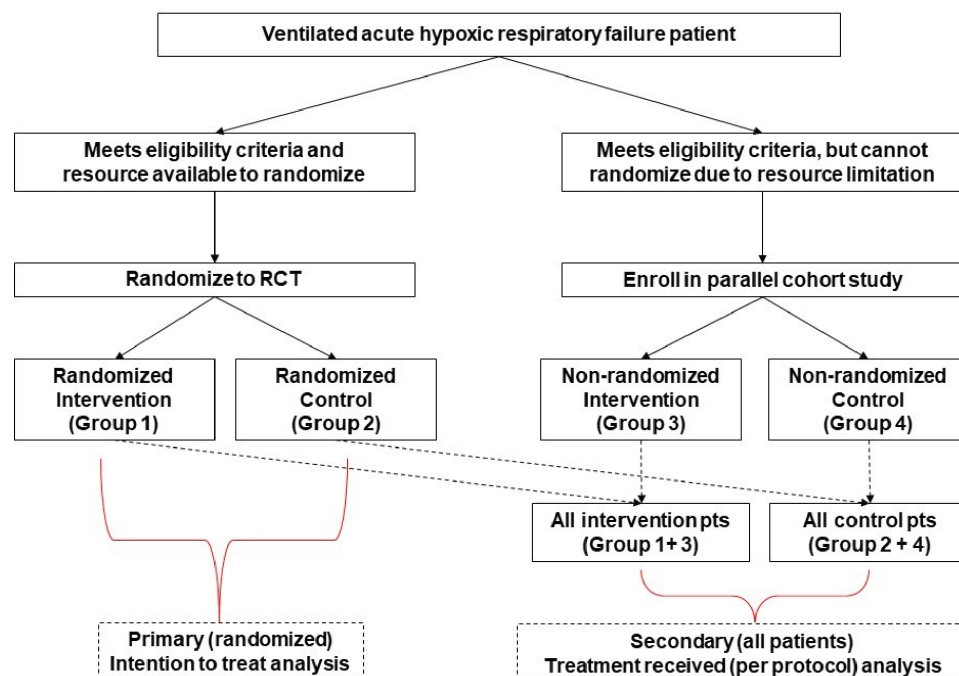


Figure 1 Outline of randomised trial and prospective cohort study. RCT, randomised controlled trial.

equipment availability in both trial groups. Patients will only be included and randomised to the RCT if both the control and intervention group drugs and delivery techniques are available at time of assessment. Eligible patients who cannot be randomised due to these limitations will be included in a parallel prospective cohort evaluating the same study objectives. Intervention and management protocols, as well as all trial outcomes for patients within the cohort study, follow the clinical trial and will be analysed separately.

This manuscript was prepared by the SAVE-ICU investigators (online supplemental file 1) on behalf of the Canadian Critical Care Trials Group in accordance with the recommendations described in the Standard Protocol Items: Recommendations for Interventional Trials reporting guideline (Online supplemental file 1).¹⁸ The planned trial start-end dates are June 2020–June 2027.

Patient and public involvement

Patient partner with lived experience is included in the development of this trial and funding application (Online supplemental file 1).

Study setting

SAVE-ICU is conducted in 14 adult ICUs across Canada and one site in the USA.

Inclusion criteria and rationale

Trial inclusion criteria are: (1) adult (≥ 18 years of age) ICU patient, (2) receiving invasive mechanical ventilation ($\pm$ ECMO) and expected to remain mechanically ventilated at the end of the calendar day after the day of assessment for trial eligibility, (3) receiving intravenous sedation by infusion or bolus for ≤ 72 hours to facilitate mechanical ventilation (intravenous sedatives include use

