**Nighttime dexmedetomidine for delirium prevention in non-mechanically ventilated patients after cardiac surgery (MINDDS): a single-centre, parallel-arm, randomised, placebo-controlled superiority trial** *(Qu et al.)*

## SUPPLEMENTARY APPENDIX

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## SUPPLEMENTARY APPENDIX 1. MINDDS Study Investigators

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**SUPPLEMENTARY APPENDIX 2. Detailed Study Protocol**

**Minimizing ICU neurological dysfunction with dexmedetomidine-induced sleep (MINDDS): A randomised placebo-controlled trial**

**Principal Investigator:** Oluwaseun Johnson-Akeju, M.D., M.M.Sc

**Version:** 12/15/2020

## 1. BACKGROUND AND SIGNIFICANCE

Delirium is an acute brain dysfunction characterised by disturbances in attention, awareness, and cognition not explained by a pre-existing neurocognitive disorder.[1] Although the increased mortality rates ascribed to delirium remain debatable, delirium remains a leading cause of preventable morbidity in hospitalised elderly patients. It is also associated with prolonged hospitalisation, prolonged institutionalisation, and long-term cognitive deficits.[2-7] Patients with pre-existing dementia, such as Alzheimer's disease, are especially vulnerable to developing delirium.[8] The total healthcare cost attributable to delirium is estimated between $143 and $152 billion annually.[9] In the United States, delirium occurs in approximately 80% of critically ill patients admitted to medical/surgical intensive care units (ICU),[10] and 15% of patients admitted to cardiac surgical (CS) ICU.[11] Most patients diagnosed with delirium also present with multiple comorbidities (sepsis, multi-organ failure) that significantly confound our understanding of this disease.[2] Thus, to date, no pharmacological intervention to treat delirium has been identified.[2] The aging process has been identified as a risk factor for developing delirium.

Normal aging is associated with a morphological shift of glia (microglia, astrocytes) to an activated state. Following a systemic challenge such as critical illness, these activated glia aid a neuroinflammatory state that contributes to delirium. The aforementioned neuroinflammatory state is exacerbated by sleep disturbances.[15-17] Thus, sleep deprivation may be a modifiable risk factor for the development of delirium. Presently, pharmacological treatment with no current medication (benzodiazepines, antipsychotics) induces natural sleep or reliably reduces the incidence of delirium. **We have found that pharmacological induction of rapid eye movement sleep (REM) and non-REM I-III sleep states using dexmedetomidine, can now be safely achieved in humans**. Our overall objective is to evaluate the efficacy of dexmedetomidine-induced sleep in preventing delirium, investigate cellular and molecular mechanisms underlying delirium, and investigate whether recently described intraoperative electroencephalogram (EEG) signatures of the aging brain are associated with developing delirium.[18] Our central hypothesis is that nightly biomimetic sleep in elderly patients admitted to the CSICU for > 24hrs will reduce the incidence of ICU delirium.

Our intervention and control groups will be comprised of extubated CSICU patients, because their homogeneity in terms of surgical procedures, anaesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients found in the medical/surgical ICU. We will perform assessments of cognition (peri-operative), obtain EEG recordings (intra-operative, ICU) and blood samples (peri-operative).

At the conclusion of these studies, we will have expanded our knowledge of the pathophysiology of delirium, evaluated a new pre-emptive therapeutic strategy for delirium, suggest neurophysiologically based monitoring strategies to reduce significantly the amount of anaesthetic administered to elderly patients – and possibly delirium – while being certain the patient is sufficiently unconscious for surgery (individualised anesthesia care), and enable continued investigation into the pathophysiology of this clinically important disorder.

## 2. SPECIFIC AIMS

We will pursue three aims. In the first aim, we will investigate the benefits of pre-emptive biomimetic sleep for reducing the risk of developing delirium in a randomised controlled trial; in the second aim, we will investigate the mechanisms of delirium using serum metabolic profiling; and in the third aim, we will investigate power spectral analyses of intraoperative and CSICU electroencephalogram dynamics.

**Table 1** shows a proposed timeline.

| Table 1: Planned Schedule | | | | | | |
|---|---|---|---|---|---|---|
| **Hypothesis** | **Short Name** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| 1·1 | Nightly pre-emptive biomimetic sleep will reduce the incidence of delirium | .. | .. | .. | | |
| 2·1 | Serum metabolic profiling will be sensitive to detect neurodegeneration of preclinical delirium | | | .. | .. | |
| 3·1 | Absence of anesthesia-induced frontal alpha oscillations will be associated with delirium | | | .. | .. | .. |
| 3·2 | Burst-suppression/anesthesia overdose will be associated with delirium | | | .. | .. | .. |

The specific aims of this study are:

**AIM 1: Investigate the benefits of pre-emptive biomimetic sleep for reducing the risk of delirium in a Randomised Controlled Trial.**

Hypothesis 1·1. Compared to standard treatments (benzodiazepines, antipsychotics), nightly pre-emptive biomimetic sleep will reduce the incidence of ICU delirium.

