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

Administrative Information

Full Study Title	**M**aximizing the **E**fficacy of Sedation and Reducing **N**eurological **D**ysfunction and Mortality in **S**eptic Patients with Acute Respiratory Failure
Acronym	MENDS2
Trial Registration	https://clinicaltrials.gov/ct2/show/NCT01739933
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TRIAL REGISTRATION:

Clinicaltrials.gov (NCT01739933)

1. INTRODUCTION

This serves as the formal Statistical Analysis Plan (SAP) for the **M**aximizing the **E**fficacy of Sedation and Reducing **N**eurological **D**ysfunction and Mortality in **S**eptic Patients with Acute Respiratory Failure (MENDS2) study, written before closure of the database and unblinding of the treatment groups. The trial is registered at https://clinicaltrials.gov/ct2/show/NCT01739933. This SAP is written based on guidelines in Gamble et al.[1] and will be the guiding document for the analyses that will be conducted in the primary manuscript. Any changes to this SAP will be presented as an addendum in the future.

1.1 Background and Rationale

The need for mechanical ventilation (MV) secondary to sepsis is the leading cause of admission to the intensive care unit, often necessitating sedation for patient safety and comfort. Sedative medications contribute to iatrogenic injury, such as prolonging ventilator time and intensive care unit (ICU) length of stay and exacerbating acute brain dysfunction. This acute brain dysfunction, manifested as delirium and coma, occurs in 50%-70% of MV 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. The gamma-aminobutyric acid (GABA)-ergic benzodiazepines, in particular, have been shown to increase brain dysfunction, promote infection, and prolong MV. Therefore, the short-acting GABA-ergic sedative propofol and the alpha2 agonist dexmedetomidine are becoming widely used to sedate septic MV patients. There are only a few randomized trials, however, to

guide clinicians when selecting between these and other sedatives, and none have explored the mechanisms underlying the differences in outcomes, though some data indicate that GABA-ergic and alpha2 agonist agents have very different effects on innate immunity, apoptosis, arousability, and respiratory drive. The MENDS2 study will determine whether sedation of mechanically ventilated severely septic patients with an alpha2 agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will increase days alive without delirium or coma and increase days alive and free from mechanical ventilation (ventilator-free days or VFDs).

1.2 Study Objectives

The MENDS2 study is a multicenter, double-blind, randomized trial investigating the effects of sedatives—the alpha2 agonist dexmedetomidine and the GABAergic propofol—in mechanically ventilated severely septic patients. The study evaluates the following aims:

- **Aim 1**: To determine whether sedation of mechanically ventilated severely septic patients with an alpha2 agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will (**Aim 1A)** increase days alive without delirium or coma (delirium/coma-free days or DCFDs) and **(Aim 1B)** increase days alive and free from mechanical ventilation (ventilator-free days or VFDs).
- **Aim 2**: To determine whether sedation of mechanically ventilated severely septic patients with an alpha2 agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will **(Aim 2A)** improve 90-day survival and **(Aim 2B)** decrease incidence and severity of long-term cognitive impairment (LTCI).
- **Aim 3**: To determine whether sedation of mechanically ventilated severely septic patients with an alpha2 agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will reduce pro- and anti-inflammatory cytokines (CRP, interleukin-1 [IL-1], IL-6, IL-10,

sTNFR1, HMGB1). We intend to present the results of Aim 3 in a subsequent manuscript.

2. STUDY METHODS

2.1 Trial Design

This is a multicenter, double-blind, randomized trial. The two treatment arms comprise an alpha2 agonist (dexmedetomidine) and a GABAergic agonist (propofol). Upon meeting inclusion and none of the exclusion criteria, patients were consented, enrolled and then randomized to either of the two treatment arms.

2.2 Inclusion and Exclusion criteria

Consecutive patients were eligible for inclusion in the MENDS2 study if they were: [1] an adult patient (≥18 years old) [2] in a medical or surgical ICU and [3] on MV, requiring sedation and [4] have a suspected or known infection. Patients were excluded if they met any of the exclusion criteria listed in Table 1.

2.3 Randomization

Randomization to dexmedetomidine and propofol was conducted in 1:1 ratio using a computer-generated permuted-block randomization scheme, stratified by study site and age (<65 vs ≥ 65 years). The randomization scheme was created by a biostatistician external to the study and distributed directly to each site's investigational pharmacy as a set of randomization lists stratified by study site and age (<65 vs ≥ 65 years). Once a consented patient entered the Interventional Trial Phase, an order for blinded study drug was placed, and the investigational pharmacist referred to the appropriate randomization list (determined by patient's age) to

establish that 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 a detailed manner.

2.4 Power and Sample Size

Power analyses and sample size calculations for Aim 1A (DCFDs): Based on the demographic data from our NIH-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) to have a mean±SD of 6.8±5.2 DCFDs during the 14-day study period. The study was repowered/resized due to concerns about the feasibility of completing study enrollment. Our initial sample size of 530 patients provided us with > 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 (DSMB), we re-sized to enroll 420 patients, which assuming a 2-sided alpha of 0.05 will provide >80% power to demonstrate a difference of 1.5 DCFDs between dexmedetomidine and propofol (primary outcome), which we believe 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 with dexmedetomidine, assuming the 90-day mortality in patients receiving propofol to be 30% (which is conservative given the 25% mortality at 28 days in the both the recent PROWESS-Shock control group and MENDS [dexmedetomidine vs lorazepam] study lorazepam group).