of one or more of the following agents: benzodiazepines, propofol, ketamine, alpha-2 agonists, barbiturates and opioids (fentanyl ≥ 50 mcg/h, hydromorphone ≥ 0.4 mg/h or bolus every hour) and either (4) mechanical ventilation $\pm$ ECMO support for (a) proven or suspected COVID-19 respiratory failure or (b) non-COVID-19 respiratory failure with $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio ≤ 300 mm Hg. These criteria were used to recruit respiratory failure patients who are likely to remain sedated and invasively ventilated beyond 24 hours. Patients with hypoxic respiratory failure not caused by COVID-19 are included in the modified trial inclusion criteria given the biologically plausible benefits of inhalational agents would apply for both COVID and non-COVID patients with respiratory failure in protocol V.5.0 (30 November 2020). For patients without an arterial line, PaO_2 is imputed from the pulse oximetry measurement. Patients transferred to recruiting ICUs requiring ongoing mechanical ventilation remained eligible for recruitment for up to 72 hours from start of intravenous sedation when commenced at the receiving trial site.

Exclusion criteria and rationale

Trial 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 (eg, 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 vapouriser, that is, target tidal volume (6 mL/kg) $< 200\text{ mL}$; (8) use of inhaled prostacyclin, which is contraindicated in the presence of a miniature vapouriser (ie, anaesthesia conserving device); (9) known pregnancy; (10) moribund patient not expected to survive >12 hours.

These criteria are used to maximise safe delivery of the intervention by avoiding patients with potential life-threatening reactions, patient disease states that impact assessment of the study outcomes and adjunctive agents that can impact vaporisation of inhalational agents.

Randomisation and treatment allocation

Eligible patients are identified by the site investigators at each participating site. Consented patients are randomised 1:1 to inhaled sedation or intravenous sedation using a central computerised randomisation system. Randomisation is stratified by study site, age (<65 years or ≥ 65 years) and $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio (<150 or $\geq 150\text{ mm Hg}$) using permuted block sequences of undisclosed sizes. If the participant cannot be randomised due to inability to source or deliver the study drugs, they will receive inhalation or intravenous sedation determined by drug/equipment availability and will be enrolled into a parallel perspective cohort study.

Inhalational anaesthetic sedation-based arm

In keeping with guidelines,² sedation, analgesia and treatments for delirium are managed using a pragmatic protocol representative of practice at all sites (figure 2). Inhalational anaesthetics such as isoflurane or sevoflurane will be titrated to meet the target sedation score goals for the participant as identified by the primary care team. This practice is in contrast to a prior sedation trial that enrolled patients with moderate-severe ARDS and titrated sevoflurane using a deep sedation protocol (Richmond Agitation-Sedation Scale of -5 to -4).¹⁷ Inhalational agents will be administered using a vaporising device (eg, anaesthesia conserving device, Sedana Medical, Sweden or anaesthesia machine) with inspired and expired gas concentrations monitored using a bedside gas analyser. Exhaust gas is scavenged from the ventilator using passive and/or active systems (eg, Flurabsorb, charcoal-based canisters or Deltasorb). Within the inhalation arm, the use of intravenous sedatives is permitted if inhalation sedation is unable to achieve satisfactory levels of sedation. Use of neuromuscular paralytic agents is permitted as deemed clinically necessary for optimising patient care. This contrasts with a prior sedation trial that enrolled patients with moderate to severe ARDS that recommended the use of continuous cisatracurium infusion to support a deep sedation protocol early in the patient treatment pathway.¹⁷ Administration and management of inhalational anaesthetics using miniature vapourisers has been previously well described and outlined in online supplemental eFigure 1.

Use of inhalational anaesthetics for sedation in the ICU is a new practice in most recruiting

centres. To support implementation of this new technique, education will be provided to the multidisciplinary ICU team (ie, physicians, nurses, respiratory therapists, pharmacists) using online and bedside training sessions (as feasible during the pandemic) with written education material throughout the duration of the trial, including in-time education of new providers.

