The MENDS II Study
Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients with Acute Respiratory Failure

NIH Grant Title: Altering Sedation Paradigms to Improve Brain Injury and Survival in Severe Sepsis

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1.0   Introduction

Severe sepsis is a life-threatening syndrome that affects more than 750,000 patients in the U.S. and is a leading cause of death worldwide, with a case fatality rate as high as 30%-50% in developed countries.[1, 2] Acute respiratory failure (ARF) is a dominant determinant of outcomes for many with severe sepsis; over 70% of patients with severe sepsis, in fact, require mechanical ventilation (MV).[3] One-third of these patients are formally diagnosed with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI), whereas all of them have severe hypoxemic/gas exchange abnormalities.[4] Patients with acute respiratory failure due to sepsis are at high risk not only for death but for significant functional and cognitive decline, which can persist for years after recovery of lung function.[1, 2, 5-9] These adverse long-term outcomes, which levy significant costs to patients and society,[5-9] are usually preceded by acute brain injury (ABI), manifested as delirium and coma, which occurs in 50%-70% of MV septic patients.[10-13] Despite advances in the management of acute respiratory failure and sepsis, there have been only marginal improvements in survival; the dearth of promising new therapeutics for the near future is marked by an absence of attention to the effects that supportive therapies may have on both short- and long-term outcomes.[14-23] Sedatives, for example, are nearly universally given to septic mechanically ventilated patients. We now know that sedatives contribute to iatrogenic injury, prolonging ventilator time and inciting acute brain injury.[12, 24-27] Compelling data now indicate that minimizing[28-30] or altering patients' exposure to specific sedative agents may be a new avenue for improving outcomes in severe sepsis with respiratory failure and acute brain injury.[31-36] The GABAergic benzodiazepines, in particular, have been repeatedly shown to increase brain dysfunction, promote infection, and prolong MV, predisposing patients to higher mortality.[12, 26, 27, 34-39] As a result of these data, the newer, shorter-acting GABAergic sedative agent, propofol, and the alpha$_2$ agonist, dexmedetomidine, are becoming widely prescribed for the sedation of septic mechanically ventilated patients.[13, 35, 36, 40-43] To date, there remain only a few randomized trials to guide clinicians regarding the beneficial effects and risks associated with these newer sedatives in patients with severe sepsis and respiratory failure, and yet there are data to indicate that GABAergic and alpha$_2$ agonist sedative agents possess distinctly different effects on innate immunity, risk of infection,[44-49] arousability,[50, 51] duration of action,[52, 53] and suppression of respiratory drive.[54] In small clinical studies[55, 56] and preclinical work,[45] dexmedetomidine appears to offer superior anti-inflammatory effects compared with GABAergic agents, including propofol. Dexmedetomidine improves bacterial clearance, whereas propofol reduces it;[49] effects that may alter outcomes for septic ventilated patients, leading to preclinical work on GABA$_A$ antagonists as anti-infective agents.[57, 58] Alpha$_2$ agonists may also inhibit neuronal apoptosis, a deleterious effect of sepsis that is likely critical to the development of brain dysfunction in these vulnerable patients.[34, 59, 60] Sedation with dexmedetomidine instead of benzodiazepines reduces delirium by 20%-30%[35, 36] and improves arousability,[50] facilitating "wake-up" strategies.[29] Endogenous sleep pathways mediate the hypnotic response of both classes of drugs,[61, 62] but GABAergic agents induce unconsciousness at the level of the hypothalamus, whereas the alpha$_2$ agonists do so in the brainstem,[61-63] an effect—more akin to natural sleep—which may improve autonomic function, immunity, and insulin resistance. These factors converge to suggest that sedation with an alpha$_2$ agonist, rather than a GABAergic agent, may improve outcomes for septic mechanically ventilated patients, including brain function and survival. **We, therefore, propose to study the effects of sedatives—the alpha$_2$ agonist dexmedetomidine and the GABAergic propofol—in severely septic patients with acute respiratory failure via a multicenter randomized, double-blind, trial.** In this study, we plan to consent approximately 580 adult medical or surgical intensive

care unit (ICU) patients with severe sepsis and on MV. Although, the study participants will span the adult age spectrum, we anticipate the majority of them will be elderly based on our ongoing BRAIN-ICU cohort demographics and those of the participating sites as well as the fact that nearly two thirds of all ICU admissions are >65 years old.[64, 65]

Specific Aims
Aim 1: To determine whether sedation of mechanically ventilated severely septic patients with an alpha$_2$ agonist (dexmedetomidine) rather than a GABAergic agent (propofol) will **(Aim 1A)** increase days alive without delirium or coma (delirium/coma-free days) and **(Aim 1B)** increase ventilator-free days.
Aim 2: To determine whether sedation of mechanically ventilated severely septic patients with an alpha$_2$ 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.
Aim 3: To determine whether sedation of mechanically ventilated severely septic patients with an alpha$_2$ 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).

To test the hypothesis, we plan to randomize mechanically ventilated, severely septic patients requiring sedation to targeted sedation with dexmedetomidine or propofol. To reach this goal, we plan to enroll and randomize 440 patients in order to have at least 420 patients randomized who received study drug. This will account for some disqualification after randomization. The study will be powered to detect a difference of 1.5 delirium/coma-free days between the two groups and an absolute difference in mortality of 10%. Patients will be assessed daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU);[10, 11] other important clinical outcomes and safety parameters will be tracked daily in the ICU. Survivors will be assessed 6-months post-randomization for cognitive impairment via a validated and reliable phone battery.

2.0 Background

"**Septic shock is the rude unhinging of the machinery of life.**" (Samuel Gross, 1862)

"**For many aging people in good physical condition who succumb to an acute illness [e.g., sepsis, ARDS] cognitive decline [e.g., delirium followed by an acquired post-ICU long-term cognitive impairment] is the main threat to their ability to recover and enjoy their favorite activities; for those whose physical activities were already limited, cognitive decline is a major additional threat to quality of life.**" National Research Council[66]

2.1   Severe sepsis, acute respiratory failure and acute brain dysfunction often occur concomitantly in mechanically ventilated patients. There are an estimated 2 to 3 million patients on MV each year in high-income countries and the majority of these patients have sepsis with ALI, ARDS or ARF due to gas exchange abnormalities, and up to 50-80% of these MV patients have acute brain dysfunction, manifesting as delirium and/or coma).[10-13, 60, 67, 68] Although separate entities, sepsis and delirium are closely linked in terms of pathophysiology and share many of the same inflammatory pathways and cellular interactions resulting in widespread effects on other organs and tissues.[60, 68-73] In the United States, severe sepsis alone accounts for an estimated 250,000 deaths,[2] and exceeds the number of annual deaths from

myocardial infarctions, HIV/AIDS, breast cancer and asthma. Indeed, while mortality from severe sepsis is upwards of 30-40% in developed countries,[2, 74, 75] with only slight temporal improvements,[74, 75] that of ST-elevation myocardial infarction is much less at 7% and on the decline.[67] Furthermore, with the aging population, the number of cases of severe sepsis is expected to increase by 50% by 2030 unless new therapeutic options are discovered.[2] *While the incidence and mortality associated with severe sepsis is staggering, and sepsis results in longer times on MV and in ICUs, a major but often missed cause of increased morbidity in ventilated septic patients is delirium, and its complications.*[69-71, 76]

2.2   Delirium in ventilated septic patients is associated with mortality and poor cognitive function and functional status. Delirium occurs in 50-80% of MV patients[10-13] and carries enormous financial[77] and societal burdens due to its association with increased mortality,[37, 38, 78] prolonged hospital stays,[79] and its relationship to long-term neuropsychological deficits.[80-82] Each additional day of delirium independently increases risk of death by 10%,[37, 38] strongly supporting **Aim 1 of this MENDS II study, aimed at reducing duration of delirium in patients with ARF and sepsis.** It is estimated that ICU delirium is associated with $4-$16 billion annually in the U.S.,[77] not including cost of lost workdays, caregiver burden, or cognitive rehabilitation for the 50-66% of patients with dementia-like deficits years later[8, 9, 80, 82-84] (**supporting Aim 2 of MENDS II aimed at reducing incidence of long-term brain dysfunction**). Sepsis, too, has been shown to independently and significantly alter the trajectory of cognitive impairment with almost a 3-fold increase in the risk of developing cognitive impairment in survivors of sepsis.[7] While it is unclear as to whether it is sepsis that contributes to worse cognitive impairment, or if this is a consequence of the closely associated brain dysfunction, it is extremely concerning that the two episodes of ICU care, on average, that each American will experience in their lifetime will result in millions of survivors suffering mild to severe ICU-acquired cognitive impairment that impairs quality of life.

2.3   Sedation used to keep ventilated septic patients comfortable can lead to delirium and iatrogenic harm. The mainstay of therapy in severe sepsis is aggressive source control, appropriate choice of antibiotics and the consideration of activated protein-C in select cases.[14, 15] Apart from these, key elements in the management of severe sepsis remain supportive (e.g., goal-directed resuscitation, ventilation management, glucose control, etc.).[85-92] Sedative and analgesic medications are part of these supportive treatments, and are almost universally used to provide patient comfort, treat pain and anxiety, and prevent agitation.[93] Yet, they have shown to prolong time on MV and in ICU.[24] Deep sedation has also been shown to be associated with burst suppression, or an obliteration of brain wave activity on an encephalogram, associated with a higher mortality in a important minority of critically ill patients.[94] While psychoactive medications have traditionally been compared using surrogate markers such as time on the ventilator and ICU and hospital length of stay, our team has found that commonly prescribed benzodiazepine GABAergic agents, such as lorazepam and midazolam, are independent (and iatrogenic) risk factors for daily development of delirium (see section 3.0) in three separate cohorts.[27, 12, 95] These data showed, for the first time, that benzodiazepines are associated with more acute brain dysfunction prompting clinicians and researchers to study alternative sedation paradigms to either decrease the exposure to sedatives or to move away from the practice of using benzodiazepines in order to improve patient outcomes.[13, 28, 29, 35, 36, 40-42] **With the pathogenesis of delirium still unclear,[96] a leading hypothesis is perturbations in inflammation[69-71] that may have common elements with pathways involved in sepsis.[60, 68]**

2.4   Sedative medications can dysregulate the body's natural control of inflammation.
To understand how sedation may play a role in dysregulating the body's natural response to inflammation, we need to first succinctly review the inflammatory response to infection. Sepsis is the systemic inflammatory response to infection and is characterized by dysregulated production of cytokines, a pathological state that causes tissue injury and consequently organ dysfunction and death.[60, 68] It is characterized by an early unrestrained production of <u>pro-inflammatory cytokines</u> such as tumor necrosis factor (TNF) and interleukins (IL) such as IL-1, IL-6 etc., and late mediators such as high-mobility group protein B1 (HMGB1), which perpetuate inflammatory response and lead to organ dysfunctions.[60] <u>Anti-inflammatory</u> cytokines such as soluble TNF receptor-1 (sTNFR-1), IL-1ra, IL-10 are released in an attempt to attenuate the pro-inflammatory response and reduce organ damage; failure or dysregulation of this compensatory anti-inflammatory response syndrome (CARS) further worsens outcomes.[60] The brain, too, responds to systemic infections and injury with an inflammatory response of its own that includes the production of cytokines, cell infiltration, and tissue damage.[97, 98] This local inflammatory response is thought to alter patterns of neuronal activity resulting in delirium. In addition to the inflammatory responses described above, the parasympathetic (cholinergic) anti-inflammatory pathway plays an important role in attenuation of pro-inflammatory cytokines from macrophages, without any effects on anti-inflammatory cytokines such as IL-10.[99, 100] **The body generally regulates this balance between the pro and anti-inflammatory cytokines; unfortunately, commonly prescribed GABAergic sedative agents have immunomodulatory properties that may alter this balance and contribute to worse outcomes.**

