Statistical analysis plan for the Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure trial

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Abstract

Background: The best sedative medication to reduce delirium, mortality and long term brain dysfunction in mechanically ventilated septic patients is unclear. This multicentre, double-blind, randomised trial investigates the short term and long term effects of dexmedetomidine versus propofol for sedation in mechanically ventilated severely septic patients.

Objectives: To describe the statistical analysis plan for this randomised clinical trial comprehensively and place it in the public domain before unblinding.

Methods: To ensure that analyses are not selectively reported, we developed a comprehensive statistical analysis plan before unblinding. This trial has an enrolment target of 420 severely septic and mechanically ventilated adult patients, randomly assigned to dexmedetomidine or propofol in a 1:1 ratio. Enrolment was completed in January 2019, and the study was estimated to be completed in September 2019. The primary endpoint is days alive without delirium or coma during first 14 study days. Secondary outcomes include 28-day ventilator-free days, 90-day all-cause mortality and cognitive function at 180 days. Time frames all begin on the day of randomisation. All analyses will be conducted on an intention-to-treat basis.

Conclusion: This study will compare the effects of two sedatives in mechanically ventilated severely septic patients. In keeping with the guidance on statistical principles for clinical trials, we have developed a comprehensive statistical analysis plan by which we will adhere, as this will avoid bias and support transparency and reproducibility.

Trial registration: ClinicalTrials.gov (NCT01739933).

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The need for mechanical ventilation secondary to sepsis is the leading cause of admission to intensive care units (ICUs), often necessitating sedation for patient safety and comfort. Sedative medications contribute to iatrogenic injury by, for example, prolonging ventilator time and ICU length of stay and exacerbating acute brain dysfunction. Such acute brain dysfunction, manifested as delirium and coma, occurs in 50–70% of mechanically ventilated septic patients and is a significant contributor not only to death but also to functional and cognitive decline, which can persist for years after recovery of lung and other organ function, levying significant costs to patients and society. In particular, the gamma-aminobutyric acid (GABA)-ergic benzodiazepines have been shown to increase brain dysfunction, promote infection and prolong mechanical ventilation. Therefore, the short-acting GABAergic sedative propofol and the α-2 agonist dexmedetomidine are becoming widely used to sedate septic mechanically ventilated patients. However, only a few randomised trials that can guide clinicians when selecting between these and other sedatives have been conducted, and none have explored the mechanisms underlying the differences in outcomes, although some data indicate that GABAergic and α-2 agonist agents have very different effects on innate immunity, apoptosis, arousability and respiratory drive.

The Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure (MENDS2) study will determine whether sedation of mechanically ventilated severely septic patients with an α-2 agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will increase days alive without delirium or coma and increase days alive and days free from mechanical ventilation (ventilator-free days). This article serves as the formal statistical analysis plan (SAP) for the MENDS2 study, and was written before closure of the database and unblinding of the treatment groups. The trial is registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01739933). This SAP was written based

Table 1. Study exclusion criteria

- Rapidly resolving organ failure, indicated by planned immediate discontinuation of mechanical ventilation, at time of screening for study enrolment
- Pregnant or breastfeeding
- Severe dementia or neurodegenerative disease, defined as either cognitive impairment that makes the patient incapable of living independently at baseline or an Informant Questionnaire on Cognitive Decline in the Elderly score of ≥ 4.5 measured using a patient's qualified surrogate
  - this exclusion criterion also pertains to mental illnesses requiring long term institutionalisation, acquired or congenital mental retardation, severe neuromuscular disorders, Parkinson disease, Huntington disease, Alzheimer disease and debilitating cerebrovascular disease
  - it also pertains to patients in a coma or with severe cognitive deficits due to structural brain diseases such as stroke, intracranial haemorrhage, cranial trauma, malignancy, anoxic brain injury or cerebral oedema
- Present history of second or third degree heart block, or persistent bradycardia of < 50 beats/min that requires intervention (eg, atropine, glycopyrrolate)
  - if the patient has a pacemaker for bradyarrythmias, then the patient does not meet this exclusion criterion and may be enrolled
- Benzodiazepine dependency or history of alcohol dependency based on the medical team's decision to institute treatment involving benzodiazepines (either as continuous infusions or intermittent intravenous boluses) for this dependency
- Active seizures during the intensive care unit admission for which intravenous benzodiazepine treatment is given
- Expected death within 24 hours of enrolment or lack of commitment to aggressive treatment by family or the medical team (eg, likely to withdraw life support measures within 24 hours of screening)
- Inability to understand English or deafness that will preclude delirium evaluation
  - the inability to understand English (eg, in Spanish-only or Mandarin-only speaking patients) will not result in exclusion at centres where the research staff are proficient in the spoken language and/or translation services are available for the spoken language
  - patients unable to understand English will not be followed in the long term follow-up phase of the trial since most of the testing materials are available in English only
  - patients with laryngectomies and those with hearing deficits are eligible for enrolment if their medical condition permits them to communicate with the research staff