Intravenous anaesthetic sedation-based arm

Sedation will be given by an intravenous analgesic-sedative regimen as per usual ICU standards (figure 2). Use of multiple intravenous sedatives is permitted to achieve adequate sedation, as deemed clinically appropriate. Inhalation sedation is not permitted, and non-protocolised crossovers are documented as protocol violations. Similar to the inhalational sedation arm, use of neuromuscular paralytic agents is permitted when clinically indicated to optimise patient care.

Sedation and patient care for both treatment arms

Patients will continue receiving allocated sedation regimen until the primary care team decides to stop sedation. Patients who cannot be successfully liberated from the ventilator and need ongoing sedation will remain in their allocated arm, with daily data collected in the ICU until 30 days after enrolment or ICU discharge or death, whichever occurs first. Patients enrolled in the trial and failing extubation in the ICU, requiring re-intubation, will be returned to their study-assigned sedation arm if the resources are available and the primary care team deems it appropriate. All patients will receive usual care for AHRF (figure 2, online supplemental file 1), which includes lung protective ventilation strategy, that is, $4\text{--}8\text{ mL/kg}$ tidal volumes, $> 5\text{ cm H}_2\text{O}$ positive end-expiratory pressure, adjunctive ARDS therapies in severe cases (eg, prone positioning, inhaled nitric oxide, paralysis with a neuromuscular blocking agent and ECMO therapy), restrictive fluid strategy, vasoactive medications, mechanical circulatory support and renal replacement therapy, as clinically indicated.

Outcomes

Designing and conducting this trial during the COVID-19 pandemic created difficulties in predicting the number of potential participants, identifying suitable trial sites and facilitating delivery of a new sedation care pathway using inhalational agents that requires substantial education and practice changes. To manage these uncertainties, the randomised trial uses a hierarchy of patient and health system outcomes that were individually powered at baseline. The trial was structured so that, depending on participant recruitment and interim safety reviews conducted during the pandemic, it could pivot to the highest-ranking outcome with sufficient statistical power if recruitment needed to be stopped prematurely due to either low numbers of eligible participants or