2.5   GABAergic sedatives, like benzodiazepines, impact the immune response.
GABAergic agents, such as midazolam, impair nuclear factor kappa B (NFkB) and mitogen activated protein kinase (MAPK) signaling, leading to reduced responsiveness to inflammatory stimuli, including pathogens.[46] This effect typically manifests itself as reduced cytokine production that may have utility in septic shock, however this mechanism also blunts bacterial killing.[46] *In vivo* animal studies have demonstrated that the GABAergic agents increase mortality in live bacterial infection with intranasal Streptococcus pneumonia, intraperitoneal Klebsiella pneumonia,[101] Mycobacterium bovis,[102] and Salmonella typhimurium infection that may be caused by impairment of neutrophil[48] and macrophage[46] function. Review of the available evidence suggests that this impaired immune response to pathogens is common to the whole class of GABA agonists studied so far.[34] In contrast, GABA$_A$ <u>antagonists</u> improve outcomes in infective models.[57, 58] Bicuculline[57] improves acute mortality in severely septic rats and securinine,[58] a GABA$_A$ antagonist, enhances killing of *Coxiella burnetii in vitro* and *in vivo* by alveolar macrophages. Consistent with the hypothesis that GABAergic agents may impair immune responses to infection, critically ill patients sedated with midazolam appear more susceptible to secondary bacterial infections than those sedated with dexmedetomidine,[35] and septic patients on lorazepam have a greater likelihood of death than patients sedated with dexmedetomidine.[36]

2.6   Propofol and dexmedetomidine may differentially affect inflammation and improve clinical outcomes in sepsis and delirium. Compelling data now indicate that a new avenue for improving outcomes in severe sepsis and delirium may be via newer sedative agents that lack the deleterious effects of benzodiazepine GABA$_A$ mediated immunomodulation.[31-36] These agents include the shorter acting GABAergic agent propofol and the alpha$_2$ agonist dexmedetomidine, which are rapidly becoming the pillars of sedation in critically ill patients, [13,

[35, 36, 40, 42, 43] and yet are different from each other in terms of receptor specificity, immunomodulation including bacterial clearance, apoptosis, maintenance of sleep architecture, delirium risk, mortality and side effect profile. **A comparison of these specific properties is provided below.**

[1]   Propofol is a 2-6 di-iso-propyl phenol intravenous GABAergic sedative agent that has been studied and found superior to benzodiazepines for sedation in the ICU with respect to time on MV, faster rousability, greater times at target sedation and faster extubations.[40, 41, 103] Dexmedetomidine is a highly selective alpha$_2$ receptor agonist that inhibits the release of norepinephrine (NE),[50] resulting in sedation and analgesia and blunting of the stress response, without respiratory depression.[54, 55, 104, 105] Dexmedetomidine has been studied against lorazepam in the MENDS[13] double-blind randomized controlled trial and was found to be superior in reducing the duration and prevalence of brain dysfunction,[13] and further time on MV and mortality in the septic subgroup, without any differences in hemodynamic profiles or adverse events.[36] The SEDCOM study,[35] compared dexmedetomidine with midazolam, and found that dexmedetomidine patients spent fewer days on MV, experienced less delirium, and developed less tachycardia and hypertension.

[2]   As mentioned earlier, the dysregulated production of pro-inflammatory cytokines[60, 68] is associated with worse outcomes in sepsis. The body itself attempts to reign this pro-inflammatory cytokine cascade by two mechanisms—(2.a) the production of anti-inflammatory cytokines,[60] and (2.b) the parasympathetic (cholinergic) reflex that attenuates inflammation.[99, 100] Propofol shows favorable properties of reducing the pro-inflammatory cytokines in animal models;[106, 107] however, human studies[55, 108] have been contradictory with an increase in the pro-inflammatory cytokine production. Additionally propofol has not been shown to influence the parasympathetic reflex. Dexmedetomidine, on the other hand, has consistently attenuated pro-inflammatory cytokines in animal and human studies, with corresponding improvements in outcomes including survival. Its vagomimetic action may also play a role in potentiating the parasympathetic reflex. [50]

[3]   Propofol, similar to the data on the other GABAergics (benzodiazepines) presented in section 2.5, impairs bacterial clearance from the lung and spleen in rabbits injected with Escherichia (E.) coli *in vivo,* and *E. coli* and *Staphylococcus aureus in vitro,*[49, 109] through inhibition both of myeloid (in particular neutrophil) and lymphoid cell function.[49, 110, 111] Dexmedetomidine, on the other hand, does not suppress neutrophil function and helps bacterial clearance (see section 3.5)[112]

[4]   Propofol has not been associated with beneficial effects on apoptosis, while dexmedetomidine inhibits neuronal apoptosis and apoptosis in other vital organs.[34, 59, 60]

[5]   Both propofol and dexmedetomidine have been associated with improving restorative sleep. Endogenous sleep pathways mediate the hypnotic response of both classes of drugs,[61, 62] but GABAergic agents induce unconsciousness at the level of the hypothalamus, whereas the alpha$_2$ agonists do so in the brainstem,[61-63] an effect— more akin to natural sleep—which may improve autonomic function and immunity.

[6]   As eluded in point [1], benzodiazepines have been associated with delirium, but data on propofol are inconclusive. Dexmedetomidine, however, has been shown to reduce duration and prevalence of brain dysfunction in two randomized controlled trials compared to benzodiazepines.[13;35, 36] A comparative trial (the PRODEX study, Orion Pharma press release) in low severity illness patients, with approximately 25% septic patients, has shown equipoise between the two agents in delirium outcomes. Dexmedetomidine, however, has been shown to be superior to propofol with regards to its effect on maintenance of cognition,[51] and improvement of attention as compared to benzodiazepines.[33]

[7]   GABAergic agents may promote infection,[49, 110] and the intralipid formulation of propofol may play a role in this. Dexmedetomidine, on the other hand, has been associated with lower secondary infections and mortality in septic patients when compared with a benzodiazepine.[35, 36]

[8]   Side effects associated with propofol include hypertriglyceridemia, pancreatitis, acidemia and propofol infusion syndrome.[113] Propofol infusion syndrome is rare. About 20 adult cases have been described, mostly in patients with acute neurological illness, acute inflammatory disease complicated by severe infections or even sepsis, and receiving catecholamines and/or steroids in addition to propofol.[113] Common side effects seen with dexmedetomidine include bradycardia (including a reported cardiac arrest in which dexmedetomidine was part of the multifactorial causes for the event) and hypotension, though in studies in critically ill patients, including septic patients, there has not been a reported increase in vasopressor use.[35, 36] Additionally, one trial reported hyperglycemia with dexmedetomidine.[35, 36]

Thus there are data supporting beneficial effects of both propofol and dexmedetomidine. While propofol offers significant benefits over benzodiazepines, data indicate that dexmedetomidine is superior to propofol with regard to its effects on innate immunity and inflammation,[44-49] cognition,[51] apoptosis,[34, 59] and delirium.[35, 36] All these factors converge to suggest that sedation with an alpha$_2$ agonist rather than a GABAergic agent may improve outcomes, including brain function and survival, for septic MV patients. **Physicians are now challenged, due to the absence of head to head comparisons of these two agents in high severity of illness, severely septic patients, to understand the benefit to risk profile. This presents an unmet scientific gap in knowledge, which has to be addressed to ensure that our most vulnerable patients are treated in the most effective and safe manner. The MENDS II trial will address this need.**

3.0   Preliminary Studies

3.1   Benzodiazepines and delirium. Of the three components of patient comfort (pain, anxiety, and delirium) included in current guidelines for use of sedatives and analgesics in ICU patients,[93] only delirium has been found to be an independent predictor of death. Pharmacological data was analyzed from 198 medical ICU patients,[37] using time-dependent multivariable analysis, to test the

Figure 1. GABA-ergic agents and delirium

p=0.003

Probability of delirium

Lorazepam Dose (mg)
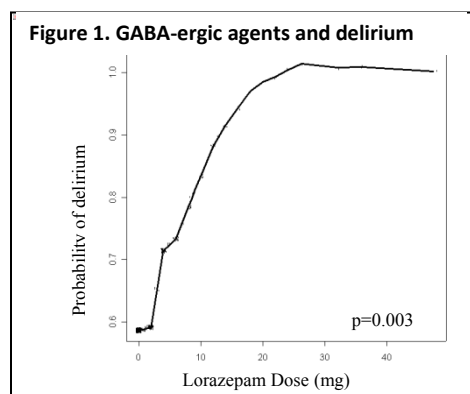
hypothesis that sedative and analgesic medications are independent risk factors for the development of delirium after adjusting for relevant covariates. Every unit dose of lorazepam in the *previous* 24 hours was associated with increased probability of development of delirium [O.R. 1.2 (95% C.I. 1.1 to 1.4), p =0.003] **(Fig 1)**, whereas propofol were associated with higher but not statistically significant odds ratios.[27] Using a similar methodology midazolam was also shown as a risk factor for delirium in surgical, trauma and burn ICU patients.[12, 95] **These data support Aim1A of MENDS II (reducing delirium by use of alpha$_2$ agonists instead of GABAergic agents).** Data on opiates is inconsistent, with opiates being risk factors for delirium in surgical patients, but not in trauma and burn patients where pain is significant and adequate treatment may offer benefit.[27]

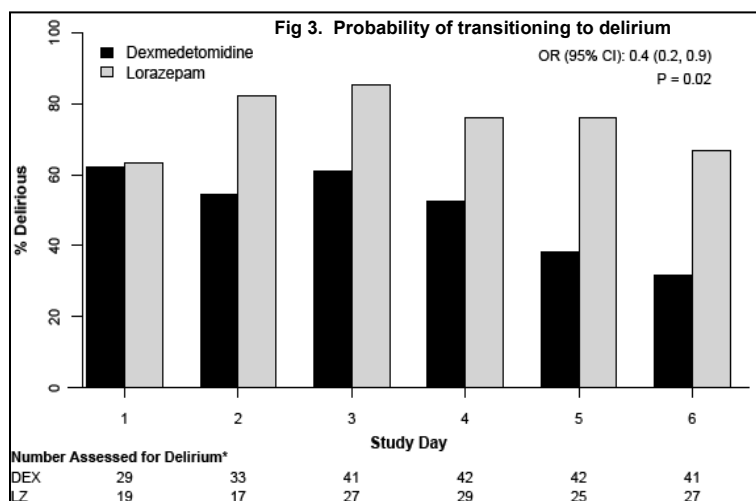**3.2   Delirium and Long-term Cognitive Impairment.** This cohort study[82] enrolled 126 adult ventilated medical ICU survivors and followed them for 12 months. Multiple linear regression was used to analyze the association between delirium duration and 12-month cognitive performance, adjusting for covariates. Follow-up data were obtained for 80% of survivors. Duration of delirium **(Fig 2)** independently predicted worse cognition at 3 months (P=0.02) and 12 months (P=0.03).[82] **These data demonstrate our coordinating center's success in achieving high long-term follow-up rates and add support for the idea that an intervention to reduce delirium duration might produce improvements in long-term cognitive function, justifying Aim 2B (cognitive function) in MENDS II.**
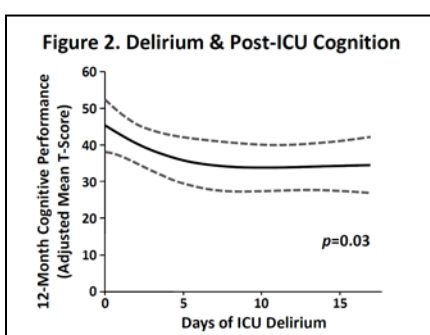
Figure 2. Delirium & Post-ICU Cognition

3.3   Changing sedation paradigms reduces duration and prevalence of brain dysfunction. The MENDS study,[13] which enrolled both medical and surgical ICU patients, was the first to evaluate the benefit of sedation targeting alpha$_2$ receptors compared to the standard of care GABAergic agents to reduce brain dysfunction. This trial showed that compared to lorazepam, patients sedated with dexmedetomidine achieved sedation targets more often and had more days alive without delirium or coma, with important trends toward a reduction in death at 28-days (27% in lorazepam versus 17% dexmedetomidine). Patients on dexmedetomidine had a 60% lower risk of developing delirium **(Fig 3)** versus lorazepam, **further supporting Aim 1A of MENDS II.**

Fig 3. Probability of transitioning to delirium

Number Assessed for Delirium*					
DEX	29	33	41	42	42	41
LZ	19	17	27	29	25	27

3.4   Alpha$_2$ agonists improve survival in patients with sepsis compared to GABAergic agents. In this *a priori*-determined subgroup analysis[36] of septic vs non-septic patients from the