Power Analyses for Long-Term Cognitive Impairment (Aim 2B): We assumed to follow ≥80% of survivors for evaluation of LTCI. Based on the expected mortality rates (see above), we expected an overall 25% mortality across the two groups and planned to test 252 (=420x0.75x0.80) patients for LTCI 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.

2.5 Study treatments and interventions

Study treatment and interventions are summarized in the study aids provided in Supplement 1.

3. STATISTICAL PRINCIPLES

Statistical analysis will be conducted in accordance to the plan outlined in this SAP. Statistical analysis will abide by these general statistical principles below.

3.1 Descriptive statistics

Patient flow information as recommended by CONSORT guidelines will be presented for patients randomized and receiving study intervention, including screening, exclusions, refusal of consent, withdrawals, deaths, and hospital discharge status. Demographics, baseline clinical status and ICU characteristics will be described overall as well as by treatment using medians and interquartile ranges for continuous variables and frequency (%) 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 randomized clinical trials.

3.2 Confidence Intervals and P-Values

Our protocol a priori specified one interim analysis at N=300 before the final analysis for early stopping due to safety and efficacy based on DCFD and 90-day mortality. To maintain the overall study wise alpha 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 O'Brien Fleming method). The level of statistical significance for all other outcomes will be at the 0.05 level. 95% confidence intervals will be reported along with all effect estimates due to it being the standard in which confidence intervals are typically reported and how statistical software outputs are constructed. Presentation of results will emphasize clinical significance, effect sizes and confidence intervals over statistical significance.

3.3 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 3 knots. To account for correlation among patients within a given site, we will adjust standard errors using Huber-White sandwich estimate[2].

3.4 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 analyzing multiple, prospectively defined outcomes in a clinical trial. For all secondary and exploratory outcomes and subgroup analyses, caution will be exercised in the interpretation of

results by noting the number of nominally significant tests that would be expected to occur by chance alone[3].

3.5 Missing Data

Data for missing in-hospital variables will be imputed using simple imputation or clinical imputation rules when appropriate; details on these rules and the imputation process for summary variables (e.g., days alive and free of delirium and coma) are detailed in the Definitions and Derived Variables section in Supplement 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 from patients that were not available at follow-up will not be imputed, but those with partially missing data will be imputed using model-based imputation with covariates age at enrollment, gender, BMI, education, first language English, insurance, Charlson comorbidities index, Benzodiazepine exposure after ICU admission to the midnight of the day before enrollment and long-term assessments (KATZ ADL, FAQ, EQ-5D, Digit Span, Logical Memory I, Logical Memory II, Similarities, COWA, Hayling Sentence Completion).

3.6 Rigor, Transparency and Reproducibility

To enhance rigor, transparency and reproducibility in research, we will ensure all aspects of this study are transparent and easily reproduced by independent investigators. The statistical analysis plan will be pre-specified and time-stamped. All the analysis code will be made publicly available post publication of the primary manuscript.

4. ADHERENCE TO THE INTERVENTION AND PROTOCOL NONCOMPLIANCE

4.1 Definition & assessment of adherence to the intervention

All analysis will be conducted based on the intention to treat principle (ITT). Patients will be considered to be in the intent-to-treat population if they (a) meet all criteria required for randomization AND (b) are assigned to and actually receive the treatment drug as indicated on the randomization log. If subjects received the study drug and form a part of the intent to treat population, they will be analyzed according to the treatment they were randomized to.

4.2 Presentation of adherence to intervention

These are process outcomes and statistical significance will not be assessed. We will describe, within each treatment group, the following:

- Patient level:
    - Days each randomized patient received study treatment
    - Time from meeting all inclusion criteria and start of study drug
    - Average daily dose of study drug
    - Whether study treatment was ever permanently discontinued, and reasons for discontinuation
    - Proportion of patients that withdrew from the study by treatment

- Time at target (+/- 1 RASS score) sedation by comparing actual RASS to ordered RASS, while on study drug
- Average daily fentanyl dose and average dose/kg, while on study drug, among users
- Proportion of patients receiving antipsychotic medications
- Days of antipsychotic medications
- Proportion of patients receiving midazolam
- Proportion of patients, mean daily dose among those exposed and days of use among exposed for open label propofol, dexmedetomidine and rescue midazolam
- Open label propofol use (proportion and days among users)
- Open label dexmedetomidine use (proportion and days among users)

4.3 Definition and description of protocol noncompliance

Any noncompliance that increased safety risk to the patient was considered protocol noncompliance. These events will be captured for a variety of causes considered related to patient safety and will be described in the final study report, broken down according to a simple categorization scheme followed prospectively during the conduct of the MENDS2 study.

4.4 Analysis Populations

All analysis will be conducted for all in-hospital outcomes on all randomized patients who received study drug in an intent-to-treat manner as defined earlier. Analysis for long-term outcomes will include all randomized 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 also include patients that were randomized to receive treatment drug but never received treatment.