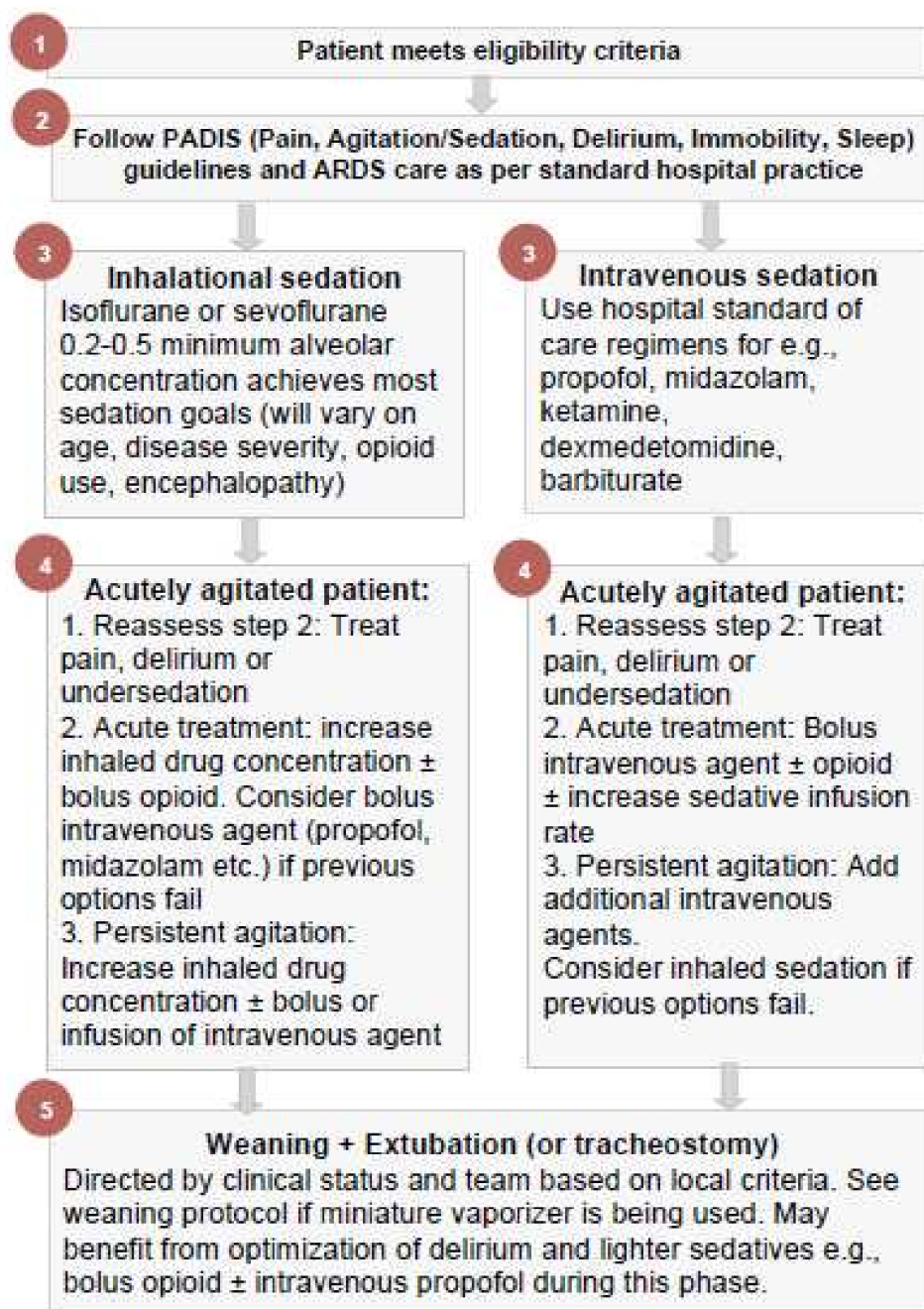


Figure 2 Trial protocol for inhaled and intravenous-based sedation arms. ARDS, acute respiratory distress syndrome.

safety concerns identified by the data safety monitoring board. Although the aim is to recruit sufficient participants to evaluate the top hierarchical outcome (hospital mortality), this design permits reporting of outcomes lower in the hierarchy if early termination is considered necessary. This ensures the trial can still generate meaningful evidence to guide patient care during and after the pandemic. The hierarchical outcomes in order of priority and sample size include: (1) hospital mortality (758 participants), (2) ventilator-free days at day 30 (200 participants), (3) quality of life at 3 months assessed using EQ (EuroQoL)-5D-5L (144 participants) and (4) ICU-free days at day 30 (128 participants); see figure 3. Due to sustained successful recruitment during the pandemic,

the easing of drug supply pressures, the absence of major safety concerns or requirement for unblinding of the study data raised by the data safety monitoring board, the trial is able to continue patient recruitment to meet the power requirement for the top hierarchical outcome of hospital mortality that is the primary outcome in trial analysis, with quality of life, ICU and ventilator-free days to be reported as secondary outcomes. Other secondary outcomes include oxygenation at day 3 assessed using the $\text{PaO}_2/\text{FIO}_2$ ratio, need for adjunctive ARDS therapies (prone positioning, inhaled nitric oxide, paralysis, ECMO) during the index ICU stay, delirium assessed as delirium and coma-free days at day 14, hospital-free days at day 60 and patient disability using WHO