on guidelines by Gamble and collegues[1] and will be the guiding document for the analyses that will be reported in the primary manuscript. Any changes to this SAP will be presented as an addendum.

Objectives

The MENDS2 study is a multicentre, double-blind, randomised trial investigating the effects of dexmedetomidine and propofol in mechanically ventilated severely septic patients. Its aims are:

- to determine whether sedation of mechanically ventilated severely septic patients with dexmedetomidine rather than propofol will (Aim 1A) increase days alive without delirium or coma (delirium/coma-free days) and (Aim 1B) increase days alive and free from mechanical ventilation (ventilator-free days);
- to determine whether sedation of mechanically ventilated severely septic patients with dexmedetomidine rather than propofol will (Aim 2A) improve 90-day survival and (Aim 2B) decrease incidence and severity of long term cognitive impairment; and
- to determine whether sedation of mechanically ventilated severely septic patients with dexmedetomidine rather than propofol will (Aim 3) reduce levels of proinflammatory and anti-inflammatory cytokines (C-reactive protein, interleukin-1, interleukin-6, interleukin-10, soluble tumour necrosis factor receptor-1, high mobility group box protein 1).

We intend to present the results relating to Aim 3 in a separate secondary manuscript.

Methods

Trial design

This is a multicentre, double-blind, randomised trial. The two treatment arms were sedation using dexmedetomidine and sedation using propofol. Consent was obtained for patients who met the inclusion criteria and none of the exclusion criteria, and these patients were then enrolled and randomly assigned to one of the treatment arms.

Inclusion and exclusion criteria

Consecutive patients were eligible for inclusion in the MENDS2 study if they: were aged 18 years or more; were

in a medical or surgical ICU; were on mechanical ventilation and required sedation; and had a suspected or known infection. Patients were excluded if they met any of the exclusion criteria listed in Table 1.

Randomisation

Randomisation to dexmedetomidine or propofol was conducted in 1:1 ratio using a computer-generated permuted block randomisation scheme, stratified by study site and age (< 65 *v* ≥ 65 years). The randomisation scheme was created by a biostatistician external to the study and distributed directly to each site's investigational pharmacy as a set of randomisation lists stratified by study site and age. Once a patient for whom consent had been provided entered the interventional trial phase, an order for blinded study drug was placed, and then the investigational pharmacist referred to the appropriate randomisation list (determined by the patient's age) to establish the patient's treatment assignment. The lists were only accessible to investigational pharmacists so that treatment assignments were known only by the investigational pharmacists. Unblinding of the treatment groups (and subsequent data lock) will be performed after data cleaning and will be documented. Any unlock of the database will be performed only to correct serious data entry errors and will be documented in detail.