**AIM 2: Investigate mechanisms of delirium using serum metabolic profiling.**

Hypothesis 2·1. Unbiased metabolic profiling will be sensitive to detect early signatures of neurodegeneration that predisposes to the development of delirium.

**AIM 3:** Investigate power spectral analyses of intraoperative and CSICU electroencephalogram dynamics.

Hypothesis 3·1. The relative absence of anesthesia-induced frontal alpha oscillations (a putative marker of brain vulnerability) is associated with delirium.

Hypothesis 3·2. Burst-suppression induced by the age-adjusted maintenance anaesthetic (a putative marker of anaesthetic overdose and brain vulnerability) is associated with the severity of delirium.

## 3. STUDY PROCEDURES

Subject Selection: We will aim to enrol 530 patients over a period of three years into a randomised, controlled, double-blinded, single-site, parallel-arm superiority trial. Our primary outcome is the incidence of delirium on postoperative day 1 upon administration of the study intervention. To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomised into the study until 370 patients receive the study intervention on postoperative day 0. Thus, patients will be censored from the study if they do not receive dexmedetomidine or placebo on postoperative day 0. The cardiac surgical case volume at Massachusetts General Hospital (MGH) will enable us to meet our recruitment goals within our projected timeline. Cardiac surgeons, cardiac intensivists, and anaesthesiologists at MGH will identify all potential study participants. This initial care provider-patient contact will ensure that eligible patients are comfortable with all study procedures. Once the potential participant confirms that he/she is comfortable with all study procedures, a copy of the consent form will be made available. Informed consent for this protocol will follow a two part process. First, a verbal consent will be obtained at the Department of Anesthesia, Critical Care and Pain Medicine pre-operative visit. This verbal consent is necessary to ensure that pre-operative baseline questionnaires can be administered. During this visit, the study protocol will also be explained to potential participants. In addition, a flyer detailing the study protocol will also be given to potential study participants. After verbal consent is obtained, the study team will allocate a study identification number, based on the study stratification schema, to the potential participant. Written consent will be obtained on the morning of surgery. The research pharmacy will allocate the participant into his/her assigned intervention group according to the randomisation key associated with each study identification number. This key will be provided to the pharmacy by the study statisticians. All study team members, including the statisticians, and all clinical care providers will be blinded to the treatment group assignments. All subjects who provide verbal consent and complete the baseline assessment, but later decline participation in the study, or fail to give signed consent, will not be subject to any study-related follow-up or intervention. However their baseline assessment, which has already been acquired, may be used to identify factors that may predispose or bias patients toward enrolment. Patients who undergo secondary surgical procedures after admittance to the CSICU, and/or remain intubated longer than the 12 hours stipulated below, will not be subject to any further study procedures as they will no longer satisfy the primary inclusion and exclusion criteria.

**Primary inclusion criteria for patients and controls:** (1) age ≥ 60; (2) scheduled for a cardiac surgical procedure with planned post-operative admission to the CSICU for ≥ 24 hours; (3) scheduled same day surgical admission.

**Primary exclusion criteria for patients and controls:** (1) blind, deafness or the inability to speak English; (2) greater than 2 days of ICU admission in the month preceding the current surgical procedure; (3) renal and liver failure requiring dialysis or Child-Pugh score > 5; (4) follow-up difficulties (i.e. active substance abuse, psychotic disorder, homelessness); (5) previous cardiac surgery within 1 year of surgical procedure; (6) allergy to dexmedetomidine; (7) chronic therapy with benzodiazepines and/or antipsychotics; (8) severe deficit due to structural or anoxic brain damage; (9) surgical procedure requiring total circulatory arrest; (10) SARS-CoV-2 positive or SARS-CoV-2-like symptoms (i.e. fever, sore throat, new cough, new nasal congestion or runny nose, muscle aches, new loss of taste or smell, shortness of breath).

**Primary objective drop criteria for patients and controls:** (1) Scheduled for a second surgical procedure during hospital stay; (2) post-operative intubation > 12 hours**;** (3) SARS-CoV-2 positive or SARS-CoV-2-like symptoms (i.e. fever, sore throat, new cough, new nasal congestion or runny nose, muscle aches, new loss of taste or smell, shortness of breath).