5. STATISTICAL ANALYSIS

5.1 Outcome Definitions

Primary outcome

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

5.2 Analysis Methods

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

In-Hospital Continuous Outcomes

We will use proportional odds logistic regression for continuous outcomes that are non-normally distributed (e.g., 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 as well as 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[5] competing risks regression.

Long-Term Outcomes

We will analyze 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 also define a patient as being cognitively impaired based on whether they are >=2 SD in 1 test OR >=1.5 SD in any two tests, where the tests we will consider are the Digit Span, Logical Memory I, Logical Memory II, Similarities, Controlled Oral Word Association, and Hayling Sentence Completion. We will analyze this outcome using multivariable logistic regression adjusting for covariates mentioned below.

Since mortality is hypothesized 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 in Lachin[6], where the composite endpoint will be defined as:

- If the patient dies prior to assessment or is missing assessments days between randomization and death/date of last follow-up (for patients who were lost to follow up)/180 days for those who were assessed but had missing TICS score
- If the patient survives and is successfully assessed: days between randomization and planned assessment (180 days) + assessment score.

Model Assumptions

Model assumptions will be evaluated graphically. Proportional odds assumptions will be checked using multiple cutoffs 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 vs 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 enrollment
- Education
- Baseline cognitive function, via the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (performed via patient or surrogate questionnaire)
- Preexisting comorbidities, via the Charlson Comorbidities Index
- Sequential Organ Failure Assessment (SOFA) on the day of enrollment excluding the central nervous system (CNS) component since delirium and coma are accounted for separately

- Level of arousal at randomization via the Richmond Agitation-Sedation Scale (RASS) closest to time of randomization - treated as a categorical variable.
- Propofol, dexmedetomidine, opioids (fentanyl equivalents), antipsychotics (haloperidol (iv) equivalents) and benzodiazepines (midazolam equivalents) between ICU admission and midnight prior to enrollment. Exposure will be defined as total dose/kg and will be cube-rooted in the models to mitigate the influence of extremely high values.
- Medical vs 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 enrollment. All other patients will be considered medical patients.
- Infection type (from 48 hours before enrollment until end of treatment period-study day 14, 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. Patients may have more than one type of infection. These will be modeled 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.

Prior to modeling, we will perform redundancy analyses to ensure that no covariates completely explain any of the others (resulting in multicollinearity) using an adjusted R^2 cutoff 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 on the day of enrollment excluding the CNS component, Medical vs surgical and Infection type as specified above.

Safety Analysis

In addition to the primary and secondary outcomes detailed above, descriptive analysis of specified safety outcomes will be performed as described below.

The safety endpoints below will be tracked starting from randomization until conclusion of the combined Treatment/Post Study Drug Period, hospital discharge, death or withdrawal (whichever happens first). For patients who do not have hospital discharge and death time available, they will be tracked until their withdrawal date.

1. Proportion of patients and days with hypotension (defined as systolic blood pressure <80 mmHg)
2. Mean daily cardiovascular (CV) SOFA for patients along with proportion of days CV SOFA >=2
3. Proportion of patients with arrhythmias (tachycardia [HR > 100] and/or bradycardia [HR < 60])
4. Proportion of patients with severe lactate acidosis (as defined by lactate > 5) as well as median days with severe lactic acidosis among those with severe lactic acidosis.
5. Mean triglyceride and cortisol levels at 7- and 14-day assessments
6. Proportion of patients with triglycerides >500 and cortisol <20 at 7- and 14-day assessments

7. Proportion of patients showing signs of withdrawal from study agent based on vital signs (tachycardia HR >100) and diaphoresis.

6. SOFTWARE DETAILS

R version 3.5.2 (2018-12-20) 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.

7. CONCLUSION

This document presents the formal Statistical Analysis Plan for the MENDS2 study. Further details regarding variable definitions, unadjusted and exploratory analyses and Database Cleaning & Lock Procedures are provided in Supplement 2.

Table 1: Study exclusion criteria

- Rapidly resolving organ failure, indicated by planned immediate discontinuation of MV, at time of screening for study enrollment
- Pregnant or breastfeeding
- Severe dementia or neurodegenerative disease, defined as either cognitive impairment that makes the patient incapable of living independently at baseline or IQCODE >4.5,123 measured using a patient's qualified surrogate. This exclusion also pertains to mental illnesses requiring long-term institutionalization, acquired or congenital mental retardation, severe neuromuscular disorders, Parkinson's disease, Huntington's disease, Alzheimer's and debilitating cerebrovascular disease. It also excludes patients in coma or with severe cognitive deficits due to structural brain diseases such as stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema.
- Present history of 2nd or 3rd degree heart block, or persistent bradycardia < 50 beats/minute that requires intervention (e.g., atropine, glycopyrrolate). If patient has a pacemaker for bradyarrythmias, then 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 a specific treatment plan involving benzodiazepines (either as continuous infusions or intermittent intravenous boluses) for this dependency.
- Active seizures during this ICU admission being treated with intravenous benzodiazepines.
- Expected death within 24 hours of enrollment or lack of commitment to aggressive treatment by family or the medical team (e.g., likely to withdraw life support measures within 24 hrs of screening).