Power and sample size

Aim 1A (delirium/coma-free days)

Based on the demographic data from our National Institutes of Health-sponsored Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) cohort, we assumed patients in the MENDS2 control group (sedation with propofol) will have a mean ± SD of 6.8 ± 5.2 delirium/coma-free days during the 14-day study period. The study was repowered and resized owing to concerns about the feasibility of completing study enrolment. Our initial sample size of 530 patients provided us with more than 90% power to detect a difference of 1.5 delirium/coma-free days between the two groups and an absolute difference in mortality of 10%. With approval from the data safety monitoring board, we resized to enrol 420 patients, which will provide (assuming a two-sided α of 0.05) more than 80% power to demonstrate a difference of 1.5 delirium/coma-free days between dexmedetomidine and propofol (the primary outcome). We believe this has face validity as a clinically meaningful difference in the duration of acute brain injury. Importantly, this sample size also provides 80% power to detect a 10% absolute improvement in 90-day survival rate with dexmedetomidine, assuming the 90-day mortality rate in patients receiving propofol is 30% (which is conservative given the 25% mortality rate at 28 days in the recent Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]-SHOCK control group and the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction [MENDS] trial [dexmedetomidine *v* lorazepam] lorazepam group).

Aim 2B (long term cognitive impairment)

We assumed that 80% or more survivors would be followed up for evaluation of long term cognitive impairment. Based on the expected mortality rates described above, we expected an overall 25% mortality rate across the two groups and planned to test 252 ($420 \times 0.75 \times 0.80$) patients for long term cognitive impairment at 6 months. With 252 patients, we will have up to 17 degrees of freedom in our multivariable linear regression to account for potential confounders. The proposed study will have adequate — indeed abundant — ability to assess the independent effect of the intervention on cognitive impairment while controlling for confounders.

Study treatments and interventions

Study treatments and interventions are summarised in the study aids provided in the online Appendix 1 (available at cicm.org.au/Resources/Publications/Journal).

Statistical principles

Statistical analysis will be conducted in accordance with this SAP and will abide by the following general statistical principles.

Descriptive statistics

Patient flow information as recommended by Consolidated Standards of Reporting Trials (CONSORT) guidelines — including information on screening, exclusions, refusal of consent, withdrawals, deaths and hospital discharge status — will be presented. Demographics, baseline clinical status and ICU characteristics will be described overall and by treatment using medians and interquartile ranges for continuous variables and frequency (percentage) for categorical variables. Significance testing of baseline differences between treatment groups will not be performed, in keeping with CONSORT 2010 guidelines for reporting parallel group randomised clinical trials.

Confidence intervals and *P* values

A priori, our protocol specified one interim analysis at n = 300 before the final analysis for early stopping due to safety and efficacy based on delirium/coma-free days and 90-day mortality. To maintain the overall study-wise α level at 0.05, with interim analysis, it was specified that the level of statistical significance for the final analyses for the primary outcome would be adjusted to 0.044 (based on the O'Brien–Fleming method). The level of statistical

significance for all other outcomes will be at the 0.05 level. The 95% confidence intervals will be reported along with all effect estimates, as this is the standard way confidence intervals are reported and reflects how statistical software outputs are constructed. Presentation of results will emphasise clinical significance, effect sizes and confidence intervals over statistical significance.

Modeling principles

Whenever possible (based on variable distribution), we will not assume linear associations between covariates and outcomes; rather, nonlinear associations between continuous covariates and outcomes will be permitted by inclusion of restricted cubic splines with three knots. To account for correlation among patients at a given site, we will adjust standard errors using the Huber–White sandwich estimate.[2]

Multiple comparisons

Regarding the analyses of all a priori-defined secondary and exploratory outcomes, no adjustments will be made for multiple comparisons, in keeping with standard practice when analysing multiple, prospectively defined outcomes in a clinical trial. For all secondary and exploratory outcomes and subgroup analyses, caution will be exercised in interpreting results by noting the number of nominally significant tests that would be expected to occur by chance alone.[3]

Missing data

Data for missing inhospital variables will be imputed using simple imputation or clinical imputation rules when appropriate; details on these rules and the imputation process for summary variables (eg, days alive and free from delirium and coma) are detailed in the "Definitions and derived variables" section of the online Appendix 2. Simple imputation of completely missing baseline covariates will be performed using available baseline covariates.