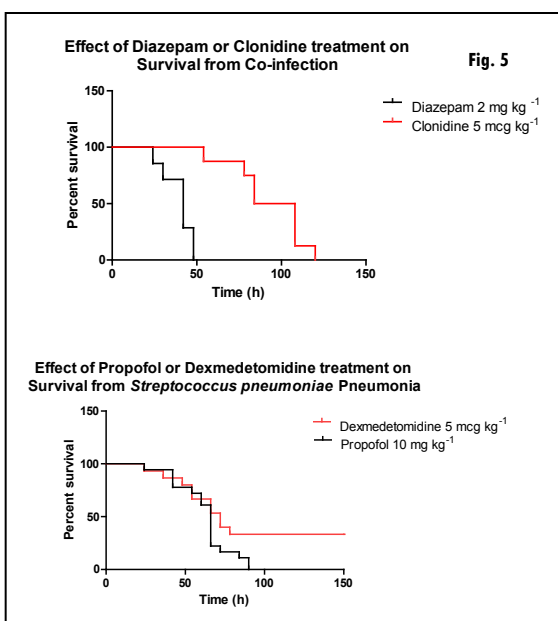MENDS double-blind randomized controlled trial, 63 (31 dexmedetomidine; 32 lorazepam) were admitted with sepsis and 40 (21 dexmedetomidine; 19 lorazepam) without sepsis. Compared with septic patients who received lorazepam, the septic patients receiving dexmedetomidine had 3.2 more delirium/coma-free days (DCFD) on average (95% CI for difference, 1.1 to 4.9), and 6 (0.3, 11.1) more ventilator-free days (VFD). The beneficial effects of dexmedetomidine were more pronounced in septic patients than in non-septic patients for both DCFDs and VFDs (**supporting Aim 1B**) (P-value for interaction = 0.09 and 0.02 respectively). Additionally, sedation with dexmedetomidine, compared with lorazepam, reduced the daily risk of delirium [OR, CI 0.3 (0.1, 0.7)] in both septic and non-septic patients. Risk of dying at 28 days was reduced by 70% [hazard ratio 0.3 (0.1, 0.9)] in dexmedetomidine patients with sepsis **(Fig 4)** as compared to the lorazepam patients; this reduction in death was not seen in non-septic patients (**supporting Aim 2A of MENDS II**).

Fig 4. Dexmedetomidine improves 28-day survival in septic patients
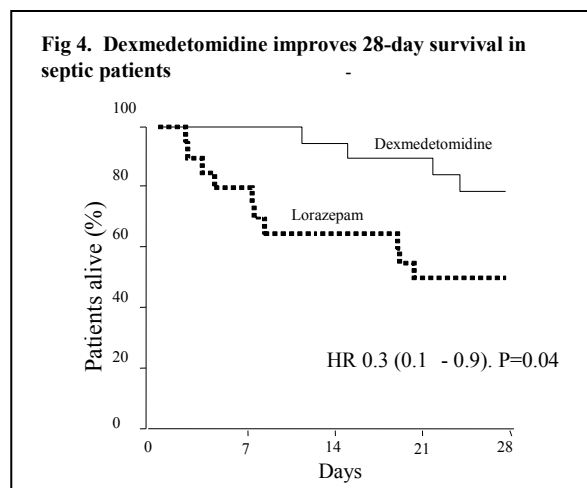
3.5 Alpha$_2$ agonists improve survival in animal models with infections compared to GABAergic agents. In order to confirm a survival benefit conferred by alpha$_2$ adrenoceptor agonists over GABAergic agents, diazepam *versus* clonidine and propofol *versus* dexmedetomidine (drugs with similar half-lives) were compared in two infection paradigms. In the prolonged infection model, adult C57BL/6 mice infected with 50HA of X31 influenza (intranasal) were administered diazepam, clonidine or placebo, 4 hours after influenza infection. Seven days later, both groups of animals were super infected with D39 (serotype 2) *Streptococcus pneumoniae* infection (1 x 10^6 colony forming units ml^{-1} intranasal). Median survival time in the placebo group was 72 hours from the time of bacterial superinfection. Clonidine increased median survival time compared to diazepam (84 versus 42 hours) and reduced the hazard ratio of death (HR 0.06 [0.01 – 0.32]; p = 0.0008) **(Fig 5)**. In the acute infection model, adult C57BL/6 mice infected with 5 x 10^4 colony forming units ml^{-1} *Streptococcus pneumoniae* intranasal had a 19% survival (3 out of 16 mice). In this model comparison of dexmedetomidine (n = 15) with propofol (n = 16) treatment started four hours after infection revealed that dexmedetomidine increased survival compared to propofol (33% versus 0%; p = 0.02). **Thus our clinical (3.4)**
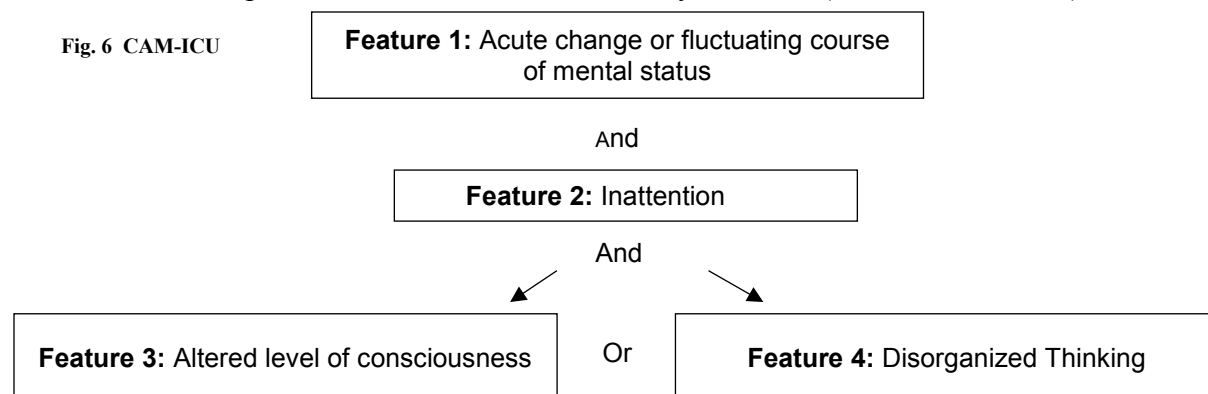
and preclinical work (3.5) are supportive of Aim 2B of MENDS II where we hypothesize that survival may be better with alpha2 agonists over GABAergic agents.

4.0 Study Objectives and Endpoints

4.1 Study Objectives. The primary objective of the **MENDS II** study is to determine the efficacy and safety of dexmedetomidine vs. propofol in mechanically ventilated medical and surgical patients with severe sepsis.

4.2 Efficacy Endpoints

4.2.1 Primary Endpoint. The **trial's primary endpoint (Aim 1A)** will be **delirium/coma-free days (DCFDs)**, defined as number of days alive and free of delirium and coma during the 14-day Treatment Period (from randomization, which will be Study Day 1, until Study Day 14). Patients will be evaluated for delirium by trained research nurses with the CAM-ICU,[10, 11] a validated instrument for diagnosing delirium, even in non-verbal ventilated patients, that takes on an average 2 minutes and can be administered by non-psychiatrist personnel (**Fig 6**). Delirium assessments will be performed twice daily while in the ICU and then once daily until conclusion of the combined Treatment/Post Study Drug Period (see section 7.2), hospital discharge or death (whichever is first). Patients who are unresponsive to voice are categorized as comatose; those responsive to voice and CAM-ICU positive are categorized as delirious; those who are CAM-ICU negative are called normal. The DCFD continuous variable represents duration of time a patient is alive and free of brain dysfunction (delirium and coma) and has

Fig. 6 CAM-ICU

Feature 1: Acute change or fluctuating course of mental status

And

Feature 2: Inattention

And

Feature 3: Altered level of consciousness	Or	**Feature 4:** Disorganized Thinking

been used in other high-impact studies.[13, 28] For example, if during a 14 day period a patient is comatose the first 3 days, then has delirium (or CAM-ICU positive) the next 4 days, and then normal or CAM-ICU negative the remaining 7 days, he will have 7 =[14-(3+4)] delirium/coma-free days. On the other hand, suppose a patient is comatose the first 3 days, then has delirium (or CAM-ICU positive) the next 4 days and then dies, he will have 0 delirium/coma-free days, since there were no days that the patient was alive <u>and</u> free of delirium or coma.

The MENDS II study will have tremendous implications for practice, based on the outcome of DCFD results, even if the secondary outcome of mortality is neutral, given ours and others' recent data that every additional day of brain dysfunction is independently associated with higher mortality and cognitive impairment in survivors.[37-39, 82] We will also assess delirium days in survivors and daily prevalence of delirium after randomization as additional brain injury outcomes. Delirium days was not chosen as a primary end point because delirium

days can be curtailed by death; similarly delirium-free days was not used because delirium-free days fails to account for coma; thus patients could artificially be considered to have more delirium-free days (thus a good outcome) when in fact the reason they were delirium-free was because of coma (an untoward outcome). The analysis of DCFDs and other secondary outcomes will be conducted using **Intention-to-Treat (ITT) population**, defined as all patients who were randomized to study drug. We chose a 14 day evaluation period for delirium, because it represents the best balance of gaining valuable clinical information, while maximizing resource utilization, given the average study drug infusion to be 7 days and maximum duration to be 14 days. Thus our follow-up period will cover 7 additional days of delirium monitoring after the study drug is stopped in the majority of our patients.

4.2.2 Secondary Endpoints

[1] **Ventilator-free days** (VFDs) **(Aim 1B),** i.e., days alive and free of MV at 28 days. This endpoint has been used by the NHLBI's ARDSNet in numerous critical care trials examining ICU populations.[88, 89, 114, 115]

[2] **90-day survival** (**Aim 2A**)

[3] **Neuropsychological function, Activities of Daily Living (ADL)[116] and Instrumental ADLs[117]** will be assessed 6 months after randomization (**Aim 2B**) using a validated and reliable telephone battery[118] for post-ICU patients, to measure incidence, duration, and severity of dysfunction in memory, attention, reasoning, and executive function domains as well as assess independence and quality of life (see section 8.1).

[4] **Markers of inflammation (Aim 3)** will be assessed on Days 1, 3, 5, 7 and 14 (see details in 7.2.3)

[5] **Organ dysfunctions** will be tracked until conclusion of the combined Treatment/Post Study Drug Period, hospital discharge or death (whichever happens first) using daily SOFA scores and continuous as well as established predefined cut offs for each organ failure: Kidney, $Cr > 2$ mg/dL or urine < 400 cc/day; Lung, $PaO_2/FiO_2 <300$ or $SaO_2/FiO_2 <315$;[119] Liver, total bilirubin > 2 mg/dL; Coagulation, Platelet count $< 100,000/mm^3$; and Hemodynamic, need for vasopressor,[120, 121] consistent with definitions utilized in published studies of organ dysfunction in critically ill patients.[122]

[6] **Acute Respiratory Distress Syndrome.** We will monitor a patient's oxygenation status by tracking daily SaO_2/FiO_2 ratios.[119] A SaO_2/FiO_2 ratio <235 correlates to a PaO_2/FiO_2 ratio of <200, which is the oxygenation threshold for ARDS.[119] Chest X-rays that are ordered as part of routine clinical care will be followed daily in patients who meet ARDS oxygenation threshold and patients with bilateral infiltrates confirmed by the medical team, will be considered to have ARDS. Time to onset of ARDS and duration of ARDS will be tracked until conclusion of the combined Treatment/Post Study Drug Period, hospital discharge, or death (whichever happens first).

4.3   Safety Endpoints. Safety endpoints tracked until conclusion of the combined Treatment/Post Study Drug Period, hospital discharge or death (whichever happens first) include <u>daily</u> monitoring for hypotension (defined as systolic blood pressure <80 mmHg, duration and dose of vasopressors/inotropes using SOFA scores), arrhythmias (tachy and/or

brady), acidosis, and <u>weekly</u> for triglyceridemia and adrenal insufficiency. Patients will be monitored for withdrawal for 48-hours after study drug termination, assessing for hypertension, tachycardia and diaphoresis. Vital signs will be monitored per established standards in the ICUs and wards. Select laboratory values from standard laboratory measures of blood counts and chemistries will be collected daily, when ordered as part of usual clinical care.