**Intervention (dexmedetomidine-induced sleep vs. placebo).** After admission to the CSICU, rewarming, discontinuation of the sedative/anaesthetic infusion and extubation of the airway, sedative medications will be administered as clinically indicated by the CSICU intensive care physician. Study patients admitted to the CSICU during the afternoon and extubated by 8:30 PM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline or D5W over 40 minutes) every night throughout their CSICU stay. A sustained infusion of dexmedetomidine would never be administered for study related purposes. The targeted sleep induction time will be 9 PM. For the second start or later surgical cases, study patients admitted to the CSICU and extubated after 8:30 PM, but before 2 AM, would either receive a sleep induction dose of dexmedetomidine (1mcg/kg over 40 minutes) or placebo (normal saline or D5W over 40 minutes). The targeted sleep induction time will be within 30 minutes of extubation, with the earliest administration time being 9 PM. However, throughout the rest of the CSICU stay the sleep induction time will be targeted for 9 PM. In contrast, those patients who are admitted to the CSICU and remain intubated past 2 AM will not begin study procedures until postoperative day 1, assuming they are extubated within 12 hours of admission to the CSICU. The maximum dose of dexmedetomidine that will be administered for any study participant will be 80mcg over a 40-minute period at any one instance. Nighttime EEG may be obtained on all participants to enable sleep stage scoring in the spectral domain. The intraoperative EEG data acquisition system (SedLine) is a four-channel EEG device approved by MGH bioengineering. This device is currently used in all operating and procedural rooms at MGH for monitoring depth-of-anesthesia. For EEG monitoring in the ICU we will use the Compumedics Somte Portable PSG monitoring device.

Post cardiac surgical patients that are admitted to the CSICU have implanted temporary pacemakers and are also on a variety vasoactive medications (including but not limited to: norepinephrine, dobutamine, dopamine, and epinephrine) to maintain hemodynamic stability. Therefore, the administration of dexmedetomidine in these patients will not unduly compromise their cardiovascular status. However, patients with active bleeding necessitating surgical intervention will be excluded from the study.

**Outcome measures and variables of interest.** The primary outcome measure for this study is the incidence delirium in the CSICU on post-operative day 1. Secondary outcome measures include ICU- and hospital-delirium/coma-free days, length of hospital stay, 30-day mortality, 90-day mortality, and 180-day mortality. Variables of interest will include age, sex, years of formal education, race, ethnicity, marital status, chronic disease burden (Charlson comorbidity index), cerebrovascular disease (Framingham Stroke Risk profile), physical function as assessed by NIH Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaires, organ failure (Sequential Organ Failure Assessment), length of cardiopulmonary bypass, presence of significant cardiac dysfunction (ejection fraction less than 35%), and sedative use in the ICU.

**Cognitive testing.** We will conduct delirium assessments twice daily (AM and PM with at least 6 hours between tests) beginning on post-operative day 1 using the Long- Confusion Assessment Method (CAM). Delirium assessments will be conducted up to day 3 or hospital discharge, whichever comes first. Patients who remain delirious past day 3 will be assessed until day 5 or hospital discharge, whichever comes first. For those patients who remain delirious past day 5, assessments will continue until day 7 or hospital discharge, whichever comes first.

**Other Cognitive Testing:** Cognitive decline will be estimated by taking into account the patient's baseline cognitive

function and sleep quality before admission to the ICU, as assessed using the PROMIS-29, abbreviated Montreal cognitive assessment and PROMIS-4A questionnaires scored at recruitment, 1 month, 3 months, 6 months. The 3-D CAM and TPS questionnaire will be administered at baseline. These questionnaires may be administered via email (REDCap), regular mail, or phone call.

**Blood Draws:** For all patients, we will acquire peri-operative blood samples. This will enable us relate the serum metabolic/inflammatory profile to primary and secondary outcomes. For all study participants, blood sampling will be acquired as follows: (1) up to 40 ml of blood may be acquired at baseline on the day of surgery prior to the induction of general anesthesia (5-10ml for TSPO genetic profiling);(2) up to 20 ml of blood may be acquired at approximately 9 am of every ICU stay up to day 5. We may apply at least three distinct LC-MS–based methods to study distinct plasma aliquots for each experimental sample.

**Anaesthetic management and EEG data acquisition:** Intraoperatively, patients will receive standard anesthesia care in which the anaesthesiologist uses age-adjusted drug dosing information, as well as heart rate, and blood pressure to set and titrate the anaesthetic. This portion of the study will follow a strictly observational nature. EEG will be recorded per clinical practice in all patients using the 4-channel SedLine EEG machine that is installed in all operating rooms at MGH. In the ICU, EEG may be acquired through the Compumedics Portable PSG monitoring device.

**Other data.** A member of the study team will review the patient's bedside nursing log and clinical notes in the patient chart. A timeline of physiological data (obtained from continuously recorded clinical data in the CSICU), sedatives, analgesics, as well as any patient events will be recorded for later analysis in relation to outcome measures and nighttime spectral sleep stage scoring.