In adjusted analyses for the long term Telephone Interview for Cognitive Status (TICS) outcome, model-based multiple imputation strategies will be used. In all cases, decisions and processes will be documented both in data management and analysis code and in statistical reports. TICS scores for patients who are not available at follow-up will not be imputed, but those with partially missing data will be imputed using model-based imputation with covariates being age at enrolment, sex, body mass index, education level, first language English, insurance status, Charlson Comorbidity Index, benzodiazepine exposure after ICU admission to midnight of the day before enrolment, and long term assessments (Katz Index of Independence in Activities of Daily Living, Functional Activities Questionnaire, EuroQOL [EQ-5D], Digit Span test, Logical Memory I test, Logical Memory II test, Wechsler Adult Intelligence Scale Similarities test, Controlled Oral Word Association test, Hayling Sentence Completion test).

Rigor, transparency and reproducibility

To enhance rigor, transparency and reproducibility in research, we will ensure that all aspects of this study are transparent and easy to reproduce by independent investigators. The SAP will be prespecified and time-stamped. All the analysis code will be made publicly available after publication of the primary manuscript.

Adherence to the intervention and protocol non-compliance

Definition and assessment of adherence to the intervention

All analyses will be conducted based on the intention-to-treat (ITT) principle. Patients will be in the ITT population if they meet all criteria required for randomisation and are assigned to and receive the treatment drug as indicated on the randomisation list. If patients received the study drug and form a part of the ITT population, they will be analysed according to the treatment they were randomly assigned to receive.

Presentation of adherence to intervention

The following are patient-level process outcomes, which will be described within each treatment group but will not be assessed for statistical significance:

- Number of days each randomly assigned patient received study drug
- Time from meeting all inclusion criteria to start of study drug
- Average daily dose of study drug
- Whether study drug was ever permanently discontinued, and reasons for discontinuation
- Proportion of patients that withdrew from the study by treatment
- Time at target sedation (± 1 Richmond Agitation–Sedation Scale [RASS] score) by comparing actual RASS to ordered RASS, while on study drug
- Average daily fentanyl dose and average fentanyl dose per kilogram body weight, while on study drug, among fentanyl users
- Proportion of patients receiving antipsychotic medications
- Number of days for which patients received antipsychotic medications
- Proportion of patients receiving midazolam

Table 2. Primary, secondary and exploratory outcomes

Variable	Description	Time frame*
Primary outcome		
Delirium/coma-free days	Number of days during the 14-day intervention period (from randomisation, which will be Study Day 1, until Study Day 14) that the patient was alive and free from delirium and coma	14 days
Secondary outcomes		
Ventilator-free days	Days alive and free from mechanical ventilation	28 days
Survival	Time to death	90 days
Long term outcomes	The TICS score will be the primary long term outcome; descriptive statistics for other long term outcomes such as Katz Index of Independence in Activities of Daily Living, Functional Activities Questionnaire, EuroQOL (EQ-5D) and a validated telephone-administered battery of neuropsychological function tests (eg, TICS, Digit Span test, Logical Memory I test, Logical Memory II test, Wechsler Adult Intelligence Scale Similarities test, Controlled Oral Word Association test, Hayling Sentence Completion test) will also be reported	6 months
Organ dysfunction	Ever versus never: kidney, creatinine > 2 mg/dL; lung, Pao_2/Fio_2 < 300 or Sao_2/Fio_2 < 315; liver, total bilirubin > 2 mg/dL ; coagulation, platelet count < 100 000/mm^3; and haemodynamic, need for vasopressor (descriptive statistics for this outcome will computed both overall and by treatment group and no hypothesis testing will be performed)	14 days
Acute respiratory distress syndrome	Any instance of acute respiratory distress syndrome during the intervention phase (descriptive statistics for this outcome will computed both overall and by treatment group and no hypothesis testing will be performed)	14 days
Exploratory outcomes		
Delirium duration	Number of days the patient had delirium	14 days
Duration of hyperactive delirium	Number of days the patient had hyperactive delirium (defined as CAM-ICU positive and RASS score +1, +2, +3 or +4)	14 days
Duration of hypoactive delirium	Number of days the patient had hypoactive delirium (defined as CAM-ICU positive and RASS –3, –2, –1 or 0)	14 days
Coma duration	Number of days the patient had coma (defined as RASS score –4 or –5 or RASS score missing and CAM-ICU assessment recorded as unable to assess)	14 days
ICU mortality	Death while in the ICU	30 days
Hospital mortality	Death while in the hospital	30 days
ICU-free days	Days alive and free from being in the ICU	28 days
Time to successful ICU discharge	"Successful" is defined as discharge followed by at least 48 hours alive	30 days
Compliance	Daily compliance on the first five elements of the ICU Liberation ABCDEF Bundle	14 days
Severity of shock	Mean daily cardiovascular SOFA score, and proportion of patients with at least one cardiovascular SOFA score ≥ 2 (the definition of organ dysfunction), then patients with at least one cardiovascular SOFA score > 2 and > 3	14 days plus 2 days post-study drug period (if longer than 14 days)
Heterogeneity of treatment effects	Assessed for age at enrolment, baseline cognition (measured by the Informant Questionnaire on Cognitive Decline in the Elderly; continuous covariate), medical *v* surgical patients	–