5.0   Inclusion/Exclusion Criteria

5.1   Inclusion Criteria. Consecutive patients will be eligible for inclusion in the MENDS II study if they are: [1] adult patients (≥18 years old) [2] in a medical or surgical ICU and [3] on MV, requiring sedation and [4] have a suspected or known infection.

5.2   Exclusion Criteria. Patients will be excluded (i.e., not consented) for any of the following reasons:

[1]   Rapidly resolving organ failure, indicated by *planned immediate discontinuation* of MV, at time of screening for study enrollment

[2]   Pregnant or breastfeeding

[3]   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.

[4]   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.

[5]   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.

[6]   Active seizures during this ICU admission being treated with intravenous benzodiazepines.

[7]   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).

[8]   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 **<u>are</u>** eligible for enrollment if their medical condition permits them to communicate with research staff.

[9]   Inability to obtain informed consent from the patient or an authorized representative within 48 hours of meeting all inclusion criteria for the following reasons:
      (a) Patient and/or surrogate refusal
      (b) Patient unable to consent and no surrogate available in the 48 hour window
      (c) 48-hour period of eligibility was exceeded prior to screen

[10]   Prisoners.

[11]   Medical team following patient unwilling to use the sedation regimens.

[12]   Documented allergy to propofol or dexmedetomidine.

[13]   Current enrollment in a study that does not allow co-enrollment or that uses delirium as a primary outcome.

[14]   Patients who are on muscle relaxant infusions at time of screening with plans to maintain paralysis >48 hours

[15]   Greater than 96 hours on mechanical ventilation prior to meeting all inclusion criteria.

6.0   Enrollment/Randomization

6.1.   Screening and Obtaining Informed Consent. Study personnel at each site will screen the ICU census. When an eligible patient is identified (i.e., inclusion criteria are met and no exclusion criteria are present), informed consent will be pursued. Surrogate consent will be required for most patients because during the initial phase of their illness they will often be comatose, sedated, on MV, or delirious. A consent/re-consent process will be used (surrogate consent at enrollment and re-consenting patients when competent), in keeping with recent literature on consenting delirious and/or ICU patients.[124, 125] All patients consented via surrogate will be re-consented for participation in the trial once competent.
Once informed consent is obtained, if not already confirmed, patients will be assessed for advanced heart block, pregnancy (female patients of childbearing potential only), and dementia via the IQCODE. When a patient's telemetry strip is negative for advanced heart block, IQCODE <4.5 and female patients of childbearing potential have a negative pregnancy test, they will be randomized and advanced to the Interventional Trial Phase of the study (see section 7.2 & 7.3). At this time the patient is assigned via randomization to one of the two treatment groups: dexmedetomidine or propofol.

      Randomization will be conducted using computer-generated, randomly chosen permuted block sizes of 6 and 8, stratified by study center and age (<65 vs $\geq$ 65 years). We will randomize patients in a 1:1 ratio to sedation with dexmedetomidine or propofol. The randomization scheme will be created by the study's primary biostatistician and distributed directly to each site's investigational pharmacy as a set of randomization lists stratified by study center and age (<65 vs $\geq$ 65 years). Once a consented patient has entered the Interventional Trial Phase, an order for blinded study drug is placed, and the investigational pharmacist will refer to the appropriate randomization list (determined by patient's age) to establish that patient's treatment assignment. The lists will only be accessible to investigational pharmacists so that treatment assignment will be known only by the investigational pharmacists.

6.2   Blinding. The challenge of blinding propofol, a milky fat emulsion, and dexmedetomidine, a clear aqueous solution, is evident. Nevertheless, apart from investigational pharmacists, all study personnel, patients, and physicians will attempt to remain blinded to each patient's treatment assignment throughout enrollment, follow-up, and data analysis. Study drug

will, therefore, be administered via intravenous infusion covered by an opaque bag along with sleeves to cover the intravenous tubing. Study personnel are prohibited from entering a patient's room during infusion bag or tubing changes to further reduce risk of unblinding of study personnel by visualization of study drug. End-points such as ventilator-free days, mortality, and long-term cognitive impairment are unlikely to be influenced, should unblinding be suspected. Instances of unblinding are anticipated and when known will be recorded in the study database. If an adverse event is considered study-drug related, unexpected and serious, the study drug will be immediately discontinued and the event will be reviewed via the usual process, which may involve unblinded evaluation by the Data Safety Monitoring Board (DSMB) Chair, as outlined in the Data Safety Monitoring Plan (see sections 9.2 &9.3).

7.0   Study Procedures

7.1   Enrollment. After informed consent is obtained, on the day of enrollment baseline data will be collected and the following procedures conducted:

[1]   As part of a Pre-Hospital Function Assessment a **dementia assessment** via surrogate interview will ascertain the patient's physical and cognitive abilities prior to the current hospitalization. Rather than relying on a "label" of dementia in the medical record, we will use the surrogate-completed IQCODE.[126-128] Any patient with severe dementia, based on an IQCODE ≥4.5,[123] will be excluded from further participation in the study, as described in the exclusion criteria (see section 5.2). The Pre-Hospital Function Assessment form will ascertain additional important information about the patient's pre-hospital functional status, including history of depression and chronic pain as well as provide information regarding tobacco, alcohol and illicit substance use

[2]   A **pregnancy test** (beta-hCG) will be done in all females of childbearing potential unless a pregnancy test (urine or serum hCG) has been performed during the current hospitalization that ruled out pregnancy.

[3]   All patients will be **assessed for advanced heart block** using a bedside telemetry strip. Advanced heart block will be defined as second or third degree block on telemetry per the MENDS II study.

7.2   In-Hospital Phase. The In-Hospital Phase will comprise of the Treatment Period (Study Days 1-14), during which time study drug will be infused per the study drug administration rules (see section 7.2.1) and the Post-Study Drug period (2 calendar days after discontinuation of study drug). In most instances (when study drug is administered for ≤ 12 days), the Post-Study Drug Period will fall within the treatment period. When study drug is required for >12 days, the Post-Study Drug period will extend beyond the treatment period such that for e.g., patients who receive study drug for the entire 14-day treatment period will have the Post-Study Drug Period last until Study Day 16.

Once it has been confirmed that the patient qualifies for randomization [e.g. patient's telemetry strip is negative for advanced heart block, female patients of childbearing potential have a negative pregnancy test (either serum or urine), and IQCODE is less than 4.5] they will advance to the Interventional Trial and enter the In-Hospital Phase of the trial.   Upon entering the Interventional Trial Phase, each patient will be assigned, via randomization, to one of the two treatment groups, and study drug will be delivered in a double-blind manner per titration rules as outlined in section 7.2.1 when in the ICU on mechanical ventilation, and needing

sedation per the managing clinical team, until study drug withdrawal, death, or for a maximum of 14 days—the Treatment Period— (whichever occurs first).

The following data will be collected during the In-Hospital Phase:

[1] On enrollment the **patient's medical records** will be used to collect demographics, preexisting conditions, admission severity of illness and organ failure. If obtained as part of routine medical care, results of additional test results will also be collected and may include hematologic laboratory values and blood chemistries, [e.g. WBC, HCT, potassium, sodium, BUN, creatinine, albumin, bilirubin, SGOT (AST), SGPT (ALT), lactate, ammonia, troponin, and glucose].

[2] Throughout the study, data reflecting current severity of illness, recent and ongoing treatments (including medications and mechanical ventilator status), vital signs (including daily worst SaO_2/FiO_2 ratios), routine lab results, tracking of sepsis and ventilator management, and complications (e.g., infections and device removals), will be collected from the **patient's medical records**. These data will be generated as part of routine clinical care and will not require study-related tests.

[3] A direct **patient assessment** will occur twice daily while in the ICU and once a day when on the wards to determine level of sedation using the RASS[129, 130], assess for pain using the Critical-Care Pain Observation Tool (CPOT), assess for delirium using the CAM-ICU, and assess for diaphoresis.[10, 11, 131]

[4] A **bedside checklist** will be used to collect data regarding adherence to the nonpharmacologic ABCDE protocol (see section 7.2.2), which includes standardized components of ventilator weaning, sedation, and delirium management. Components of the ABCDE protocol will be documented as complete or incomplete on a daily basis by ICU staff and/or study personnel after they are implemented.

[5] **Co-administered psychoactive medications**, including sedatives, analgesics, and antipsychotics, will be tracked daily in the study.

[6] **Blood specimens** will be collected as outlined in section 7.2.3 on all consented patients.

[7] **Assessment for Catatonia**: At select participating sites and in a convenience sample, patients will be screened up to twice daily while in the ICU and up to once daily when on the wards with the Bush Francis Catatonia Rating Scale (BFCRS), a bedside clinical tool used widely in psychiatric consultations to diagnose catatonia, and for motor symptoms with the Delirium Motor Subtype Scale (DMSS). Together these assessments will take 5 minutes on average to perform. These evaluations will for the first time evaluate the prevalence of catatonia in critically ill patients, and prospectively explore the extent to which an overlap syndrome exists between delirium and catatonia. For those patients who receive a catatonia assessment - a telephone assessment identical to the 6 month neuropsychological battery will also be conducted 12 months after randomization. These patients will also receive a depression inventory (BDI-II) and a PTSD screening tool (PCL-5) at both 6 and 12 months.

[8] At select participating sites, and in a convenience sample of patients, we will connect patients to the noninvasive Root® patient monitoring and connectivity platform by Massimo for up to 7 days. This enables the monitoring of several physiologic parameters, including electroencephalography (EEG), cerebral oximetry,

and capnography with one portable monitoring platform. We will monitor the raw (EEG) and spectral analysis patterns of patients randomized to dexmedetomidine and propofol, using the portable SedLine Sedation Monitor through the Root® platform. The SedLine Sedation Monitor is a patient-connected, 4-channel processed EEG monitor. It displays electrode status, EEG waveforms, Density Spectral Array (DSA), and Patient State Index (PSI). It is intended to monitor the state of the brain by real-time data acquisition and processing of EEG. We will use the Masimo Rainbow SET® through the Root® platform to continuously measure additional blood constituents and physiologic parameter like the Oxygen Saturation (SpO_2) and the non invasive hemoglobin (Sphb). We will use the O3regional oximetry that uses near-infrared spectroscopy (NIRS) to continuously measure cerebral tissue oxygen saturation(rSO2) on the Root® platform. Finally, the Root® platform will allow the ISA^{TM} CO2 module for capnography monitoring, end-tidal carbon dioxide (EtCO2) waveform and measurements and trend of EtCO2, fractional concentration of inspiration of CO2 (FiCO2), and respiratory rate (RR). The research team and medical team will be blinded to the raw EEG and spectral analysis cerebral oximetry, and all other monitoring parameters which will be downloaded directly from the monitor to a USB port and then stored in the database. These evaluations will for the first time evaluate the EEG patterns and spectral analysis of critically ill septic patients on dexmedetomidine and propofol and provide insights into its relationship with sleep, delirium, coma, and long-term cognitive outcomes.

7.2.1 Study Drug Administration. Upon entry into the Interventional Trial, randomization will be carried out by the investigational pharmacist at each study center according to the randomization scheme provided by the study biostatistician. The pharmacist at each site will prepare and deliver study drug to the bedside nurse according to orders placed by study personnel at each site. Study drug will be titrated by the bedside nurse in accordance with the weight-based titration table (Table 2).

[1]   **Route and Concentration**. All study drug will be administered intravenously (IV) by continuous infusion at concentrations of 10 mg/mL propofol or 5 mcg/mL dexmedetomidine. Patients will only receive study drug while in the ICU and on mechanical ventilation, and thus will be monitored with continuous telemetry as per usual ICU practice.