## 4. DATA ANALYSIS PLAN

Data will be analysed using an intention-to-treat approach defined as all randomised patients who receive an intervention. Continuous data will be described using median and interquartile range, and categorical data using frequencies and proportions. The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomised group assignment. Any randomisation imbalances, or other potential treatment effect modifiers will be further examined as covariates in sensitivity analyses. Secondary analyses will be evaluated using tests that are appropriate for the outcomes. We will use Pearson $\chi 2$ tests to compare categorical variables between the 2 study groups and independent t-tests or Wilcoxon rank-sum tests to compare continuous variables. Time-to-event analyses will be used to compare the effects of dexmedetomidine-induced sleep and normal care on mortality, CSICU and hospital lengths of stay, CSICU and hospital readmission rates. Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event analyses and log-rank statistics to assess the effects of biomimetic sleep and normal care. For mortality analyses, patients will be censored at the time of last contact alive or days from enrolment, whichever was first. Censoring for CSICU or hospital discharge readiness analyses will occur time of death or study withdrawal. Two-sided *P* values of 0·05 or less were considered to indicate statistical significance. Because missing data rarely occur entirely at random, we will assess the associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing risk factors and outcomes in regression modelling.

Metabolite concentrations will be log transformed to reduce heteroscedasticity of case-control differences. Metabolite levels will be compared in persons who developed delirium versus those who did not using two-tailed t tests. To screen these associations in the context of the balance of type-I and type-II errors, we will consider both FDR adjusted and Bonferroni-corrected P value thresholds. For metabolites meeting the less conservative FDR P value threshold, logistic regression analyses to estimate the OR of developing cognitive deficits will be performed at different metabolite values. Metabolites will be analysed as continuous variables (log transformed and scaled to SD of 1), and regressions adjusted for age, sex, delirium assessment, CT-ICU length of stay, and surgical duration. To examine the unique predictive ability of these metabolites, we will conduct an exploratory stepwise logistic model including all metabolites meeting our threshold, and conduct cross-validation procedures to examine the internal consistency of these estimates. We will then construct a multimarker score based on the regression coefficients of the metabolites that were significant and consistent in our multivariable model, and then assess whether a model including clinical risk factors plus the multimarker panel improves delirium prediction compared with the model including clinical risk

factors only.

All EEG data will be downloaded for off-line computational analysis. Data will be visualised and analysed using signal processing and statistical algorithms available in MatLab, and using algorithms developed in house by the study investigators. To address hypothesis 3·1, we will employ multitaper power spectral analysis,[21] multitaper bivariate coherence analysis.[18] We will also perform phase-amplitude modulation between low and high frequency EEG components.[21] To address hypothesis 3·2, Segmentation of EEG recordings into burst and suppression periods will be performed in a semi-automated manner using an adaptation of previously described methods.[22-24] We will quantify the depth of burst suppression using the burst suppression probability (BSP), a number between 0 and 1, which describes the instantaneous probability of the EEG being in a state of suppression. A BSP value of 0 corresponds to a continuously active EEG with no suppression, whereas a value of 1 corresponds to a completely isoelectric or suppressed EEG.

## 5. POWER ANALYSIS

The primary objective of this study is to detect a difference in the incidence of ICU delirium between the dexmedetomidine-induced sleep and normal care groups. Assuming a delirium event rate of 15%, a type I error of 0·05, and power of 0·90, an n = 185 patients per group will enable us to detect an absolute difference 10% (i.e., 15% versus 5%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 370 patients total who receive the study intervention on postoperative day 0.

## 6. REMUNERATION

Patients will not be compensated for this study.

## 7. RISK AND DISCOMFORT

**Dexmedetomidine risks:** The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in patients with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. All subject hemodynamic parameters will be continuously monitored to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes. In addition, most of our study subjects will have temporary pacemakers in place for routine post-surgical heart-rate management. Since dexmedetomidine maintains the respiratory rate and we are only administering a one-time dose (similar to our recently completed proof of concept study in healthy volunteers; NCT01485393), there is no concern for respiratory compromise.

**EEG risks**: The risks associated with EEG electrodes are redness and irritation at placement site.

**Psychological risks:** Psychological risks include the possibility of claustrophobia within the scanner.

**Questionnaire risks:** Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning.

**Data risks:** Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on partners approved devices/portals. However, there is a small risk that people outside of this study may be exposed to information about study subjects.

## 8. POTENTIAL BENEFITS

Subjects will have no direct benefit from taking part in this study. Findings from these studies will help advance our understanding of the pathophysiology of delirium. In particular, this project will assess the role of sleep induction and neuroinflammation in the establishment and/or maintenance of delirium. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of delirium.

## 9. MONITORING AND QUALITY ASSURANCE

No identifiers other than study ID's will be included in the dataset. Thus, all data will be deidentified and data will be stored on password protected partners computers and cluster for off-line analysis. The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data and adherence to the IRB-approved protocol. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and wellbeing of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee. A DSMB will also oversee this study.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines, as well as the RDRC within 5 days.

## 10. SUPPLEMENTARY ANALYSIS

In a supplementary analysis data from the MINDDS study will be combined with data and specimens from the **M**aximizing tr**E**atment of **N**eurological **D**ysfunction using **IN**travenous **G**uanfacine (**MENDING**) study in an effort to help determine future routes of study of the alpha2 agonism on delirium and acquired-dementia/Alzheimer's disease and related dementias (ADRD). This collaboration will be established between MGH and Vanderbilt University Medical Center in order to share data and specimens for analysis.