- Inability to understand English or deafness that will preclude delirium evaluation. The inability to understand English (for example in Spanish-only or Mandarin-only speaking patients) will not result in exclusion at centers where the research staff is proficient and/or translation services are actively available in that particular language; these patients will not be followed in the long-term follow-up phase of the trial since the testing materials are primarily available only in English. Patients with laryngectomies and those with hearing deficits are eligible for enrollment if their medical condition permits them to communicate with research staff.

Table 2: Primary, secondary and exploratory outcomes

Variable	Description	*Time frame
Primary outcome		
Delirium/coma-free days (DCFD)	Number of days during the 14-day intervention period (from randomization, which will be Study Day 1, until Study Day 14) that the patient was alive and free of delirium and coma	14 days
Secondary outcomes		
Ventilator-Free Days (VFD)	Days alive and free of 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 ADL, Functional Activities Questionnaire (FAQ), EQ-5D and a validated phone battery for neuropsychological function testing (e.g., TICS, Digit Span, Logical Memory I, Logical Memory II, Similarities, Controlled Oral Word Association, Hayling Sentence Completion) will be reported.	6 months
Organ Dysfunction	Will be defined as ever vs never. Kidney, Cr > 2 mg/dL; Lung, PaO2/FiO2 <300 or SaO2/FiO2 <315; Liver, total bilirubin > 2 mg/dL; Coagulation, Platelet count < 100,000/mm3; and Hemodynamic, need for vasopressor. *Descriptives for this outcome will computed both overall and by treatment group and no hypothesis testing will be performed.*	14 days
Acute Respiratory Distress Syndrome	Ever had ARDS during intervention phase? *Descriptives 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 +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 -4 or -5 or RASS missing and CAM-ICU 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 of 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 CV SOFA • Proportion of patients with at least one CV SOFA >= 2 (the definition of organ dysfunction) and then >2 and then >3	14 days plus 2 days post-study drug period (if longer than 14 days)
Heterogeneity of treatment effects	Heterogeneity of treatment effects will be assessed for age at enrollment, Baseline cognition (measured by the IQCODE; continuous covariate), Medical vs surgical patients	-

*Time frames all begin the day of randomization

Table 3: Study timelines and assessments

***Variable**	**Enrollment**	**Treatment Period & Post-Study Drug Period**	**6 Month Follow-up**	**12 Month Follow-up**
Pre-Hospital Function Assessment (ADL, IADL/FAQ, IQCODE, AUDIT)	X			
Demographics, Comorbidities,APACHE II	X			
SOFA	X	Daily		
Rhythm strip assessment for advanced heart block	X	Daily		
Pregnancy test (either urine or serum Beta hCG)	X			
Blood draw: IL-1, IL-6, IL-10, CRP, sTNFR1, HMGB1		Approximately Days 1,3,5,7,14		
Blood draw: whole blood AChE and BuChE *at participating sites* (Blood draw above will be used when possible)		Approximately Days 1,3,5,7,14		
Hematology/Chemistry, Neuroimaging	X	Daily		
Co-administered sedative/analgesic/antipsychotic medications		Daily		
RASS (target/actual), CAM-ICU		1-2x daily		
Bush Francis Catatonia Rating Scale (BFCRS), and Delirium Motor Subtype Scale (DMSS) *at participating site*s		1-2x daily		
Hospital-acquired infections (blood, urine, sputum)		Daily		
ABCDE Protocol Compliance & Sepsis/Ventilator tracking		Daily		
Safety assessments. As part of routine ICU care		Daily		
Plasma triglycerides & cortisol		Approximately Days 7,14		
SaO2/FiO2, PaO2/FiO2 ratio, Chest X-ray to evaluate ARDS		Daily		
EEG via portable SedLine Sedation Monitor *at participating sites*		Up to 7 days		
Delirium Experience Questionnaire and Chronic Pain Questions		X		
Long-term telephone follow-up: CAM, neuropsychological battery, ADL, IADL/FAQ, EuroQOL quality of life (EQ-5D), BPI			X	

*<u>*Abbreviations (alphabetical)*</u>: **AChE-** acetylcholinesterase **ADL**- activities of daily living, **APACHE II**- Acute Physiologic Chronic Health Evaluation II, **AUDIT**- Alcohol Use Disorders Identification Test, **BPI**- Brief Pain Inventory, **BuChE-** butyrylcholinesterase, **CAM**- Confusion Assessment Method, **CAM-ICU**- Confusion Assessment Method for ICU, **CRP**- C-reactive protein, **EEG**- Electroencephalograph, **FAQ**- Functional Activities Questionnaire for IADLs, **HMGB1**- High-mobility group protein 1, **IADL**- instrumental activities of daily living, **IL**- interleukin, **IQCODE**- Informant Questionnaire of Cognitive Decline in Elderly, **MV**-mechanical ventilation, **RASS**- Richmond Agitation Sedation Scale, **SOFA**- Sequential Organ Failure Assessment, **sTNFr1**- soluble TNF receptor 1

Supplement 2

Exploratory Analyses

In addition to the primary and secondary outcomes listed on clinicaltrials.gov, the following additional analyses will be used to inform specific decisions on missing data and modeling, to elucidate findings from primary outcomes, and more fully describe the course of the intervention:

- Exploration and description of outcome and covariate missingness
- Distribution of all continuous covariates, to determine ability to use restricted cubic splines and knot placement
- To describe patient status from randomization to the end of the assessment period, we will create a sankey plot where a patient's' status would displayed.
- Durations of a) delirium b) hyperactive and c) hypoactive delirium as additional outcomes, to describe any relationship between treatment and delirium and specific types of delirium. We will use proportional odds logistic regression for these outcomes since they are non-normally distributed. Coma duration as an additional outcome, to aid in elucidating relationship between treatment and primary outcome of DCFDs; will be analyzed in the same manner as delirium duration.
- ICU and Hospital mortality: To model this outcome, discharged alive from hospital will be considered a competing event for hospital mortality, and discharged alive from ICU will be a competing event for ICU mortality. Patients who withdrew in the hospital with no discharge or death information available are censored at the time of withdrawal. Cumulative incidences of both the outcome and competing risk along with a modified chi-squared test for the difference between groups in the subdistribution of interest will be described. For the adjusted analysis, will we use Fine-Gray competing risks regression, treating discharge as our competing risk.
- ICU-free days: This outcome will be analyzed similar to VFDs and DCFDs.
- Time to successful ICU discharge in 30-days: Since ICU Discharge has the competing risk of death, we will describe the cumulative incidences of both the outcome of interest and competing risk, along with a modified chi-squared test for the difference between groups in the subdistribution of interest. For the adjusted analysis, will we use Fine-Gray competing risks regression, treating death as our competing risk. Patients who withdrew in the hospital with no discharge or death information available are censored at the time of withdrawal; we censor at x.01 days anyone who has experienced neither death nor the outcome of interest by x days (where x is the end of the time frame specified for the outcome). We will detail how many and when patients were censored for each analysis.
- Daily compliance on the first five elements (A-E) of the ICU Liberation ABCDEF Bundle during the intervention period (number and % of eligible days compliant; descriptive statistics only).
- Severity of Shock: Descriptive statistics only
- Heterogeneity of treatment effects: We will assess heterogeneity of treatment effects using separate multivariable regression models that include interaction terms between treatment group and the following clinical characteristics:
    - Age at enrollment (continuous)
    - Baseline cognition (measured by the IQCODE; continuous covariate)

- Medical vs surgical patients

Definitions and Derived Variables

Delirium/Coma-Free Days

This primary outcome variable is calculated over the intervention period (14 days including and immediately following randomization). It is defined as days alive and without delirium and coma. This definition makes no assumptions about the sequence in which delirium, coma or normal mental states occurred during the 14-day treatment period; all days during which a participant was alive and free of delirium and coma will contribute to the total number of delirium/coma-free days regardless of whether or not they occurred consecutively.

Mental Status (Delirium and Coma)

Determining Mental Status Using CAM and RASS

We will determine mental status for a given *assessment* using the following criteria:

1. Comatose: RASS -4 or -5, or RASS missing and CAM Unable to Assess
2. Delirious: RASS missing or >= -3, and CAM Positive
3. Normal: RASS missing or >= -3, and CAM Negative

Patients could have multiple assessments on a given study day. On a given day, a patient will be considered delirious if any assessment was considered delirious; comatose if no assessments met criteria for delirium and at least one was considered comatose; and normal if no assessments met criteria for delirium or coma, and at least one was considered normal. If there are conflicting assessments where CAM is 'Unable to Assess' and RASS -4 or -5, then patient will be assigned a mental status of coma. If RASS is -3 or -2, since prior studies state that this highly correlates with delirium, patients will be assigned a mental status of delirium. RASS assessment of 0 to -1 will be considered to be normal.

Handling Missing Data

In order to compute this composite outcome, it is necessary to have a value (alive and normal vs. delirious vs. comatose vs. deceased) for every single day during the treatment period; ignoring missingness would have the unintended consequence of implying that patients were alive and free of brain dysfunction on all missing days. Therefore, for eligible patient-days with missing mental status, we will perform simple imputation, including the following variables as covariates in the imputation.

- Baseline: age at enrollment; gender; BMI; education; first language English?; insurance; Charlson comorbidities index; , benzodiazepine exposure after ICU admission and midnight of the day before randomization (Yes/No).
- Daily:

- Medications (antipsychotics, opioids, benzodiazepine)
- Variables indicating severity of illness (CV SOFA, creatinine, platelets, P/F ratio, S/F ratio, bilirubin)
- Any mental status data available the day of, the day before, and the day after the missing day (such as RASS, CAM, Critical-Care Pain Observation Tool (CPOT), and CAM-ICU Feature 1(cam_f1), and CAM-ICU Feature 2(cam_f2), and CAM-ICU Feature 3(cam_f3), and CAM-ICU Feature 4(cam_f4))

All summary variables (e.g. delirium/coma-free days, delirium duration, and coma duration, VFD) are presented using imputed mental status. For VFD's and ICU-Free days, patients who withdrew will have their last observation carried forward.

Severity of Illness

Missing values for SOFA components will be handled in the following ways:

SOFA (Enrollment + daily throughout intervention period)

- Substitutions for specific components:
  - Respiratory: If P/F ratio is not available, we will use the lowest S/F ratio[8].
  - Central nervous system: Since GCS was not collected, we will use the lowest RASS available that day[9].
- Missing data at enrollment: For patients missing at least one SOFA component score, we will impute the next available value within the following two calendar days. If none are available, we will assume a normal value (0 points).