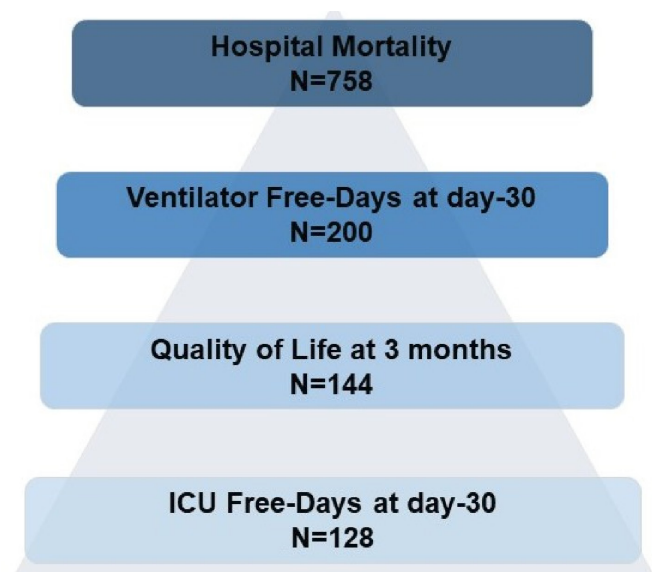


Figure 3 Hierarchy of outcomes. ICU, intensive care unit.

Disability Assessment Schedule 2.0 at 3 months and 12 months. Outcomes using free days are chosen to manage competing risks such as death and recurrent events. Substudies will evaluate differences in cost-utility, biological markers and long-term neurocognition function in randomised participants.

Follow-up

Patients will be followed in the ICU and hospital by the local research team until discharge or death. Assessment of mortality, quality of life and disability is performed by telephone at 3 months and 12 months by the trial coordinating centre.

Adverse events

All adverse events will be reported to the trial coordinating centre using a case report form with a clear description of the event, severity and likelihood that the event was related to study treatment (intravenous or inhaled agent) or equipment. Serious events are classified to have resulted in either a life-threatening reaction, resulted in death or hospitalisation or caused persistent or significant disability or congenital anomaly. Expected serious reactions include drug allergic reaction, drug associated hepatitis, malignant hyperthermia and propofol infusion syndrome. Serious events are reported to sponsor and regulatory bodies. Adverse events of special interest include shivering and nausea/vomiting needing pharmacological treatment, accidental device removal (ie, self-extubation, loss of invasive lines and other medical devices), technical equipment failure associated with intravenous and inhaled sedatives and (in the inhaled anaesthetic arm) removal of vaporising device secondary to low tidal ventilation (<200 mL). All adverse events are reviewed by the data safety and monitoring board.

Risk of bias

This is an open-label study that uses different equipment for delivery of the intervention but blinding of the patient and data analyst will be maintained. Eligible, consecutive patients will be randomised whenever possible to minimise bias. Patients will only enter the non-randomised (cohort) arm if they cannot be randomised for legitimate a priori identified reasons (ie, poor staffing level, lack of sedative drug or equipment). A primary intention-to-treat analysis will be used for randomised patients only to minimise bias. A 'treatment received' analysis is a secondary exploratory analysis. Crossovers will be included in a per protocol analysis. Patients randomised in error will be withdrawn from the trial. Data from participants who later withdraw consent will be included in a modified intention-to-treat analysis up to the point of withdrawal unless they explicitly declined permission to use their data.

Statistical analysis

The following sample size assessment and analysis applies only to randomised trial participants and excludes any participants enrolled as part of the cohort study. A full statistical analytical plan will be separately published.

Sample size

The hierarchical outcomes for the RCT were selected on the basis for evaluating the effectiveness of inhaled sedation that are important for patients, clinicians and health resource use. We prospectively planned that, once the sample size was achieved for each outcome, enrolment would continue to the next outcome without unblinding the data, thus minimising potential bias during continuing recruitment during the COVID-19 pandemic. We will not unblind any study outcomes at any time point for final analysis due to successful continuing recruitment and no safety concerns identified. Final analysis of all outcomes is planned on trial recruitment completion with hospital mortality as the primary outcome.