ABCDEF = A, assess, prevent, and manage pain; B, both spontaneous awakening and spontaneous breathing trials; C, choice of analgesic and sedation; D, delirium: assess, prevent, and manage; E, early mobility and exercise; and F, family engagement and empowerment; CAM-ICU = Confusion Assessment Method for ICU; Fio_2 = fraction of inspired oxygen; ICU = intensive care unit; Pao_2 = arterial partial pressure of oxygen; SOFA = Sequential Organ Failure Assessment; RASS = Richmond Agitation–Sedation Scale; Sao_2 = arterial oxygen saturation; TICS = Telephone Interview for Cognitive Status. * Time frames all begin on the day of randomisation.

Table 3. Study timelines and assessments

Variable	Enrolment	Treatment period and post-study drug period	6-month follow-up	12-month follow-up
Prehospital function assessment (Activities of Daily Living Questionnaire, Functional Activities Questionnaire, Informant Questionnaire of Cognitive Decline in the Elderly, Alcohol Use Disorders Identification Test)	X			
Demographics, comorbidities, APACHE II score	X			
Sequential Organ Failure Assessment	X	Daily		
Rhythm strip assessment for advanced heart block	X	Daily		
Pregnancy test (either urine or serum beta human chorionic gonadotropin)	X			
Blood draw: C-reactive protein, interleukin-1, interleukin-6, interleukin-10, soluble tumour necrosis factor receptor-1, high mobility group box protein 1		About Days 1, 3, 5, 7, 14		
Blood draw: whole blood acetylcholinesterase and butyrylcholinesterase at participating sites (blood draw above will be used when possible)		About Days 1, 3, 5, 7, 14		
Hematology/chemistry, neuroimaging	X	Daily		
Co-administered sedative/analgesic/antipsychotic medications		Daily		
Richmond Agitation Sedation Scale (target/actual), Confusion Assessment Method for ICU		1 or 2 times daily		
Bush–Francis Catatonia Rating Scale, Delirium Motor Subtype Scale at participating sites		1 or 2 times daily		
Hospital-acquired infections (blood, urine, sputum)		Daily		
ABCDE protocol compliance and sepsis/ventilator tracking		Daily		
Safety assessments, as part of routine ICU care		Daily		
Plasma triglycerides and cortisol		About Days 7, 14		
Sao_2/Fio_2, Pao_2/Fio_2 ratio, chest x-ray to evaluate for acute respiratory distress syndrome		Daily		
Electroencephalograph via portable SedLine Sedation Monitor (Masimo, Neuchatel, Switzerland) at participating sites		Up to 7 days		
Delirium Experience Questionnaire and Chronic Pain Questions		X		
Long term telephone follow-up: Confusion Assessment Method, neuropsychological battery, Activities of Daily Living Questionnaire, Functional Activities Questionnaire, EuroQOL (EQ-5D), Brief Pain Inventory			X	

ABCDE = Awakening and Breathing Coordination, Delirium monitoring and management, and Early mobility. APACHE II = Acute Physiologic Chronic Health Evaluation II. Fio_2 = fraction of inspired oxygen; ICU = intensive care unit; Pao_2 = arterial partial pressure of oxygen; Sao_2 = arterial oxygen saturation.