Medications

- Benzodiazepines include midazolam, lorazepam, and/or diazepam. Doses are expressed in midazolam equivalents.
- Opioids include fentanyl, morphine, remifentanil and/or hydromorphone. Doses are expressed in fentanyl equivalents.
- Antipsychotics include haloperidol, ziprasidone, quetiapine, olanzapine, and/or risperidone. Doses are expressed in haloperidol (iv) equivalents.

Baseline IQCODE: If no questions (out of 16) are answered, then the patient's IQCODE score is considered as missing. If data are partially available, then patient mean will be imputed for missing questions (i.e., mean of all non-missing questions). Final IQCODE score will be calculated by taking the mean of all the questions.

Baseline KATZ ADL: If no questions (out of 6) are answered, then the patient's KATZ ADL score is considered as missing. If data are partially available, then patient mean will be imputed for missing questions. (i.e., mean of all non-missing questions). Final ADL score will be calculated by adding up all the questions.

Baseline FAQ: If no questions (out of 10) are answered, then the patient's FAQ score is considered as missing. If data are partially available, then patient mean will be imputed for missing questions (i.e., mean of all non-missing questions). Final FAQ score will be calculated by adding up all the questions.

Unadjusted Analyses

Continuous Outcomes

We will analyze non-normally distributed continuous outcomes (delirium/coma-free days; ventilator-free days) using the Mann-Whitney test. These outcomes are typically not normally distributed; therefore, the assumptions for a test assuming normality would be violated. The nonparametric Mann-Whitney test does not assume that the outcome has a normal distribution and thus provides more power and reliability in the case of a non-normal distribution.

The primary long-term outcome will be the TICS score. Depending on the distribution of this outcome, we will use either the independent two-sample t-test or the Mann-Whitney test. The distribution of the other long-term outcome measures (Digit Span, Logical Memory I, Logical Memory II, ADL, FAQ, Quality of Life EQ - 5D[10], Similarities, Controlled Oral Word Association, Hayling Sentence Completion, Logical Memory I and Logical Memory II) will be described overall as well as by treatment group. We do not plan to compare these outcome measures between treatment groups using formal hypothesis testing in the primary manuscript.

Time to Event Outcomes

We will describe and test for differences in 90-day survival using Kaplan-Meier curves and the log-rank test, respectively. "Time 0" will be the time of randomization. For analysis of time-to-event outcomes with competing risks, we will describe the cumulative incidences of both the outcome of interest and each competing risk, along with a modified chi-squared test for the difference between groups in the subdistribution of interest. We will detail how many and when patients were censored for each analysis.

Timing of Final Analysis

In-Hospital Database Cleaning & Lock Procedures

MENDS2 uses the REDCap electronic data capture platform for data collection. Upon completion of the in-hospital portion of the MENDS2 study, the following procedures will be followed and documented within the Database Cleaning & Lock SOP:

1. The Vanderbilt Coordinating Center (VCC) will work with site coordinators to address all data issues revealed by ongoing data cleaning. This process will continue until all issues have been addressed.
2. Upon completion of In-Hospital data cleaning, the REDCap database **MENDS2 Study: Exclusion Log** will be locked in the following way:
    a. Initially all users with current "view and edit" user privileges will be moved to "read only" user privileges.
    b. After the window closes for sites to export their data the database will be permanently moved to inactive status (meaning that no data can be changed).
3. Upon completion of In-Hospital data cleaning, the REDCap database **MENDS2 Study: In-Hospital Database** will be locked in the following way:

. Initially all study site personnel will be restricted to "read-only" user access for the entire database. VCC Project Managers and the Follow-Up Team will be restricted to read-only access for all fields except those needed for patient contact, reconsenting, DNA permissions, notes to file and event reporting, and tracking dates of death and study withdrawal. All fields not needed by these teams will be restricted to read only by use of the @readonly action tags. The follow-up team will continue to be blinded (via restricted access) to all information about the hospital course, as has been the case throughout the study.

	VCC Project Managers	**Follow-Up Team**
Dates Tracking Form - all variables made read-only (using action tag @readonly) to all users except variables pertaining to consenting, death and study withdrawal	View and Edit	View and Edit
Contact Form - all fields	Read Only	View and Edit
NTF - all fields	View and Edit	View and Edit
Adverse Events - all fields	View and Edit	View and Edit
DNA Log - all fields	View and Edit	No Access
All other forms/fields	Read Only	No Access

    b. During the remaining Follow-Up period, the sites will be given a window for downloading their data for local storage.

c. Once 6-month follow-up is completed, we will conduct final data cleans on the updated information and then permanently move the entire database to inactive status, meaning that no data can be changed unless serious errors are noted.

A log of all steps in this process will be maintained in the Database Cleaning & Lock SOP.

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MENDS2

Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Sepsis

Hypothesis: Sedation of mechanically ventilated septic patients with an alpha$_2$ agonist (**dexmedetomidine**) rather than a GABAergic agent (**propofol**) will improve short and long-term patient outcomes.