All sample size calculations are based on 80% power and two-sided alpha at 5%. The first hierarchical outcome will assess the superiority of inhalational sedation on ICU-free days at day 30 based on an expected median control group event rate of 10 ICU-free days at 30 days (SD, 10 days) with a difference of 5 days; this outcome will require 128 patients.¹⁹ The second hierarchical outcome will evaluate the superiority of inhaled sedation on 3-month quality of life measured using EQ-5D. Based on an expected control group EQ-5D of 0.6 (SD 0.1) and a minimum important difference of 0.06, a total of 144 patients will be required, including an anticipated patient loss from death (30%) up to 1 year after ICU discharge and an additional loss to follow-up after discharge (10%).^{20 21} The third hierarchical outcome will evaluate the superiority of inhaled sedation on ventilator-free days at day 30 based on a control group event rate of 16 days (SD 10 days) with a target difference of 4 days and will require 200 patients.^{22 23} If superiority is not reached at this time point, the *non-inferiority*

Table 1 Schedule of events

Data points and instruments	Screening/baseline	Study days 1-30*	ICU discharge	Safety follow-up (30±3 days from last dose of treatment)	Follow-up D60 (±3 days from enrolment)	Follow-up D90 (±14 days from enrolment)	Follow-up D365 (±14 days from enrolment)
Obtain consent	X						
Eligibility review/ confirmation	X						
Demographics (eg, age, sex)	X						
Admission data (eg, MODS, CCI)	X						
COVID-19 status	X		X				
Mechanical ventilation	X	X	X				
Sedation information	X	X	X				
Delirium and coma assessment	X	X					
Concomitant medications/ therapies	X	X	X				
Study treatment		X					
Survival status		X	X	X	X	X	X
ICU and hospital discharge			X		X	X	X
Adverse events		X		X			
EQ-5D-5L						X	X
WHODAS 2.0						X	X

*Data will be collected until 30 days, discharge or death, whichever occurs first.

CCI, Charlson comorbidity index; D, day; EQ-5D-5L, Euroqol-5D-5L; ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; WHODAS, World Health Organization Disability Assessment Schedule.

of inhaled agents will be assessed using a non-inferiority margin HR of 0.85 to evaluate time to extubation and alive to ICU discharge. Assessment of free-day outcomes will be in accordance with current recommendations.²⁴ This combined approach has been successfully used in clinical trials and will provide important evidence on the effectiveness of inhaled anaesthetics.^{25–27} The fourth and top hierarchical outcome assesses the superiority of inhaled sedation on in-hospital mortality based on the control group event rate of 40% with an ARR (absolute risk reduction) of 10% and will require 758 patients.¹ To meet a participant number of 758 patients after an estimated 5% study withdrawals (38 patients), we will enrol a total of 800 randomised participants.

Data analysis

Analyses will be performed on trial completion after data cleaning and trial data queries completion. Primary analysis will use intention-to-treat for all randomised patients. Descriptive analyses for continuous variables will use median (IQR) or mean (SD) depending on the distribution, and categorical variables will be summarised as frequency (%). Hospital mortality will be analysed using log-binomial or modified Poisson regression and results will be presented as risk ratios and 95% CIs adjusted for the stratification variables of age, site and PaO₂/F_IO₂ ratio. Fine and Gray models will be used for outcomes using free-days (ie, ventilator, ICU and hospital-free days (recommended model²⁴ with death as competing risk or quantile regression as appropriate for the distribution

of the outcome)). Secondary analysis uses a treatment received or per protocol analysis that includes both randomised and non-randomised cohort. All analyses will be conducted using SAS V.9.4 (Cary, North Carolina, USA) and R (V.5.1; R Foundation for Statistical Computing, Vienna). Two-sided p values of <0.05 will be considered statistically significant.

Data management, trial monitoring and oversight

Data management

Centre for Clinical Trial Support (CCTS) at Sunnybrook Research Institute will co-ordinate the trial and oversee regulatory approvals, REDCAP data management, procurement of drugs and equipment and site management. Patient data are collected manually from electronic health records and stored in a secure REDCap file. Patient confidentiality will be maintained by removing all personal identifiers and use of a study identification number. Type of data collected at various time points is summarised in [table 1](#). Data will be stored for 25 years as per Health Canada regulations.