Briefly, the MENDING trial leverages resources from three ongoing NIH-funded trials. Patients in the MENDING trial have been enrolled into one of the ongoing prospective studies through the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center at Vanderbilt, all of which have daily delirium monitoring and 3- and 12-month cognitive assessments. These include the Illuminating Neuropsychological Dysfunction and Systemic Inflammatory Mechanisms Gleaned After Hospitalisation in Trauma-ICU (INSIGHT-ICU) study (R01GM120484, PI: Patel), the Measuring Outcomes of Activity in Intensive Care (MOSAIC) study (K76AG054864, PI: Brummel); and the Bringing to light the Risk factors And Incidence of Neuropsychological dysfunction in ICU Survivors, 2nd (BRAIN-ICU-2) study (R01AG058639, PI: Ely). Patients enrolled into one of these parent observational studies will subsequently be consented for enrolment into the MENDING clinical trial, which evaluates the role of the alpha-2 agonist guanfacine. All study procedures for the MENDING trial at Vanderbilt are covered under their local IRB (Protocol 202000). Additionally, the consent for all MENDING studies includes approval to share data and specimens to evaluate mechanisms and associations with delirium, consistent with the aims of the MINDDS study. Thus, sharing of specimens and data will be consistent with future use described in the informed consent. Data collected from the MENDING study will be used in conjunction with neurocognitive data from the MINDDS study in interpreting the potential of alpha-2 agonism on delirium and ADRD.

All data shared between institutions will be coded so that the collaborating institution cannot identify individual participants. This limited dataset will only include dates (of neurocognitive assessments, admission/discharge) and ages over 89. All other identifiable aspects of data will be removed. No other identifiable information will be shared. If possible a completely deidentified data set will be shared between institutions. Data and specimen sharing will be bi-directional in order to study of the alpha2 agonism on delirium. Appropriate data and material transfer agreements will be obtained between sites prior to sharing of any data or specimens.

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**SUPPLEMENTARY APPENDIX 3. History of Changes to the IRB Approved Protocol**

| Protocol Version | Summary of Changes |
|---|---|
| 09/22/2016 | Original IRB Approved Protocol |
| 12/15/2016 | The use of the Mini Cog as an alternative was removed. Timing of assessments was changed from 1, 2, 3 and 12 months to only evaluate patients up to six months postoperatively. The use of a Compumedics Portable PSG monitoring device was added for exploratory data collection.<br><br>*Rationale: Changes to the cognitive assessment battery were removed to streamline the number of assessments performed and reduce variation in reliability across measures.* |
| 04/12/2017 | The amount of compensation was reduced to $45 per study participant.<br><br>*Rationale: Given existing issues collecting in which social security number was required in order to process reimbursements, the amount of compensation as reduced so that this would no longer be required in order to process the payment.* |
| 4/18/2017 | This amendment changes the duration of drug administration from 10 minutes to 40 minutes. Sampling timepoints for blood biomarkers were changed from daily in the cardiac surgical ICU to an intraoperative sample (collected on the morning of surgery in the operating room) and a sample collected on the morning of postoperative day 1.<br><br>*Rationale: Changes in the drug administration duration were made in order to reduce the possibility of unblinding because of hemodynamic instability, thus ensuring the integrity of randomisation and concealment. Changes to the blood sampling timepoints were made in relation to resource considerations but it is believed these amended timepoints represent clinically important timepoints in which proteomic and inflammatory profiles of patients will be most robust.* |
| 06/05/2017 | This amendment involves the addition of the PROMIS-4A Sleep Disturbance questionnaire to be assessed at the same time point as the other PROMIS assessments (baseline, 30, 90, and 180 days). The study exclusion criteria was also amended to remove the following criterion: (1) obstructive sleep apnoea (OSA) requiring nighttime mechanical ventilation assistance, and (2) residence greater than 100 miles from MGH.<br><br>*Rationale: Eligibility criteria was updated to be consistent with the targeted patient population for enrolment. Exclusions for distance from the hospital were originally implemented because of restrictions to return to the hospital at follow up, however given the ability to perform telephonic assessments, this was removed. Recent literature has suggested that OSA is associated with an increased risk of delirium, so the exclusion criteria was removed to ensure patients with OSA, who are at risk of the primary outcome, were not inappropriately excluded, thus limiting the generalisability of the study findings. The addition of the sleep questionnaire was implemented because of recommendations by the DSMB to capture quality of sleep at baseline.* |
| 07/31/2017 | The following changes were included in this amendment: (1) Patients will be censored from the study if they do not receive the study intervention. (2) Only patients whose surgeries are the first case of the day, and/or commence by 12pm on the day of surgery, will be approached for written consent. (3) Patients who undergo a second surgery during their hospital stay and/or remain intubated for over 12 hours will not be subject to further study procedures. (4) Length of hospital stay will be tracked as a secondary |