Specific Aims:

Aim 1: To determine whether dexmedetomidine for sedation of septic medical/surgical ICU patients will increase days alive without delirium or coma and increase days alive without mechanical ventilation compared with propofol

Aim 2: To determine whether dexmedetomidine for sedation of septic medical/surgical ICU patients will increase survival at 90 days compared with propofol and decrease long-term cognitive impairment after critical illness

Aim 3: To determine whether dexmedetomidine for sedation of septic medical/surgical ICU patients will decrease the pro-inflammatory cascade following sepsis compared with propofol

Study Procedures by Research Coordinators

- Study staff evaluate patients twice daily with RASS and CAM-ICU
- Study staff collect blood samples on study day 1, 3, 5, 7, and 14 (if still in hospital)
- Study staff will complete telephone follow-up interviews for cognitive function at 6 months

Bedside Nurse Responsibilities:

- Initiate and titrate study drug per weight-based table using clinical team's RASS target
- Document study drug infusion rates in HED/electronic medical record (Under "Other"- annotation should be "study drug." **Do not write PROPOFOL or DEXMEDETOMIDINE**)
- Document study drug titrations the "MENDS2 Study Drug Titration Form"
- Cover infusion bag & infusion tubing with black sleeve as provided by pharmacy
- Change study drug infusion bag & tubing a minimum of every 12 hours
- Maintain study blinding by ensuring infusion remains covered with black sleeve, no study personnel are present for bag changes, & no verbal cues are given to the study/clinical teams about study drug
- Utilize the rescue protocol for pain, undersedation with max study drug, chemical paralysis, or delirium
- Screening and utilization of ABCDE protocol with patient including daily spontaneous awakening & breathing trials per unit protocol

Research Coordinator(s):

- (Coordinator Name), (Title), Pager (###-####)
- (Coordinator Name), (Title), Pager (###-####)
- (Coordinator Name), (Title), Pager (###-####)

Rescue Protocol

Revised 11/03/16

PAIN

- First try to treat with **intermittent boluses of 0.5-1 mcg/kg of fentanyl** or other opiates such as morphine or hydromorphone
- If needed, continuous fentanyl infusions may be used

RESCUE SEDATION

- **If on max study drug & still undersedated** first try additional **intermittent opiates** (e.g. fentanyl, morphine, hydromorphone) **or increase the continuous fentanyl infusion**
- **If on max study drug & cont fentanyl** is $\geq$ 4-5 mcg/kg/hr & pt is still undersedated use **intermittent dose midazolam**

CHEMICAL PARALYSIS

- **Midazolam** intermittent or via continuous infusion may be used
- Reduce study drug to the **lowest infusion rate** on the weight based titation table & maintain at this level during chemical paralysis
- **Continuous midazolam** infusions should be dc'd 1 hour after the paralytic infusion is dc'd & study drug titration should resume per protocol
- When a bolus of chemical paralysis is required for procedures, **intermittent midazolam** or **propofol** will be permitted to provide amnesia

HYPERACTIVE DELIRIUM

Defined as CAM-ICU + and RASS +1 to +4

- May give **haloperidol** per tube or as 2-5mg IV intermittent doses
- **Quetiapine** (oral or per tube) prn or scheduled with recommended starting doses of 25-50 mg & titration per primary team
- **ABCDE Bundle** Nonpharmalocigal interventions such as early mobility if passes safety screen

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Study Drug Administration

Treatment Period – Trial Days 1 to 14

Study drug can be administered for a maximum of 14 days. Patients have to be in the ICU, on invasive ventilation, and in need of sedation to get the study drug.

Blinding

- It is essential to keep the clinical team and research team blinded to the patient's treatment assignment. Only the patient's primary nurse will know which drug the patient is receiving.
- The study drug bag and IV tubing should always remain covered.
- The bedside nurse should not disclose the treatment assignment to anyone at any time. Do not disclose the assignment to the research staff, the family, the patient, or the medical/nursing staff.

Initiation

- No bolus dose of study medication will be allowed.
- Bedside nurse will initiate infusion based on patient weight in kg (see Titration Table).
- Study drug dose will be titrated by the bedside nurse in mL/hr according to the titration table to achieve the sedation (RASS) target set by the clinical (ICU) team.

Titrating UP (Undersedation)

- Undersedation is defined as patient's RASS is 1 or more levels higher than the clinical team's sedation target RASS (e.g. patient RASS = +1 and target RASS = 0 or -1).
- If patient is undersedated, study drug rate will be increased according to the Titration Table every **10 minutes** until the max dose is reached or the patient reaches the target RASS.

Titrating DOWN (Oversedation)

- Oversedation is defined as when the patient is more than 1 RASS level deeper than ICU team's sedation target (e.g. patient RASS = -3 and target RASS = 0 or -1).
- If patient is oversedated, study drug rate will be decreased every **30 minutes** per the Titration Table until the patient is within 1 RASS level of the target RASS.
- Study drug will only be held for oversedation **if** other sedatives (including fentanyl infusion if used for analgosedation) have been held, study drug has been titrated to lowest volume, and the patient remains oversedated **for >30 minutes**.

Titrating Study Drug during a Spontaneous Awakening Trial (SAT)

- Patient will be evaluated daily for readiness for a SAT by first evaluating with a SAT safety screen.
- If patient passes the safety screen, study drug will be held until patient shows signs of failing the SAT. Intermittent pain meds are allowed to be delivered during this time, if needed.
- Study drug that is held for a SAT will be restarted, if needed, at ≤ 50% of the dose the patient required just prior to the SAT and then titrated to achieve target sedation score.