[2]   **Dosing Range**. Study drug dose will be titrated in a double-blind manner according to clinical effect to achieve a "goal" or "target" Richmond Agitation-Sedation Score (Table 3) set by the managing clinical team (see **Titration** section below). For sites that do not utilize the RASS scale, the VCC will provide titration instructions using their local sedation-agitation scale. For patients in the propofol group, dose will range from 5-50 mcg/kg/min. For patients in the dexmedetomidine group, dose will range from 0.15-1.5 mcg/kg/hr. For example, a 70 kg patient would receive 10.5 mL of study drug per hour, which would provide either 25 mcg/kg/min of propofol or 0.75 mcg/kg/hr of dexmedetomidine. These dose ranges have been selected after literature review and discussions with critical care practitioners, investigational pharmacists, and the MENDS II study steering committee. [13, 35, 40, 132] Patient doses will be calculated based on each patient's enrollment weight, with no cap to the maximum weight. Table 2 includes the infusion rates for patients weighing 40-140kg; an additional titration table for patients >140 kg is available to sites from the VCC.

Table 2. Study drug concentration and weight-based titration table for 40-140kgs

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

Patient Weight (kg)	Infusion Rate (ml/hr)									
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

Propofol 1% Concentration – (10mg/ml)

Infusion Rate (ml/hr) = (Dose * 60 * weight) ÷ 10,000

Dexmedetomidine Concentration – (5mcg/ml)

Infusion Rate (ml/hr) = (Dose * weight) ÷ 5

[3] **Initiation**. No bolus dose of study medication will be allowed. Since most patients are already receiving sedation prior to enrollment this is often not required. The bedside nurse will initiate this infusion based on patient weight in kg starting at 5-15 mcg/kg/min propofol and 0.15-0.45 mcg/kg/hr dexmedetomidine. (see Table 2) starting at 5-15 mcg/kg/min propofol and 0.15-0.45 mcg/kg/hr dexmedetomidine.

[4] **Titration**. Study drug dose will be titrated every 10 minutes by the bedside nurse in mL/hr according the weight-based titration table (see Table 2) to achieve the RASS target (Table 3) set by the managing clinical team.

Table 3. Richmond Agitation-Sedation Scale (RASS)[129, 130]

+4	**Combative**	Combative, violent, immediate danger to staff
+3	**Very agitated**	Pulls or removes tube(s) or catheter(s); aggressive
+2	**Agitated**	Frequent nonpurposeful movement, fights ventilator
+1	**Restless**	Anxious, apprehensive but movements are not aggressive or vigorous
0	**Alert and calm**	
-1	**Drowsy**	Not fully alert, but sustained awakening to voice (eye opening & contact > 10 sec)
-2	**Light sedation**	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	**Moderate sedation**	Movement or eye opening to voice (but no eye contact)
-4	**Deep sedation**	No response to voice, but movement or eye opening to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

(a) <u>Titrating Up (undersedation: Patient RASS > Target RASS)</u>. If a patient's RASS is 1 or more levels higher than the Target RASS (e.g. patient RASS +1 & target RASS 0 or -1), study drug volume will be increased according to weight-based titration table (see Table 2) every 10 minutes in increments of 5 mcg/kg/min for propofol or 0.15 mcg/kg/hr for dexmedetomidine, until the maximum dose is reached (1.5 mcg/kg/hr dexmedetomidine or 50 mcg/kg/min propofol) or the patient reaches the target RASS.

(b) <u>Titrating Down (oversedation: Patient RASS < Target RASS)</u>. If oversedated (i.e., more than 1 RASS level deeper than ICU team's sedation target), **study drug** volume will be decreased every 30 minutes per the weight-based titration table (see Table 2) in decrements of 5 mcg/kg/min for propofol or 0.15 mcg/kg/hr for dexmedetomidine until the patient is within 1 RASS level of the target RASS. **Study drug** will be held if other sedatives have been held, study drug has been titrated to lowest volume (5 mcg/kg/min for propofol or 0.15 mcg/kg/), and the patient remains oversedated (i.e., more than 1 RASS level deeper than ICU team's sedation target) for >30 minutes.

(c) <u>Titrating Study Drug during a Spontaneous Awakening Trial (SAT)</u> (see section 7.2.2). Patients will be evaluated daily for readiness for a SAT by first evaluating patients with a SAT safety screen. In patients passing the safety screen, study drug will be held until patients show signs of failing the SAT indicating a need for sedation. Study drug that is held for the spontaneous awakening trial will be restarted, if needed, to the lowest possible infusion rate that is needed to achieve target RASS (see section 7.2.2).

(d) <u>Restarting Study Drug (with exception of restarting after SAT as outlined in section 7.2.1[4]c above)</u>. Study drug will be discontinued if a patient is liberated from mechanical ventilation, or if the managing clinical team determines the patient does not need ongoing sedation. If, however, at any time during the 14-day Treatment Period (starting from enrollment day, which is Trial Day 1, through Trial Day 14) a patient again requires sedative therapy and is still on mechanical ventilation, the study drug will be restarted according to initiation rules (see **Initiation** section <u>7.2.1[3]</u> above), as long as study drug was not discontinued permanently for safety reasons (see **Permanent Discontinuation** section 7.2.1[6] below). No study drug will be continued beyond Trial Day 14, irrespective of the duration of therapy within the 14-day Treatment Period.

[5] **Holding**. Throughout the treatment period, study drug may be temporarily held for the following reasons:

(a) <u>Hypotension.</u> If a patient's systolic blood pressure is <80 mmHg <u>and</u> 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. Since this is a study in severely septic patients, hypotension may occur frequently and will be monitored as a safety outcome.

(b) <u>New onset symptomatic bradycardia (<50 beats/minute and systolic blood pressure <80 mm Hg)</u>. Study drug may be held if deemed necessary by the

managing clinical team until atropine is administered and patients heart rate is >50 beats/min.

  (c). Oversedation despite titration to lowest study drug rate. Study drug may be held if patient continues to be oversedated (i.e., more than 1 RASS level deeper than ICU team's sedation target), all other sedatives have been held and study has been titrated to lowest volume (5 mcg/kg/min for propofol or 0.15 mcg/kg/) for >30 minutes, until patients RASS level is at target.

  (d) General anesthesia. Study drug may be held if patient is receiving general anesthesia for a surgical operation. Study drug may be held until the patient returns to the ICU setting and resumes sedation per ICU target sedation scale orders.

[6] **Permanent Discontinuation**. Study drug will be permanently discontinued at any time during the trial for any of the following safety reasons. Management of these conditions is left to the discretion of the medical team.

  (a) Second episode of symptomatic bradycardia (<50 beats/minute and systolic blood pressure <80 mm Hg) while on study drug. As described above in 7.2.1[5]b, study drug may be continued, titrated down or held during the first episode of symptomatic bradycardia, at the discretion of the medical team. Medical team would manage the bradycardia and once it resolves, study drug should be restarted, if it had been stopped. Symptomatic bradycardia that reoccurs while back on study drug will result in permanent discontinuation.

  (b) New onset 2nd or 3rd degree heart block. Degree of heart block should be confirmed with medical team or PI before discontinuation.

  (c) Serious allergic reactions to study drug as determined by the managing clinical team and principal investigator.

  (d) New onset coma due to a known structural brain disease such as stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema.

  (e) Suspected Propofol 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. These are considered severe clinical outcomes and tracked.

  (e) Any other study drug-related, life-threatening, serious adverse reactions.

  (f) Withdrawal from study drug treatment at the discretion of the principal investigator, the patient/family, or the attending physician.

In the event that study drug is permanently discontinued, the managing clinical team will be notified by study personnel, and may then order sedative/analgesia management per standard ICU sedation protocol.

7.2.2 Management Components.

[1] **Management of pain, rescue sedation, and the chemically paralyzed patient**. Patients will be monitored for pain using the Critical-Care Pain Observation Tool (CPOT), and intermittent boluses of 0.5-1 mcg/kg of fentanyl (or other standard of care opiates such as morphine or hydromorphone) or continuous fentanyl infusions will be permitted for analgesia as determined necessary by the managing clinical team. In circumstances where sedation target is not met with maximum study drug infusion, additional intermittent opiates (IV opiates such as fentanyl, morphine or

hydromorphone or po opiates) or continuous fentanyl may be used to help attain sedation target. Occasionally, despite maximum study drug and use of significant (4-5 mcg/kg/hr) continuous fentanyl, patients may still be undersedated; in these rare circumstances intermittent dose midazolam will be permitted and tracked. In the rare instance, when sedation is required beyond the 14 day Treatment Period, sedation will be administered per existing ICU protocol and tracked until hospital discharge, death or the end of the Post-Study Drug Period (whichever is earlier). Chemical paralysis is used in < 5% of patients in ICUs, and when needed, intermittent midazolam or continuous midazolam will be permitted and tracked, since dexmedetomidine may not provide adequate amnesia. Study drug will be reduced to the lowest infusion rate for the patient's weight according to the weight based titration table being used for the patient and maintained at this level during the time chemical paralysis is ongoing. Midazolam infusions that are started to provide amnesia during sustained chemical paralysis will be discontinued approximately one hour after discontinuation of chemical paralysis, while study drug will continue and management will be per titration rules. We expect our rescue protocol to minimize, and the randomization to balance the effects of these medications. Similarly intermittent midazolam or propofol will be permitted to provide amnesia when short-term muscle relaxation is employed during procedures e.g. bronchoscopies, tracheostomies, etc.

[2] **Delirium Protocol (ABCDE Protocol)**.[28, 133-136] During the Treatment Period, we will standardize and/or track components of ICU care that may influence delirium risk via an evidence-based non-pharmacologic protocol referred to as the ABCDE protocol. Study personnel will be well-trained with this protocol during the MENDS II startup meeting and compliance will be emphasized and tracked throughout the study. Local ICU nursing staff at each study center will receive a standardized educational packet that focuses on delirium recognition, risk factors, and prevention. When knowledge gaps are identified or compliance drops below 80%, as measured by daily compliance checks, additional education will be provided. The ABCDE protocol has 3 components:

(a) **ABCDE (Awakening and Breathing Coordination)**. Based on our "Wake Up and Breathe" protocol proven to improve outcomes, including one-year survival,[28, 136] the ABC component includes standardized SATs (i.e., daily interruption of sedation) paired with spontaneous breathing trials (SBTs),[137] both administered only when specific safety criteria are met. Study drug that is held for the spontaneous awakening trial will be restarted, if needed, at the lowest possible infusion rate that is needed to achieve target RASS. All study centers use validated sedation scales to facilitate goal-directed sedation, a practice that will continue throughout the MENDS II study. Ventilator management will be standardized according to each institution's approved protocols, including the use of low tidal volume ventilation for acute lung injury.[88]

(b) **ABCDE (Delirium monitoring and management)**. The Delirium component of ABCDE will include nonpharmacologic strategies, given that the majority of delirium in ICUs is the hypoactive subtype.[138, 139] The protocol includes nonpharmacologic strategies that have been shown to reduce delirium in non-

ICU settings[140-150] Study personnel will encourage members of the ICU team to perform the following tasks:

- Reorient and cognitively stimulate patients by conveying the day, date, place, and reason for hospitalization, updating whiteboards with caregiver names, requesting placement of a clock and calendar in the room, and discussing current events.[140-143, 145, 146, 148, 151-153]
- Determine need for hearing aids and/or eye glasses from the surrogate and request that the surrogate provide these to the patient when appropriate.[141-143, 145, 146, 148, 151, 152]
- Monitor and manage pain level in all patients daily with the CPOT or other assessments, in accordance with practice guidelines and local ICU policies.[93, 152, 154-157]
- Maintain sleep preservation using techniques including noise reduction strategies (e.g., minimize noise outside the room, offer white noise or earplugs), normalizing day-night variation in illumination, minimizing interruptions during normal sleeping hours via "time out" strategy, maintaining ventilator synchrony, and promoting comfort and relaxation (e.g., back care, massage, oral care, washing face/hands, and daytime bath).[141, 143, 145, 146, 151, 158-163]
- Patients with hyperactive (agitated) delirium (i.e. RASS +1 to +4 and CAM-ICU positive) will be permitted either per tube or intravenously haloperidol starting between 0.5-5 mg. Patients with either an allergy to haloperidol or in patients where the treating clinical team desires to use an oral atypical antipsychotic, quetiapine will be permitted as needed (prn) or scheduled with recommended starting doses of 25-50 mg and titration per primary team. All antipsychotic medication will be tracked in the database until the end of the combined Treatment/Post Study Drug Period, hospital discharge or death (whichever is earlier).