| | |
|---|---|
| | outcome measure rather than readiness for CSICU and hospital discharge. (5) Nighttime EEG data may be collected during the patients' intensive care unit stay.<br><br>*Rationale: Censoring criteria was added to truly reflect 300 subjects who receive the intervention on study day 0, in an effort to better elucidate the true relationship between dexmedetomidine and placebo among patients who received the study drug on day 0. Limits were placed on second case surgery because of the perception that these patients would not be extubated prior to the drug administration cut-offs on postoperative day 0, thus excluding them from the possibility of receiving the study drug. Outcomes were adapted as Epic reporting of patient readiness for discharge are variable an instead dates of hospital discharge are more objective. Criteria was added to ensure protocol procedures for ancillary, exploratory outcomes were appropriately reflected in the study procedures.* |
| 10/03/2017 | The dropout criteria added in the previous amendment has been removed. Instead all patients extubated before 2AM are now eligible for drug administration. The duration of delirium assessments has been limited to day 3 for patients who did not experience delirium, with an option to continue to assess delirious patients until day 7 depending on their status.<br><br>Rationale: The dropout criteria has been removed to ensure generalisability of our results and increase accrual rates. Reduction in the number of assessments of non-delirious patient was performed in an effort to improve retention rates for subsequent long term follow up. |
| 12/13/2017 | Based off a suggestion during publication of the protocol paper, the power calculation was updated to reflect a lower incidence of delirium.<br><br>*Rationale: At the time of peer review of the protocol paper it was suggested that the power be re-evaluated given the current literature that suggested an incidence of delirium was much lower that the effect estimates on which the study was based (i.e. 48% vs 15%). The power was thus estimated without unblinding the data and instead the study was powered to a baseline incidence of 15% in the control group. The sample size was thus adjusted accordingly.* |
| 01/04/2018 | The study protocol was amended to allow D5W to be supplemented in place of normal saline in the event of a saline shortage. *Rationale: These changes were made as a result of a nationwide hospital shortage of saline supply.* |
| 07/02/2018 | This amendment removed compensation for subjects and updated the study contacts.<br><br>*Rationale: This amendment was required because of a new institutional policy requiring social security numbers from all enrolled participants in order to receive compensation. Based off existing and previous issues obtaining this from participants, the study team decided to cease all renumerations.* |
| 01/25/2019 | This amendment replaced the current primary care physician care satisfaction questions in the subjects' baseline assessments with the Trust in Physician Scale (TPS) survey. The study population was also be updated from 300 to 370.<br><br>*Rationale: The previous care satisfaction was team-generated, and was replaced in order to use a validated, reliable measure for assessment, and to allow comparison with previous literation. The study sample was updated from 300 consented to 370 consented individuals to account for potential dropout of participants who might consent at clinic verbally but would ultimately decline to participate on the day of surgery.* |

| | |
|---|---|
| 07/06/2020 | SARS-CoV-2 or SARS-CoV-2-like symptoms were added to the study protocol as both study exclusion and dropout criteria. *Rationale: This amendment to the study inclusion was implemented to reduce the possibility of transmission, particularly for the safety of the study team.* |
| 10/28/2020 | The detailed protocol was edited to clarify that we intend to enrol 370 patients in the study who receive the study intervention on postoperative day 0. Therefore, we will aim to enrol/consent 530 patients total.<br><br>*Rationale: Although the study still aims to only enrol 370 subjects who received the study intervention on day 0, this amendment was required in order to allow screening and consent of additional subjects who may ultimately dropout after not meeting the eligibility criteria. This amendment was required to clarify that point in the protocol.* |
| 12/15/2020 | This study protocol was amended to include the addition of data and specimen sharing with Vanderbilt University Medical Center.<br><br>*Rationale: Data and blood specimens from the study Maximizing trEatment of Neurological Dysfunction using INtravenous Guanfacine (MENDING) may be shared with investigators in order to evaluate characteristics of delirium between the MENDING and MINDDS study cohorts.* |

**SUPPLEMENTARY APPENDIX 4. Statistical Analysis Plan**

**Minimizing ICU neurological dysfunction with dexmedetomidine-induced sleep (MINDDS): A randomised placebo-controlled trial**
NCT02856594

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**Statistical Analysis Plan**

Statistical Analysis Plan (SAP) Version: 1·0: August 22, 2021

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## Introduction

*Background and Rationale*

Delirium is an acute brain dysfunction characterised by disturbances in attention, awareness and cognition not explained by a pre-existing neurocognitive disorder. Although the increased mortality rates ascribed to delirium remain debatable, delirium remains a leading cause of preventable morbidity in hospitalised elderly patients. It is also associated with prolonged hospitalisation, prolonged institutionalisation, and long-term cognitive deficits. Patients with pre-existing dementia, such as Alzheimer's disease, are especially vulnerable to developing delirium. The total healthcare cost attributable to delirium is estimated between $143 and $152 billion annually. In the United States, delirium occurs in approximately 80% of critically ill patients admitted to medical/surgical intensive care units (ICU), and 43% of patients admitted to cardiac surgical (CS) ICU. Most patients diagnosed with delirium also present with multiple comorbidities (sepsis, multi-organ failure) that significantly confound our understanding of this disease. Thus, to date, no pharmacological intervention to treat delirium has been identified.