Discontinuation

- Discontinue study drug if patient is liberated from invasive mechanical ventilation.
- Discontinue study drug if the managing clinical team determines the patient does not need ongoing sedation.

Study drug bag & tubing must be changed at least every 12 hours.

Restarting Study Drug (with exception of restarting after SATs)

- If patient requires sedative therapy (and is still on mechanical ventilation) during the 14-day treatment period, the study drug will be restarted according to initiation rules (see Initiation section above), as long as study drug was not discontinued permanently for safety reasons (see Permanent Discontinuation section below).
- No study drug will be continued beyond Trial Day 14. After this point if patient requires sedation, it will be solely managed at the discretion of the clinical team.

Temporary Holding

- **Hypotension**. If a patient's systolic blood pressure is <80 mmHg and if deemed necessary by the managing clinical team, study drug will be held until fluid and/or vasopressor/inotrope therapy can be initiated and systolic blood pressure has increased to ≥80 mmHg.
- **New onset symptomatic bradycardia** (<50 beats/minute and systolic blood pressure <80 mm Hg). Study drug may be held by the managing clinical team until patient's heart rate is >50 beats/min (either spontaneously or after administration of atropine or glycopyrrolate).
- **Oversedation despite titration to lowest study drug rate**. Study drug may be held until patient's RASS level is at target if patient continues to be oversedated (i.e., more than 1 RASS level deeper than clinical team's sedation target) despite other sedatives (including fentanyl infusions if used for analgosedation) being held and study drug being titrated to lowest volume for >30 minutes.

Permanent Discontinuation

If any of the following below occur, hold the study drug and contact the study team ASAP who will determine if a criteria for permanent discontinuation has been met.

- **Second episode of symptomatic bradycardia** (<50 beats/minute and systolic blood pressure <80 mm Hg) **while on study drug.** Study drug may be continued, titrated down, or held during the first episode of symptomatic bradycardia, at the discretion of the clinical team. Clinical team would manage the bradycardia, and study drug should be restarted once it resolves. **Symptomatic bradycardia** that reoccurs while back on study drug will result in permanent discontinuation of study drug.
- **New onset 2nd or 3rd degree heart block**. Degree of heart block should be confirmed with clinical team or study PI before discontinuation.
- **Serious allergic reaction** to study drug as determined by the managing clinical team and principal investigator.
- **New onset coma due to a known structural brain disease** such as a stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema.
- **Suspected Propofol Related Infusion Syndrome** (commonly presents as cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure) **or acidosis** that cannot be explained by the medical condition of the patient.
- **Any other study drug-related, life-threatening, serious adverse reaction**.
- **Withdrawal from study drug treatment** at the discretion of the principal investigator, the patient/family, or the attending clinical physician.

MENDS2

Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Sepsis

Please note that the bedside nurse is responsible to keep everyone blinded from identifying the study drug and to keep study drug concealed with IV coverings provided by the Investigational Pharmacy. Never tell the study team what drug you think the patient is receiving or give description of the color of study drug. Thank you for helping protect the integrity of this study and for helping us answer important questions regarding the efficacy of sedation and reducing neurological dysfunction and mortality!

Patient's weight in kg:_____

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Propofol (mcg/kg/min)	5	10	15	20	25	30	35	40	45	50
Dexmedetomidine (mcg/kg/hr)	0.15	0.30	0.45	0.60	0.75	0.90	1.05	1.20	1.35	1.50

		Infusion Rate (ml/hr)									
Patient Weight (kg)	40	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
	45	1.4	2.7	4.1	5.4	6.8	8.1	9.5	10.8	12.2	13.5
	50	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0
	55	1.7	3.3	5.0	6.6	8.3	9.9	11.6	13.2	14.9	16.5
	60	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
	65	2.0	3.9	5.9	7.8	9.8	11.7	13.7	15.6	17.6	19.5
	70	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21.0
	75	2.3	4.5	6.8	9.0	11.3	13.5	15.8	18.0	20.3	22.5
	80	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
	85	2.6	5.1	7.7	10.2	12.8	15.3	17.9	20.4	23.0	25.5
	90	2.7	5.4	8.1	10.8	13.5	16.2	18.9	21.6	24.3	27.0
	95	2.9	5.7	8.6	11.4	14.3	17.1	20.0	22.8	25.7	28.5
	100	3.0	6.0	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0
	105	3.2	6.3	9.5	12.6	15.8	18.9	22.1	25.2	28.4	31.5
	110	3.3	6.6	9.9	13.2	16.5	19.8	23.1	26.4	29.7	33.0
	115	3.5	6.9	10.4	13.8	17.3	20.7	24.2	27.6	31.1	34.5
	120	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
	125	3.8	7.5	11.3	15.0	18.8	22.5	26.3	30.0	33.8	37.5
	130	3.9	7.8	11.7	15.6	19.5	23.4	27.3	31.2	35.1	39.0
	135	4.1	8.1	12.2	16.2	20.3	24.3	28.4	32.4	36.5	40.5
	140	4.2	8.4	12.6	16.8	21.0	25.2	29.4	33.6	37.8	42.0