- Proportion of patients, mean daily dose among those exposed and days of use among patients exposed to open label propofol, dexmedetomidine and rescue midazolam
- Open label propofol use (proportion and days of use among users)
- Open label dexmedetomidine use (proportion and days of use among users)

Definition and description of protocol non-compliance

Any non-compliance that increases safety risk to the patient is considered protocol non-compliance. These events will be captured for a variety of causes that are considered related to patient safety. They will be described in the final study report, broken down according to a simple categorisation scheme followed prospectively during the conduct of the MENDS2 study.

Analysis populations

All analyses will be conducted for all inhospital outcomes on all randomly assigned patients who received study drug in an ITT manner as defined above. Analyses relating to long term outcomes will include all randomly assigned patients who received study drug, and who survived and have at least partial data for their assessments.

For the primary outcome delirium/coma-free days and for the secondary outcomes ventilator-free days and 90-day mortality, we will also perform a sensitivity analysis that will include patients who were randomly assigned to receive study drug but never received the treatment.

Statistical analysis

Primary outcome

The primary outcome is delirium/coma-free days over a 14-day study period, defined as the number of days during the 14-day intervention period (from randomisation, which will be Study Day 1, until Study Day 14) that the patient was alive and free from delirium and coma. Study outcomes are presented in Table 2, and study timelines and assessments are provided in Table 3.

Analysis methods

All inhospital outcomes will be analysed using both univariate methods and multivariable regression, adjusting for covariates noted below. Although baseline patient characteristics should theoretically be balanced between treatment groups owing to randomisation, adjustment increases our power and precision. Adjusted analyses will be considered the primary analyses. We will adjust all coefficient variances using the Huber–White sandwich estimation, clustered by study site. This will help account for unmeasured variability and correlation among patients at a given site.

Inhospital continuous outcomes

We will use proportional odds logistic regression for continuous outcomes that are non-normally distributed (eg, delirium/coma-free days, ventilator-free days) with covariates as listed below. This method assumes an ordinal outcome but does not assume that it follows a specific statistical distribution. Both adjusted odds ratios and adjusted medians will be reported as estimates.[4]

Time-to-event outcomes

We will use Cox proportional hazards regression for mortality with covariates as listed below. For time-to-event outcomes with competing risks, we will use Fine–Gray competing risks regression.[5]

Long term outcomes

We will analyse the primary long term outcome, the TICS score, using multivariable regression with treatment and adjusting for other covariates mentioned below. Depending on the distribution of the outcome, we will use linear regression or proportional odds logistic regression, as appropriate. This will be the primary analysis model for this outcome.

As a sensitivity analysis, we will define a patient as being cognitively impaired if they are ≥ 2 standard deviations below the mean in one test or 1.5 or more standard deviations below the mean in any two tests, from the following the tests: Digit Span test, Logical Memory I test, Logical Memory II test, Similarities test, Controlled Oral Word Association test, and Hayling Sentence Completion test. We will analyse this outcome using multivariable logistic regression adjusting for covariates mentioned below.

Since mortality is hypothesised to have an association with treatment, the analysis of survivors with assessments may be susceptible to survivor bias. To deal with this potential bias, we will conduct a sensitivity analyses using the continuous TICS score. We will use the unadjusted composite endpoint approach described by Lachin,[6] where the composite endpoint will be defined as:

- if the patient dies before assessment or is missing assessments: days between randomisation and death or date of last follow-up (for patients lost to follow-up); 180 days for those who are assessed but have a missing TICS score; or
- if the patient survives and is successfully assessed: days between randomisation and planned assessment (180 days) plus assessment score.

Model assumptions

Model assumptions will be evaluated graphically. Proportional odds assumptions will be checked using multiple cut-offs for proportional odds assumption,[7] and Schoenfeld residuals will be used for proportional hazards. If linear regression is used for long term outcomes, we will check residual versus fitted plots and quantile–quantile plots to ensure assumptions are met.