The aging process has previously been identified as a risk factor for developing delirium. Normal aging is associated with a morphological shift of glia (microglia, astrocytes) to an activated state. Following a systemic challenge such as critical illness, this activated glia aid a neuroinflammatory state that contributes to delirium. The neuroinflammatory state is exacerbated by sleep disturbances. Thus, sleep deprivation may be a modifiable risk factor for the development of delirium. Presently, pharmacological treatment with no current medication (benzodiazepines, antipsychotics) induces natural sleep or reliably reduces the incidence of delirium. We have found that pharmacological induction of rapid eye movement sleep (REM) and non-REM I-III sleep states using dexmedetomidine, can now be safely achieved in humans. Our overall objective is to evaluate the efficacy of dexmedetomidine-induced sleep-in preventing delirium, investigate cellular and molecular mechanisms underlying delirium, and investigate whether recently described intraoperative electroencephalogram (EEG) signatures of the aging brain are associated with developing delirium. Our central hypothesis is that nightly biomimetic sleep-in elderly patients admitted to the CSICU for greater than 24 hours will reduce the incidence of ICU delirium.

Our intervention and control groups will be comprised of extubated CSICU patients, because their homogeneity in terms of surgical procedures, anaesthetic management, and systemic inflammatory response represents a unique opportunity to study the mechanisms underlying delirium, while limiting confounding factors that may otherwise be encountered in heterogeneous patients found in the medical/surgical ICU. We will perform assessments of cognition (perioperative), obtain EEG recordings (intraoperative, ICU) and blood samples (perioperative).

At the conclusion of these studies, we will have expanded our knowledge of the pathophysiology of delirium, evaluated a new pre-emptive therapeutic strategy for delirium, suggest neurophysiologically based monitoring strategies to reduce significantly the amount of anaesthetic administered to elderly patients – and possibly delirium – while being certain the patient is sufficiently unconscious for surgery (individualised anesthesia care), and enabling continued investigation into the pathophysiology of this clinically important disorder.

## Objectives

*Primary Objectives*

The primary aim of the study is to investigate, via administration of dexmedetomidine or placebo postoperatively, the benefits of pre-emptive biomimetic sleep for reducing the risk of postoperative delirium in a randomised controlled trial.

> *Hypothesis 1. Incidence of Delirium*
>
> The null hypothesis ($H_0$) is that the probability of delirium in the placebo group is equal to the probability of delirium in the dexmedetomidine-induced sleep group. The alternative hypothesis ($H_1$) is that the probability of delirium in the dexmedetomidine-induced sleep group is less than the probability of delirium in placebo group. In statistical terms:
>
> $$H_0: P_{dexmedetomidine} = P_{placebo}$$
> $$H_1: P_{dexmedetomidine} < P_{placebo,}$$
>
> where P is the probability of delirium.

*Secondary Objectives*

There are six main secondary objectives. We aimed to investigate the influence of pre-emptive biomimetic sleep on ICU- and hospital-delirium/coma-free days, length of hospital stay, 30-day, 90-day, and 180-day mortality, cognitive testing variables and other health related quality of life measures.

*Hypothesis 2. ICU and Hospital Delirium/Coma Free Days*

The null hypothesis is that the ICU and hospital delirium/coma free days in the placebo group is equal to the ICU and hospital delirium/coma free days in the dexmedetomidine-induced sleep group. The alternative hypothesis is that the ICU and hospital delirium/coma free days in dexmedetomidine-induced sleep group is greater than the ICU and hospital delirium/coma free days in the placebo group. In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} > \mu_{placebo,}$$

where μ is the ICU and Hospital delirium/coma free days.

*Hypothesis 3. Severity of Delirium*

The null hypothesis is that the severity of delirium in the placebo group is equal to the severity of delirium in the dexmedetomidine-induced sleep group. The alternative hypothesis is that the severity of delirium in the dexmedetomidine-induced sleep group is less than the severity of delirium in placebo group. In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} < \mu_{placebo,}$$

where μ is the severity of delirium.

*Hypotheses 4a and 4b. Length of Hospital and ICU Stay*

The null hypothesis is that the length of hospital/ICU stay in the placebo group is equal to the length of hospital/ICU stay in the dexmedetomidine-induced sleep group. The alternative hypothesis is that the length of hospital/ICU stay in the dexmedetomidine-induced sleep group is less than the length of hospital/ICU stays in placebo group. In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} < \mu_{placebo,}$$

where μ is the length of hospital/ICU stay.