(c) **ABCDE (Early mobility and Exercise)**. The Exercise component of the ABCDE protocol will include strategies to promote mobility and exercise in the earliest phases of critical illness. Early physical/occupational therapy significantly reduced delirium duration for mechanically ventilated ICU patients in a recent randomized controlled trial.[133] Study personnel will encourage members of the ICU team, including the bedside nurses and physical/occupational therapists, to evaluate each patient's readiness for mobility and exercise and coordinate the following activities: removal of restraints, active range of motion, sitting on the side of the bed, sitting in a chair, standing in place, and ambulation. [133, 141, 145, 151-153, 164, 165]

(d) **Barriers and Facilitators to the ABCDE bundle**. At sites that would like to participate, critical care providers (i.e., nurses, respiratory therapists, pharmacists, physicians, occupational therapists [OT], and/or physical therapists [PT]) will be asked to complete a voluntary electronic survey (i.e., the ABCDE Bundle Provider Survey) designed to identify barriers and facilitators to the use of the ABCDE bundle. In addition, managers (e.g., nurse manager, respiratory therapy manager, and/or PT/OT manager) will be asked to provide details about key organizational structures and processes that

may influence a provider's ability to use the ABCDE bundle. Lastly, units will be observed for accessibility of equipment useful for applying the ABCDE bundle and unit layout. Both the manager evaluation and the unit observation will be accomplished utilizing the ABCDE Unit Observation and Manager Questionnaire. When barriers and facilitators are identified, this information will be provided to study personnel and/or managers at each site.

[3] **Sepsis and Mechanical Ventilation.** Management of sepsis and MV will be directed by standard ICU protocols based on the surviving sepsis guidelines.[15] The managing clinical team will dictate use of these guidelines according to patient need. Study personnel will track important determinants of care including: choice of antibiotic, vasopressor and inotrope use, and blood glucose levels.[15] Patients will be evaluated daily by the medical team as part of standard ICU protocols for readiness for SATs, SBTs, and subsequently extubation.

7.2.3 Monitoring. The risks of propofol and dexmedetomidine include oversedation, bradycardia, hypotension, acidosis, hypertriglyceridemia, hyperglycemia, adrenal insufficiency, and propofol infusion syndrome. Throughout the Interventional Trial Period, study personnel will carefully monitor all patients daily for evidence of these potential adverse effects, determine study drug efficacy and safety, and monitor other factors that may influence outcome. Should adverse effects occur, the above section (7.2.1) describes how study drug will be titrated, held, or permanently discontinued. Additionally, patients will be monitored for two full days following discontinuation of the study drug. This will be the Post-Study Drug Period and will be contained within the treatment period if study drug is discontinued prior to or on study day 12. For those patients that receive study drug for more than 12 days during the treatment period of 14 days, the Post-Study Drug Period will extend beyond the Treatment period.

[1] **Efficacy**. In addition to delirium, coma, and ventilator-free days, time-to-event outcomes including ICU length of stay and survival, will be assessed until the outcome in question or a censoring event occurs. Twice daily, while in ICU and once thereafter until end of Post-Study Drug Period, hospital discharge or death (whichever is first), study personnel will determine level of sedation using the RASS[129, 130] and assess for delirium using the CAM-ICU.[10, 11, 131]

[2] **Safety**. Patients will be monitored as part of routine ICU care for adverse clinical outcomes including but not limited to oversedation, bradycardia, hypotension, acidosis, hypertriglyceridemia, hyperglycemia, adrenal insufficiency, and propofol infusion syndrome. Additionally, study personnel will specifically assess patients for the following safety outcomes:

   (a) Triglycerides according to plasma level drawn on Trial Days 7 (or earlier if planned hospital discharge is before Day 7) and 14 (or earlier if planned hospital discharge is before Day 14).

   (b) Cortisol according to plasma level drawn on Trial Days 7(or earlier if planned hospital discharge is before Day 7) and 14 (or earlier if planned hospital discharge is before Day 14).

   (c) Arrhythmia and/or Heart Block according to telemetry or a12-Lead electrocardiogram while in the ICU until the end of the combined Treatment/Post-Study Drug Period.

(d) Hyperactivity or agitation according to daily RASS[139] until the end of the combined Treatment/Post-Study Drug Period (see section 7.2.2 for rescue protocol).

(e) Development of new cases of ARDS based on criteria described in 4.2.2 until the end of the combined Treatment/Post-Study Drug Period. All aspects of management of patient's ARDS will be determined by the medical team, including if deemed necessary, stopping of the study drug.

(f) Organ dysfunctions will be tracked until conclusion of the combined Treatment/Post-Study Drug Period using daily SOFA scores and continuous as well as established predefined cut offs for each organ failure: Kidney, $Cr > 2$ mg/dL or urine < 400 cc/day; Lung, $PaO_2/FiO_2 < 300$ or $SaO_2/FiO_2 < 315$;[119] Liver, total bilirubin > 2 mg/dL; Coagulation, Platelet count $< 100,000/mm^3$; and Hemodynamic, need for vasopressor,[120, 121] consistent with definitions utilized in published studies of organ dysfunction in critically ill patients.[122]

[3] **Biological specimens**. Plasma will be obtained on approximately Trial Days 1, 3, 5, 7 and 14. A maximum of 30 mL of blood will be collected at each time point (150 mL max during the study), processed, and stored at -80º C prior to being shipped to the Vanderbilt Coordinating Center biorepository for storage and batched analyses of the following:

(a) Genetic predictors of delirium duration, including, but not limited to, the apolipoprotein E4 polymorphism.[166-168]

(b) Inflammatory/coagulopathic biomarkers, (e.g., IL-1, IL-6, IL-10, CRP, sTNFR1, and HMGB1) based on their importance in sepsis and kinetic responses.[169-171, 171, 172, 172, 173, 173, 174, 174-177] Furthermore, combination of pro- and anti-inflammatory cytokine markers improves the predictive quality of these biomarkers for mortality.[178]

(c) Other biomarkers to be determined by ongoing and future studies.

(d) At select participating sites, the Cholinesterase Activity and DeliriUm during Critical illness Study (CADUCeuS) – a substudy within the MENDS II study will examine whole blood acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities as biomarkers for delirium during critical illness and for long-term cognitive impairment in survivors of critical illness. During the blood collection on study days 1, 3, 5, 7, & 14 AChE and BuChE activities in the collected blood will additionally be measured using ChE Check (LISA-CHE, Dr. F. Köhler Chemie [DFKC] Bensheim, Germany), a point-of-care device that reliably measures AChE and BuChE activities in whole blood within 4 minutes of specimen collection[194,195,196].

[4] **Delirium Experience and Baseline Chronic Pain Evaluation.** After resolution of delirium and prior to hospital discharge, patients will be asked to recall their memory and delirium experience using a modified Delirium Experience Questionnaire (DEQ) [193]. Additionally, patients will be asked about the presence of chronic pain prior to this hospital admission and any medications that were taken to manage that pain.

[5] **Other data**. The patient's medical records will be used during the In-Hospital Phase to collect vital signs and other data reflecting current severity of illness, recent and

ongoing treatments (including medications and mechanical ventilator status), routine lab results, and complications (e.g., infections and device removals). These data will be generated as part of routine care and will not require study-related tests.

7.3 **Long-term Follow-up Phase**. We will evaluate long-term outcomes among survivors (**Aim 2B**), including neuropsychological function and ADL/IADLs **6 months** after randomization. Under the direction of the Vanderbilt Coordinating Center's lead neuropsychologist, trained study personnel will assess patients using the following validated telephone assessments:

[1]   **Delirium** will be evaluated via the "phone" Confusion Assessment Method[179] algorithm. Patients diagnosed with delirium will not be assessed further at that time, but contacted at weekly intervals and tested if/when delirium resolves.

[2]   A **neuropsychological phone battery**[118] derived from standard cognitive tests and proven feasible and valid for phone use in a study of ICU survivors (with similar characteristics to those targeted for enrollment in the MENDS II study) will be used to assess memory, attention, reasoning, and executive functioning.

[3]   **Activities of Daily Living (ADL)**[116] and **Instrumental ADLs (IADLs)**[117]

[4]   **Quality of Life** will be assessed using the **EQ-5D**, a short, easy to administer, well-validated, and widely used instrument.[180-182]

[5]   **Brief Pain Inventory Short Form (BPI)** [183] will be used to assess patients for the presence of chronic pain. The BPI is one of the most widely used measurement tools for assessing clinical pain and consists of 9 questions, taking only a few minutes to complete. In addition to examining prevalence of chronic pain and chronic pain interference in ICU survivors, we will utilize the BPI to identify potential risk factors (e.g., sedative and analgesic exposure in the hospital) for chronic pain after critical illness.

In addition to the battery described, data will be collected regarding intervening events that happened since hospital discharge including, but not limited to, death and re-hospitalizations. Vital status at 6 months after randomization and date of death (if applicable) will be determined via medical records or the Social Security Death Index if not already known at hospital discharge.

7.3.1   Long-term Follow-Up Patient Retention Plan. In order to maximize full 6-month participation of the randomized patients, the Long-Term Follow-Up Committee will rely on strategies refined over the past 10 years to produce a Follow-Up assessment rate of >85%. Study personnel will be instructed to obtain as much contact information as possible at time of enrollment (e.g. multiple phone numbers, mailing addresses, discharge destination, etc.). The Neuropsychology Coordinator will perform the following interventions to maintain >85% Follow-Up assessment rates:

[1]   Following hospital discharge a letter will be sent to patients reminding them about the Follow-Up Period and introducing them to the Follow-Up staff.

[2]   A periodic phone call, letter, postcard, or email will serve as an additional reminder of study participation.

[3]   Weekly meetings will be conducted with study staff to evaluate the status of follow-up evaluations, with a particular focus on devising and implementing effective strategies to reach patients who may be difficult to contact.

7.4   Data Collection/Case Report Form Details. During all study phases, all data will be directly entered into electronic case report forms (eCRFs) in a secured password-protected database with the exception of the Pre-Hospital Function Assessment and the assessments in the Long-Term Follow-Up Assessment, which will be collected on paper CRFs (due to copyright restrictions) and later entered into the eCRFs for storage in the secured password-protected database. Additionally, all signed Informed Consent Documents will be uploaded to the study database. This will allow the VCC ready access to review the consent forms for appropriate version use and completeness. This study will utilize Research Electronic Data Capture (REDCap) for data collection, transmission and storage. REDCap is a secure, web-based application for building and managing online databases. Vanderbilt University, with collaboration from a consortium of institutional partners, including the Vanderbilt Institute for Clinical and Translation Research (VICTR) Informatics Core, developed and manages a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. All study data will be entered via a password protected, study unique REDCap database website. REDCap servers are housed in a local data center at Vanderbilt and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended by both the Vanderbilt University Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports > 140 academic/non-profit consortium partners and 11,000 research end-users (www.project-redcap.org).

7.5   Schedule of Events

*Variable	Enrollment	Treatment Period & Post-Study Drug Period	6 Month Follow-up	12 Month Follow-up
Pre-Hospital Function Assessment (ADL,[116] IADL/FAQ,[117] IQCODE,[123, 126-128], AUDIT)	X			
Demographics, Comorbidities[184],APACHE II[185]	X			
SOFA[120, 186]	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*[194,195,196] (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),[129, 130] CAM-ICU[10, 11]		1-2x daily		
Bush Francis Catatonia Rating Scale (BFCRS), and Delirium Motor Subtype Scale (DMSS) *at participating sites*		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[193] and Chronic Pain Questions		X	
Long-term telephone follow-up: CAM,[179] neuropsychological battery,[118] ADL,[116] IADL/FAQ,[117] EuroQOL quality of life (EQ-5D)[180-182], BPI[183]			X
Catatonia Patients ONLY: At both the 6 and 12 month follow-up dates, patients will be assessed with the long-term telephone battery along with the BDI-II and PCL-5.			X	X

Abbreviations (alphabetical): **AChE-** acetylcholinesterase **ADL-** activities of daily living, **APACHE II-** Acute Physiologic Chronic Health Evaluation II, **AUDIT-** Alcohol Use Disorders Identification Test, **BDI-II** – Beck Depression Inventory II, **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, **PCL-5 -** PTSD Checklist, **RASS-** Richmond Agitation Sedation Scale, **SOFA-** Sequential Organ Failure Assessment, **sTNFr1-** soluble TNF receptor 1

7.6   The Vanderbilt Coordinating Center (VCC). The VCC has extensive experience in the conduct of large, phase III clinical trials over the past decade. The VCC will perform (among other functions) the following: communicate with the FDA using a schedule of reporting in accordance with IND policies, design the database and data collection tool, conduct startup meetings and site-training regarding protocol implementation and delirium monitoring to standardize all research activities during the trial, monitor enrollment pace and quality to ensure patients meet the inclusion/exclusion criteria, maintain blinding, track adverse events and ensure safety reporting, ensure protocol compliance, store plasma, serum, and genetic samples for planned and future analyses, conduct follow-up phone testing of neuropsychological function and quality of life via neuropsychology technicians, and work with the study centers and local study personnel using multiple proven patient retention techniques that have consistently achieved over 80% follow-up during previous studies.