Site monitoring

Use of inhalational anaesthetics is a new care pathway for most ICUs participating within this study. Optimal use and safe delivery of inhalational drugs requires engagement of ICU physicians, nurses, respiratory therapists and pharmacists. To support a new practice change, ICUs will be supported with virtual, in-person (when permitted around COVID-19 restrictions) and written education

material. In addition, sites will receive training to meet regulatory requirements and support study screening, data collection, management of adverse events and standard operating procedures. Regulatory monitoring will be performed remotely, and in-person visits will be performed for select sites by the study investigative team. Site updates will be performed by (1) recruitment update emails for all sites shared every 2 weeks, (2) newsletter every 3–6 months sharing protocol changes, adverse events, new publications and recruitment updates and (3) virtual steering committee meetings every 3–6 months sharing data and safety monitoring board (DSMB) updates, discussion around recruitment challenges and study updates. Working group committee (Jerath, Slesarev, Cuthbertson, Martin, the trial manager and CCTS manager) meetings will be held weekly to manage day-to-day trial activities.

Data safety monitoring board

DSMB consisting of an independent intensivist and senior trialist (DSMB chair), anaesthesiologist and statistician acts in an advisory capacity to monitor behavioural, procedural and organisational aspects of data monitoring in the RCT. The DSMB will review trial conduct, blinded recruitment rates and interim safety events at 64 patients (half-way to first outcome), 128 patients (sample for assessment of ICU-free days) and 200 patients (sample for assessment of ventilator-free days). Each interim safety review was considered satisfactory and patient recruitment continued during the COVID-19 period. At 379 patients (half-way point of hospital mortality), the DSMB will conduct a blinded analysis to study for harm using two one-sided tests to assess for excess mortality (one-sided test, O'Brien-Fleming criterion $p < 0.0026$). The data will be directly shared with the DSMB only, with no information shared with the study team or study statistician to ensure blinding of the study groups is maintained. After each safety and interim analysis review, the DSMB will advise the study team on continuing patient recruitment and any protocol changes.

Ethics and dissemination

Regulatory approval

The SAVE-ICU protocol was approved by Sunnybrook Health Sciences Centre (ethics board of record, reference number 2149), University of Alberta Hospital (reference number Pro00103619), Centre Hospitalier de l'Université de Montréal Québec (reference number MP-02-2021-9165) research ethics board and Health Canada (reference number 240138). SAVE-ICU is an investigator-initiated trial funded by Sunnybrook Medical Services Alternative Funding Plan Association, Canadian Institute for Health Research (CIHR COVID-19 Rapid Research Fund, Number 447612), Ontario Government and London Health Sciences Foundation and was first registered with clinical.trials.gov (NCT04415060) on 4 June 2020 with first patient recruited on 10 September 2020. All protocol updates were documented by a dated

new version, approved by our regulatory board and shared with participating sites; see Supplemental File 2 for all protocol updates. Research co-ordinators will obtain informed consent from substitute decision makers via telephone or inperson interviews or deferred consent (as permitted by site research ethics board) and from patients when they regain capacity; see Online supplemental file 3 for sample consent forms. Deferred consent was approved at select participating sites depending on local site ethics board and their preferred practices; see online supplemental file 3 for sites with deferred consent and research ethics approval numbers. Participation will be voluntary and participants can withdraw from the study at any time. Data will be used up to the time of study withdrawal. Permission will be sought to continue data collection after the time of withdrawal.