Covariates

Covariates for all multivariable regression models except 90-day mortality include:

- age at study enrolment;
- education level;
- baseline cognitive function, via the Informant Questionnaire on Cognitive Decline in the Elderly (performed via patient or surrogate questionnaire);
- pre-existing comorbidities, via the Charlson Comorbidity Index;
- Sequential Organ Failure Assessment (SOFA) score on the day of enrolment, excluding the central nervous system

component since delirium and coma are accounted for separately;
- level of arousal at randomisation via the RASS score closest to time of randomisation, treated as a categorical variable;
- propofol, dexmedetomidine, opioids (fentanyl equivalents), antipsychotics (haloperidol [intravenous] equivalents) and benzodiazepines (midazolam equivalents) between ICU admission and midnight before enrolment, with exposure defined as total dose per kilogram body weight and cube-rooted in the models to mitigate the influence of extremely high values;
- medical versus surgical: surgical patients are those who have a recorded ICU admission reason involving surgery, had surgery between hospital admission and ICU admission, and/or went to the operating room between ICU admission and study enrolment (all other patients will be considered medical patients); and
- infection type (from 48 hours before enrolment until end of Study Day 14 of the treatment period, treatment withdrawal, hospital discharge or death): confirmed Gram-positive (yes/no), Gram-negative (yes/no), viral (yes/no), fungal (yes/no) or suspected infection but culture-negative.

For the covariate infection type, patients may have more than one type of infection. These will be modelled as separate variables in the model. If there is very limited variability that causes convergence issues, we will combine the fungal and viral variables. If the convergence issues persist, we will create a single variable with multiple levels: Gram-positive, Gram-negative, culture-negative, viral/fungal.

Before modelling, we will perform redundancy analyses to ensure that no covariates completely explain any of the others (resulting in multicollinearity) using an adjusted R^2 cut-off of 0.7. If any covariates are highly correlated, only one of them based on clinical relevance will be kept in the model. If there are covariates with very limited variability that cause the model to not converge, they will be removed from the model.

Covariates for 90-day mortality will include age, baseline cognitive function, pre-existing comorbidities, SOFA score on the day of enrolment excluding the central nervous system component, medical versus surgical, and infection type as specified above.

Safety analysis

In addition to the primary and secondary outcomes detailed above, descriptive analyses of specified safety outcomes will be performed as described below. Safety endpoints will be tracked from randomisation until conclusion of the combined treatment and post-study drug period, hospital discharge, death or withdrawal (whichever happens first). Patients who do not have hospital discharge or death time available will be tracked until their withdrawal date. The following are the safety endpoints:

- proportion of patients having hypotension and number of days of hypotension (defined as systolic blood pressure < 80 mmHg);
- mean daily cardiovascular SOFA score for patients, and proportion of days with cardiovascular SOFA score of 2 or greater;
- proportion of patients with arrhythmias (tachycardia [heart rate > 100 beats/min] and/or bradycardia [heart rate < 60 beats/min]);
- proportion of patients with severe lactate acidosis (as defined by lactate level > 5 mmol/L), and median number of days with severe lactic acidosis among those with severe lactic acidosis;
- mean triglyceride and cortisol levels at 7-day and 14-day assessments;
- proportion of patients with triglyceride level greater than 500 μg/dL and cortisol level greater than 20 mg/dL at 7-day and 14-day assessments; and
- proportion of patients showing signs of withdrawal from study agent based on vital signs (tachycardia [heart rate > 100 beats/min]) and diaphoresis.

Software details

R version 3.5.2 (20 December 2018) or above will be used for all analyses. Versions of specific packages used for analysis will be noted in the analysis report. The checkpoint package will be used to preserve R package versions throughout the manuscript submission and review process.

Conclusion

This article presents the formal SAP for the MENDS2 study. Further details regarding variable definitions, unadjusted and exploratory analyses, and database cleaning and lock procedures are provided in the online Appendix 2.

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Competing interests

None declared.

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