8.0   Risks of Investigational Agents/Devices (side effects)

8.1   Side Effects of Study Drug (Propofol and Dexmedetomidine). The risks of the sedative medications include oversedation, hypotension, bradycardia, acidosis, triglyceridemia, propofol infusion syndrome, and adrenal insufficiency. Study personnel will carefully monitor all patients for evidence of potential adverse effects from the study drugs until conclusion of the combined Treatment/Post-Study Drug Period. These assessments are described in section 7.2.3. Should any of these occur, adverse events will be reported to the coordinating center, with Adverse Events reported within 24 hours (see section 9.0). From an immediate clinical management perspective, section 7.2.2 describes how study drug will be titrated, held, or permanently discontinued, depending on the adverse effect.

8.2   Risks from Blood Draws. All patients will have blood drawn for research purposes. The risks of drawing blood are uncommon and may include bleeding and bruising. Commonly, having blood drawn is painful and rarely can lead to infection at the site of the blood draw. For this reason, it will be our standard approach whenever possible to obtain the majority of blood for research purposes through existing intravenous peripheral, central or arterial catheters since these patients routinely have such catheters while in the ICU. Rarely the AChE and BuChe testing[194,195,196] will require a finger stick to be performed. The amount of blood drawn for

biological specimens is minimal, represents a small percentage of the amount of blood taken during the course of a standard ICU stay, and will not represent a significant risk to the patient.

8.3   Risks from ECG and SedLine Sedation Monitoring. As mentioned above an ECG may be done to evaluate heart rhythms and heart block. The ECG electrode pads may cause skin irritation. While it is rare, there may also be local allergic reactions and/or skin tears from the SedLine Sedation Monitor sensors. This study staff will monitor the skin condition daily when using the sensors.

8.4   Steps Taken to Reduce Risks and Increase Impact of Study. The following are a highlighted "top ten" list of actions we have explicitly taken to minimize risk for the study population and to maximize the ultimate impact of this investigation on the field of medicine.[187]

[1]   Interventions included in the MENDS II study are supported by a well-grounded and clearly described rationale suggesting potential, though unproven, benefit for eligible patients.

[2]   All interventions are common and with established equipoise within the context of usual care and considered good or competent care in light of an absence of clear proof in favor of one over the other.

[3]   Experts in the fields of critical care, neuropsychology, nursing, pharmacology, and clinical trial design have developed the interventions being studied.

[4]   The management of patients in both treatment groups will be guided by explicit MENDS II protocols so that the results of the trial can be clearly interpreted and imitated, where appropriate, in clinical practice. This will also allow for the use of the "superior group" as a control in future trials.

[5]   The MENDS II protocol will adjust study drug dose to meet individual patient needs in the attempt to deliver safe and effective care to critically ill old and younger patients. This protocol is explicitly designed and drafted from landmark trials to meet patients' needs over time and provide individualized care.

[6]   The titration protocol for study drug and the management components for pain, rescue sedation, and hyperactive delirium are designed to minimize risks in comparison to anticipated benefits.

[7]   Because most previous comparator trials of either dexmedetomidine or propofol versus benzodiazepines have shown superior outcomes with dexmedetomidine and propofol, no benzodiazepine control arm was included, to safeguard patients from receiving sedative agents whose use is on the decline.

[8]   An independent and qualified Data Safety Monitoring Board (DSMB) will be established (see **section 9.5.1, 9.5.2 and 9.5.3.**) to review the research protocol prior to the start of the study and conduct interim analyses for safety and review data on serious adverse events as close to real-time as possible.

[9]   We will work very closely with the regulatory authorities including our IRB and the FDA to make certain that this proposal is safe and that they agree with our planned oversight and approach to due diligence in monitoring and reviewing all adverse events during the conduct of the trial. The FDA-IND for this study is #68658.

[10]   Rigorous monitoring and reporting of prospectively defined Adverse Events (AEs) including Suspected Unexpected Serious Adverse Reactions (SUSARs) and unexpected problems (UPs) will be conducted as outlined in **section 9.2 and 9.3,** to comprehensively monitor safety during the trial.

9.0   Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

A system has been established to report and track clinical outcomes, (AEs) including SUSARs and UPs that increased risk. Study personnel will monitor the safety of subjects and follow them until the event resolves or is explained.

9.1   Clinical Outcomes (not considered Adverse Events). In this study of critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, clinical outcomes including death and organ dysfunction, will be systematically tracked (collected in the CRF) and will be included as part of the safety and efficacy analyses for this study. For the purposes of reporting, death and organ dysfunction will not be recorded as adverse events unless the investigator believes the event may have been caused by study drug and is more severe or prolonged than expected given the underlying critical illness (investigator's discretion). This approach (considering death and organ dysfunction as outcomes rather than adverse events) is common in ICU trials because these outcomes occur commonly in the ICU and because it mandates that data regarding death, organ dysfunction, and expected safety outcomes be tracked systematically for all patients and analyzed appropriately. All clinical outcomes (with the exception of death and duration of MV- **see 9.1.1 and 9.1.2 below**) will be systemically tracked until conclusion of the combined Treatment/Post-Study Drug Period, i.e., they will be tracked from randomization until Study Day 16 at a maximum, hospital discharge, or death, whichever comes earlier. Listed below are events that will be tracked as clinical outcomes and will not therefore be required to be reported as adverse events during this study (unless believed to be study-drug related and more severe or prolonged than expected given the underlying critical illness):

[1]   Death. All deaths occurring within the Interventional Trial will be reported on the CRF in the death summary section. For deaths thought to be caused by study drug, an AE/SUSAR will be reported along with the death summary

[2]   Respiratory failure, including need for MV (invasive or noninvasive) or episodes of hypoxemia. Duration of MV will be tracked for up to 28 days to evaluate VFDs

[3]   Circulatory failure, including shock (whether requiring vasopressors or not) and cardiac arrhythmias, and hypo/hypertension

[4]   Hepatic failure or injury leading to increased bilirubin, AST, or ALT

[5]   Renal failure or injury leading to an increased creatinine or acute hemodialysis

[6]   Coagulation derangements (e.g., thrombocytopenia)

[7]   Neuropsychological dysfunction that is believed to be newly acquired

[8]   Alterations in vital signs (e.g., temperature, heart rate, blood pressure, oxygen saturation)

[9]   ICU readmissions

[10]   Infections

[11]   Alterations in routine safety labs (e.g., liver function tests, creatine kinase, creatinine, cortisol, triglyceride, and lactate).

[12]   The following known adverse reactions to propofol and/or dexmedetomidine:

(a) bradycardia

(b) tachycardia

(c) hypotension

(d) hypertension
(e) triglyceridemia
(f) sedation
(g) respiratory depression
(h) lactic acidosis
(i) cardiac rhythm disturbances
(j) propofol infusion syndrome

9.2　Adverse Events (AEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), and Unanticipated Problems (UPs)

[1]　**Adverse Event (AE)** is defined as any untoward medical occurrence for a patient enrolled in the trial that is not tracked as a clinical outcome (see **section 9.1**), regardless of whether the event is considered study drug-related or not. If a subject experiences an AE after informed consent is signed but before receiving study drug, the event will be reported as an "AE not study drug related." Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s). During the study, site personnel will note changes in these condition(s) and/or the occurrence and nature of any AEs. All AEs occurring after consent and until the end of combined Treatment/Post-Study Drug Period, hospital discharge, or death (whichever comes first) will be recorded in the database. This period is the window of time during which study drug-related adverse reactions are expected based on the duration of the Treatment Period and the Post-Study Drug Period. An AE that later meets criteria for an UP or SUSAR between the start of study drug and hospital discharge will be reported as an UP or SUSAR. If study drug is discontinued as a result of an AE, study personnel will document the circumstances leading to discontinuation of study drug. In cases where the investigator notes an unanticipated benefit to the subject, study site personnel will enter "unanticipated benefit" with the actual event description (e.g., "unanticipated benefit - sleeping longer").

　　All AEs will be evaluated for the following three criteria: relatedness to study drug, expectedness, and seriousness. An AE will be considered serious if it results in any of the criteria below (regardless of whether it is deemed study drug related):

(a)　Life-threatening condition with immediate risk of death within the context of a patient's event (i.e., a well-tolerated bradyarrhythmia is not an SAE, whereas the same rhythm resulting in cardiac arrest and CPR is an SAE)

(b)　Inpatient hospitalization or prolongation of existing hospitalization

(c)　Persistent or significant incapacitation or substantial disruption of the ability to conduct normal life functions

(d)　Significant hazard, contraindication, or side effect according to the PI

(e)　Any breech in the confidentiality of patient's data

(f)　Investigators will determine whether an AE is related to study drug based on a temporal relationship to administration, as well as whether the event is unanticipated and unexplained given clinical course, previous conditions, and concomitant medications.

[2]　All AEs that are (1) suspected to be study drug related, (2) unexpected, and (3) meet any of the following seriousness criteria must be reported as **Suspected Unexpected Serious Adverse Reactions (SUSAR)**:

(a) Death
(b) A life-threatening episode requiring immediate intervention
(c) An event resulting in hospitalization or that prolongs existing hospitalization
(d) Events resulting in persistent or significant incapacitation or disability
(e) An episode that requires intervention to prevent the above and/or permanent impairment or damage

[3] **Unanticipated problems (UPs)** are defined as any incident, experience, or outcome that meets all of the following criteria: unexpected, related or possibly related to participation in the research; and suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized. UPs may result in adverse events and they may not. Protocol noncompliance that results in harm to a patient would be both a UP and AE whereas protocol noncompliance that increased risk to a patient but did not result in harm would only be classified as a UP that increased risk.

9.3 Communication and Reporting of Adverse Events and Unexpected Problems with Coordinating Center and Regulatory Bodies.

In order to ensure proper and timely reporting of all AEs and UPs, there will be a clear communication plan for all sites to follow. Sites will be responsible for reporting all AEs and UPs that increased risk to patients to the VCC; they will also follow their local IRB policies to determine when AEs and UPs should be reported to the local IRB. The VCC will be responsible for reporting the events to the proper regulatory bodies (i.e., FDA, NIH, DSMB, and Coordinating Center IRB) in a timely manner and in communicating any responses from those bodies back to the sites. The procedures for reporting the various events will be as follows:

[1] **SUSARs**. In the event that a SUSAR occurs the study drug should be permanently discontinued immediately. The event will be recorded in the patient's study chart in the electronic database. All SUSARs will be reported to the VCC within 24 hours of occurrence by telephone call. As required, VCC will report the event within 48 hours to the DSMB Chair. The DSMB report will be due and sent to the Vanderbilt IRB and NIH within 7 days. When the DSMB Chair/DSMB suspects an event is study-drug related, they will have the opportunity to access unblinded data in order to conduct appropriate safety monitoring. There should be no need for the site investigators to be unblinded since the study drug should have been stopped at the time of event occurrence per titrating rules of the study protocol. The DSMB Chair will work in concert with the rest of the DSMB to determine if any necessary actions need to occur as result of the event in order to increase the safety of the protocol. If the Data Safety Monitor or the DSMB suspect an imbalance between the SUSARs in the study groups, they will have the right to convene a full DSMB meeting and have access to other supporting data to determine safety and ongoing conduct of the study, without having to wait for the set meetings annually and N=236 as discussed in 9.5.3.