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REFERENCES

- Bellani G, Laffey JG, Pham T, *et al.* Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315:788–800.
- Devlin JW, Skrobik Y, Gélinas C, *et al.* Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018;46:e825–73.
- Cuningham S, Jerath A, Gorsky K, *et al.* Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis. *Br J Anaesth* 2023;131:314–27.
- Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation for COVID-19 pneumonia and ARDS. *Intensive Care Med* 2020;46:1563–6.
- O'Gara B, Boncyk C, Meiser A, *et al.* Volatile Anesthetic Sedation for Critically Ill Patients. *Anesthesiology* 2024;141:163–74.
- Jabaudon M, Boucher P, Imhoff E, *et al.* Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am J Respir Crit Care Med* 2017;195:792–800.
- Jerath A, Panckhurst J, Parotto M, *et al.* Safety and Efficacy of Volatile Anesthetic Agents Compared With Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth Analg* 2017;124:1190–9.
- Meiser A, Volk T, Wallenborn J, *et al.* Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. *Lancet Respir Med* 2021;9:1231–40.
- Jerath A, Ferguson ND, Steel A, *et al.* The use of volatile anesthetic agents for long-term critical care sedation (VALTS): study protocol for a pilot randomized controlled trial. *Trials* 2015;16:560.
- Jerath A, Parotto M, Wasowicz M, *et al.* Opportunity Knocks? The Expansion of Volatile Agent Use in New Clinical Settings. *J Cardiothorac Vasc Anesth* 2018;32:1946–54.
- Jerath A, Beattie SW, Chandy T, *et al.* Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. *Crit Care Med* 2015;43:1062–9.
- Gorsky K, Cuningham S, Jayaraj K, *et al.* Inhaled Volatiles for Status Asthmaticus, Epilepsy, and Difficult Sedation in Adult ICU and PICU: A Systematic Review. *Crit Care Explor* 2024;6:e1050.
- Ferrando C, Aguilar G, Piqueras L, *et al.* Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. *Eur J Anaesthesiol* 2013;30:455–63.
- Englert JA, Macias AA, Amador-Munoz D, *et al.* Isoflurane Ameliorates Acute Lung Injury by Preserving Epithelial Tight Junction Integrity. *Anesthesiology* 2015;123:377–88.
- O'Gara B, Talmor D. Lung protective properties of the volatile anaesthetics. *Intensive Care Med* 2016;42:1487–9.
- Bellgardt M, Bomberg H, Herzog-Niescery J, *et al.* Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients. *Eur J Anaesthesiol* 2016;33:6–13.
- Jabaudon M, Quenot J-P, Badie J, *et al.* Inhaled Sedation in Acute Respiratory Distress Syndrome: The SESAR Randomized Clinical Trial. *JAMA* 2025;333:1608–17.
- Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* 2013;158:200–7.
- The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2019;380:1997–2008.
- Marti J, Hall P, Hamilton P, *et al.* One-year resource utilisation, costs and quality of life in patients with acute respiratory distress syndrome (ARDS): secondary analysis of a randomised controlled trial. *J Intensive Care* 2016;4:56.
- McClure NS, Sayah FA, Ohinmaa A, *et al.* Minimally Important Difference of the EQ-5D-5L Index Score in Adults with Type 2 Diabetes. *Value Health* 2018;21:1090–7.
- Hodgson CL, Cooper DJ, Arabi Y, *et al.* Maximal Recruitment Open Lung Ventilation in Acute Respiratory Distress Syndrome (PHARLAP). A Phase II, Multicenter Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med* 2019;200:1363–72.
- Ferguson ND, Cook DJ, Guyatt GH, *et al.* High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795–805.
- Yehya N, Harhay MO, Curley MAQ, *et al.* Reappraisal of Ventilator-Free Days in Critical Care Research. *Am J Respir Crit Care Med* 2019;200:828–36.
- Dunn DT, Copas AJ, Brocklehurst P. Superiority and non-inferiority: two sides of the same coin? *Trials* 2018;19:499.
- Granger CB, Alexander JH, McMurray JJV, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
- Mauri L, D'Agostino RB Sr. Challenges in the Design and Interpretation of Noninferiority Trials. *N Engl J Med* 2017;377:1357–67.