Appendix 1

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

Appendix 2. This supplement was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

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
Protocol Version	1.12 (October 1st, 2018)
Principal Investigators	Pratik P. Pandharipande, MD, MSCI Christopher G. Hughes, MD, MS E. Wesley Ely, MD, MPH
Biostatistician	Rameela Chandrasekhar, PhD Onur M Orun, MS
Date of version	October 10th, 2019
SAP Version	1.1
SAP Revision History	Version 1.0 - January 4th, 2019
SAP Revision Justification	To modify content for clarity; to reduce number of covariates based on limited sample size for mortality outcome.

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[1].
    - Central nervous system: Since GCS was not collected, we will use the lowest RASS available that day[2].

- 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 - $5D^3$, 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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