[2] **UPs.** All suspected UPs that possibly increase the risk to patients will be recorded in the patient's study chart in the electronic database, reported to the site IRB within 5 days of occurrence, and reported to the VCC within 5 days of occurrence. Any of these reports that the site IRB determines to meet the OHRP definition of UP and thus the requirement for reporting to the OHRP, will subsequently be reported by

the VCC to the DSMB within 15 days of receipt of the site IRB notification and to the NIH within 30 days of receipt of the site IRB notification.

[3] **All remaining AEs** (i.e., AEs that are not SUSARS or UPs) will be recorded in the patient's study chart in the electronic database and reported to the VCC within 5 days of occurrence. As required, the VCC will provide a batched report of all study wide AEs annually to each regulatory body as part of the annual review process.

9.4   Data Monitoring Plan. To ensure data is accurately and completely collected during the MENDS II study, the VCC will follow a specific Data Monitoring Plan modeled after the FDA's guidelines for the monitoring of clinical investigations. Once each year, a VCC member will visit each study site to assure that the facilities continue to be acceptable for the purpose of the study, the study protocol is being followed, changes to the protocol have been approved by the local IRB, and the site investigator is carrying out the agreed-upon activities and has not delegated them to other unspecified staff. Also, the monitor will review subject records to determine whether data collected is accurate, complete, and current. Per the FDA guidelines, the monitor will compare *a representative number* of subject records and other supporting documents with the investigator's reports. Specifically, site visits will include the following:

[1] A **Technical Review** will occur annually and will consist of a VCC research nurse examining the quality and accuracy of data, regulatory documents and drug accountability. Data quality and accuracy will be reviewed through a CRF data and source document review. The monitor will randomly select three subjects (or 10% of the subjects enrolled since the last site visit, if more than 30 were enrolled in that time) to serve as a representative sample. Regulatory Document Review will consist of a review of IRB approvals, informed consents, critical documents, and protocols/amendments.

[2] A **Scientific Review** will occur at the discretion of the VCC as needed and could consist of presentations by the site staff on their organizational structure, patient recruitment, and staff training, and quality control procedures. The site monitoring team will include a VCC research nurse as well as the MENDS II Principal or Co-Investigator (alternating).

The site monitoring reports from these reviews will be submitted to the DSMB and other regulatory bodies (IRB, FDA and NIH) as requested and/or required. Data accuracy reports (including site comparisons) as well as site monitoring updates will be presented to the VCC. This Monitoring Plan will serve as a method for identifying systematic problems and provide a means in which to institute resolution and follow-up and therefore increase data quality.

9.5   Data Safety Monitoring Board (DSMB)

9.5.1   Membership. The DSMB will include 5 independent members (3 members will constitute a quorum) who are not study investigators and have no financial, scientific, or other conflict of interest with the trial; written documentation attesting to absence of conflict of interest will be required. Potential members will be chosen by the MENDS II steering committee and study PI in discussion with the NHLBI Program Official. The PI will recommend experts/representatives from the following fields as potential members of the DSMB: **critical care medicine, ethics, clinical trial methodology, and biostatistics**. A chairperson will be selected and will be responsible for overseeing meetings, developing agendas in consultation with the PI, and being the contact person for the DSMB.

9.5.2   Initial Meeting. Prior to the initiation of the trial, the DSMB will meet and review the entire IRB-approved study protocol with regard to subject safety, recruitment, randomization, intervention, data management, quality control and analysis. If the protocol is deemed satisfactory by the DSMB, they will recommend to the VCC that subject recruitment begin. If, alternatively, modifications to the protocol or other study documents are needed, the DSMB will recommend such modifications and postpone its recommendation to begin recruitment. This initial meeting may occur via conference call or in person and will begin with an introduction by the PI and VCC Co-Investigator, then continue as a closed session, including only DSMB members and (if available) NHLBI program staff.

9.5.3   Additional Meetings. The DSMB is responsible for identifying problems related to safety (including all AEs/SUSARs), requesting additional data relevant to safety (including all AEs/SUSARs), proposing analyses of safety endpoints as needed, and considering the rationale for continuation of the study in light of safety data, progress of randomization, retention, protocol adherence, and data management. After the initial meeting, the DSMB will meet at the end of each calendar year for annual safety reviews and also at the specified interim analyses (at N=236, see section 11.4, for detailed description). Reports of AEs and SUSARs for the interim look at the data will initially be provided to the DSMB in a blinded fashion (i.e., treatment group assignment will not be revealed), but the DSMB will retain the right to request an unblinded report. Only DSMB members will have access to unblinded data in order to preserve the integrity of data and minimize potential for bias while maintaining appropriate safety monitoring. After each DSMB meeting, the chairperson will provide a written report to the VCC and the NHLBI program official. In addition, the VCC, in turn, will provide the reports to the Vanderbilt University IRB and to all sites for submission to their local IRBs.

10.0   Study Withdrawal / Discontinuation. Subjects may be withdrawn from study participation at the discretion of the investigator or if the patient/family or attending physician requests that the subject be withdrawn. The reason and date of every withdrawal will be recorded. The Informed Consent Document will notify participants that their participation is voluntary, and they can tell the study staff at any time if they decide to stop participating. In addition, if they choose to withdraw their authorization for study staff to access protected health information (PHI) in the medical record, they may do so by notifying study staff in writing (the address is provided). If a participant chooses to no longer participate but does not notify study staff that they withdraw authorization for access to PHI, their medical record may be accessed to obtain outcomes and safety data. Follow-up will be performed for all discontinuations due to an SAE or other safety concern until resolution, until deemed chronic and stable, or as long as clinically appropriate. Data and specimen destruction will be over seen by the Vanderbilt Coordinating Center for patients that withdraw from the study and want to have their data and specimens destroyed.

11.0   Statistical Considerations

11.1   Power analyses and sample size calculations for Aim 1A (DCFDs). Based on the demographic data from our NIH-sponsored BRAIN-ICU cohort, we anticipate patients in the MENDS II control group will have a mean±SD of 6.8±5.2 DCFDs during the 14-day study period. The study has been repowered/resized due to concerns about the feasibility of completing study enrollment. With approval from the DSMB, we will randomize at least 210

patients in each group to receive study drug, and with a 2-sided alpha of 0.05, we will have 85% power to demonstrate a difference of 1.5 DCFDs between dexmedetomidine and propofol (primary outcome), which we believe has face validity as a <u>clinically meaningful difference in the duration of acute brain injury</u>. **Importantly, this sample size will also provide 80% power to detect a 12% 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 lorazepam group). The ability to detect a 12% improvement in 90-days mortality is also realistic given the 25% absolute reduction in mortality at 28 days in the MENDS septic subgroup with dexmedetomidine. In order to achieve this sample size of at least 420 patients enrolled, randomized and receiving study drug, we will randomize approximately 440 in order to account for disqualifications post randomization.

11.2   Power Analyses for Long-Term Cognitive Impairment (Aim 2B). We expect to follow ≥80% of survivors for evaluation of LTCI. Based on the expected mortality rates (see above), we expect an overall 25% mortality across the two groups and plan 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.

11.3   Data Analysis Plan. To determine the effect of the two sedative regimens on DCFDs and other continuous outcomes, we will use the Mann-Whitney test (Wilcoxon rank-sum tests). For ICU LOS, and 90-day mortality, Kaplan-Meier curves and log-rank test will be used, while censoring patients at time of death. We will perform sensitivity analyses using multivariable regression to adjust for imbalances in baseline factors; linear regression will be used for DCFDs and Cox regression for time-to-event outcomes (ICU LOS, mortality). Proportionality assumptions for Cox regression will be assessed using partial residual plots. No adjustments will be made for multiple comparisons when examining secondary outcomes in keeping with authoritative recommendations[188-190] and standard practice in analyzing multiple, prospectively defined outcomes in a trial.

11.4   Interim Examination of Results by DSMB. In addition to the final analysis of 420 randomized patients who received study drug, we plan yearly safety reviews and then one interim analysis at 300 patients by the DSMB. The yearly safety reviews will only review protocol compliance, collated adverse event reporting, selected outcomes (excluding the primary outcome) and quality control. At N=236 patients (~118 patients per group), we will conduct data analysis for early stopping due to safety and efficacy based on DCFDs and mortality outcomes. Using the O'Brien-Fleming method[191, 192] (adjusting for two planned analyses at N=236 and 420) with a 2-sided significance level at 5 %, the study will be stopped early if test statistics reach a critical value (standardized Z score) of ± 2.76 (corresponding to p-value of 0.006) at the interim analysis of 236 patients. Statistical significance at the final analysis will be referred by a critical level of 1.976 or 2-sided significance level of 0.044.

11.5   Intention-to-Treat (ITT) Principle and Missing Data. For all primary analyses, we will employ intention-to-treat (ITT) (see section 4.2.1). When data cannot be collected, we will

impute missing variables via multiple imputation methods. For Aim 2B, missing data are common due to deaths and loss to follow-up. While our team has a proven track record of achieving high follow-up we will carefully analyze whether particular baseline demographics are associated with missing evaluations of long-term testing among ICU survivors. Loss due to deaths is not random and may be associated with more severe cognitive or functional deficits among those not tested, which will likely bias towards the null.

11.6 Statistical Meetings. The VCC will work regularly with our statisticians at the ongoing weekly biostatistics meetings. Final analyses will occur during the last 6 months of the study period, when monitoring, quality checks, data lock, archiving and manuscript preparation will take place.

12.0 Privacy/Confidentiality Issues

At no time will we reveal subject identities in any manner, whether in presentation, description or publication of the research for scientific purposes. All data obtained with subject or provider identifiers will be kept in locked file cabinets to ensure confidentiality, and all paper file contents will be shredded before disposal. All subjects will be assigned a unique study number for use in the computer database, and all electronic data will be kept in password-protected computer files to ensure confidentiality. All biological specimens (serum, plasma, and DNA samples), maintain for batched assay after trial completion, will be stored in a locked –80 °C freezer and labeled with date and study ID# only, without any patient identifiers. These samples will be accessible only to designated co-investigators. Results of the specified laboratory tests will be maintained in a password-protected database to be accessed only by designated co-investigators.

Most data will be collected from medical records or direct assessments and entered directly into the study database via electronic case report forms (eCRFs). Paper CRFs will be used for baseline dementia, quality of life, and follow-up neuropsychological battery (some require copyrighted forms). Once collected on paper, data will be directly entered into the database. The study will utilize a centralized database located on Vanderbilt's secure REDCap database system.

Access to the database will be secured by **two layers of passwords:** <u>First</u> the staff must access the trial based website and <u>only then</u> will they be able to access the link to the database *via another password*. Each study site will only have access to their local study patients' data. **Only the Coordinating Center will have access to all the patient data.**

13.0 Follow-up and Record Retention

13.1 Duration of Record Retention. Information stored in the database will be stored for an indefinite period of time for future reference, including for use in subsequent data analyses. Throughout the study, all collected data will be entered directly in to the secure password-protected web-based database.

13.2 Method for Indefinite Archival of Information. Biological specimens will be stored for an indefinite period of time for use in future studies (as described in the informed consent document). Because genetic markers of risk for delirium and other study outcomes are not currently known, storage of specimens for later research use is required to advance this

knowledge of ICU delirium. It is our hope that polymorphisms will eventually be identified that will help us better understand the pathogenesis of delirium and patients' response (or lack thereof) to therapy. When such information is available, it would be invaluable to have a bank of genetic samples available for testing that can be coupled with a comprehensive set of clinical data such as the database being collected in this investigation.

13.3   Timeline and Duration of Study. As shown in **Figure 7**, the study is planned to last 7 years and recruit and randomize approximately 440 patients into the Interventional Trial (i.e., clinical trial). We will begin with a 6-month start-up, during which the VCC will continue to work diligently with each site through weekly calls, start-up meetings, and the ongoing processes with regulatory authorities (e.g., NIH, FDA, DSMB, and IRBs) to solidify infrastructure and begin enrollment. Recruitment will be completed over 60-66 months with an additional 6 months of follow-up; each site is expected to consent and randomize approximately 25 patients per year. During recruitment and testing, VCC will diligently monitor data collection (see section **9.4**), conduct data cleaning, conference calls, in-person meetings with study personnel at all sites to ensure compliance, and overall efficiency of study implementation. We will also work regularly with our statisticians to execute the planned analyses. The final analyses will occur during the last 6 months of the study period, when monitoring, quality checks, archiving and manuscript preparation will take place.

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