*Hypotheses 5a, 5b, and 5c. 30-day, 90-day, and 180-day Mortality*

The null hypothesis is that the mortality in the placebo group is equal to the mortality in the dexmedetomidine-induced sleep group. The alternative hypothesis is that the mortality in the dexmedetomidine-induced sleep group is less than the mortality in placebo group. In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} < \mu_{placebo,}$$

where μ is the 30-day, 90-day, or 180-day mortality.

*Hypothesis 6. Postoperative Cognitive Status*

The null hypothesis is that for all scales related to postoperative cognitive status in the placebo group is equal to that in the dexmedetomidine-induced sleep group. The alternative hypothesis is that for all scales related to postoperative cognitive status the dexmedetomidine-induced sleep group will be superior to the placebo group. In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} > \mu_{placebo,}$$

where $\mu$ is all scales related to postoperative cognitive status.

*Hypothesis 7. Postoperative Health Related Quality of Life*

The null hypothesis is that for all scales related to postoperative health related quality of life in the placebo group is equal to that in the dexmedetomidine-induced sleep group. The alternative hypothesis is that for all scales related to postoperative health related quality of life in the dexmedetomidine-induced sleep group will be superior to the placebo group (with direction of effect appropriate to scaling of each scale/subscale). In statistical terms:

$$H_0: \mu_{dexmedetomidine} = \mu_{placebo}$$
$$H_1: \mu_{dexmedetomidine} > \mu_{placebo,}$$

where $\mu$ is all scales related to postoperative health related quality of life.

**Trial Methods**

*Overall Design*
In this randomised, double-blinded, controlled, single-site, parallel-arm superiority trial, eligible patients will be randomised to receive either dexmedetomidine or placebo with a 1:1 allocation.

The primary outcome – incidence of delirium – will be defined as the presence or absence of a positive delirium assessment at either the morning or afternoon assessment on postoperative day one using the Confusion Assessment Measure (CAM), as described below. Multiple sources of outcome assessment such as clinical assessment, adjudication committee assessment and a natural language processing (NLP) method are available, therefore these three methods will be evaluated in planned sensitivity analysis.

For secondary outcomes, ICU and hospital delirium/coma-free days assessed two times per day until postoperative day three. Delirious patients will be assessed until postoperative day five. If delirium does not resolve by postoperative day five, assessments will continue until postoperative day seven or hospital discharge, whichever comes first. Severity of delirium will be assessed using the CAM delirium severity scoring long form at the time of delirium assessments. Length of hospital stays will be measured from admission until discharge and assessed by chart review. Mortality up to day 180 will be assessed by chart review, and/or elicited from family members during follow-up calls at 30 days, 90 days, and 180 days postoperatively. Postoperative cognitive status and health related quality of life will be assessed via telephone interviews and/or online questionnaires at 30 days, 90 days, and 180 days postoperatively.

*Randomisation*
Participants will be randomised into treatment arms in a 1:1 ratio using permuted blocks of sizes 4 to 8. Randomisation assignments will be stratified by cardiac surgery status (i.e., cardiac vs non-cardiac surgery). The 'blockrand' package in R will be used and the randomisation will be conducted by a statistician otherwise uninvolved with the study. Allocation concealment will be maintained using a centralised pharmacy administration of study drug. Participants will be allocated to a treatment arm by a member of the research team at confirmation that the participant meets eligibility criteria. Both study agents are designed to look identical to each other to maintain blinding, and study staff will remain blinded throughout the study.

**Outcomes**

*Primary Outcomes*
The primary outcome will be the presence or absence of a positive delirium assessment on postoperative day 1 using the long-Confusion Assessment Measure (CAM). Patients will be assessed twice daily, therefore the patient will be considered delirious on postoperative day one if delirium is present at either the morning or afternoon assessment.

*Secondary Outcomes*
For the secondary measures, in-hospital outcomes will be evaluated by in-person assessments during hospitalisation and medical record review. Post-discharge measures will be assessed via the medical record or by telephone interview at 30, 90, and 180 days post-procedure. The following variables will be measured:

*ICU and Hospital Delirium/Coma-Free Days*
ICU and hospital delirium/coma-free days will be assessed two times per day until postoperative day 3. Delirious patients will be assessed until postoperative day 5. If delirium does not resolve by postoperative day 5, assessments will continue until postoperative day 7 or hospital discharge, whichever comes first. The risk period for Delirium/Coma-Free Days will be calculated out of 3 days (i.e., 3 – number of days of delirium). On days where delirium is not assessed due to participant discharge, 'no delirium' will be imputed.

*Severity of Delirium*
Severity of delirium features scored using the CAM delirium severity score long form will be assessed in all participants. The severity score will be calculated as the maximum score from the twice-daily assessments. If only one daily assessment is completed, that score will be used as the severity score.

*Length of Hospital Stay*
Length of hospital stay (date of discharge – date of surgery).

*Inpatient Mortality and Major Inpatient Morbidity*
Inpatient mortality and major inpatient morbidity. The following specific outcomes will be evaluated: readmission, surgical site infection, reoperation for bleeding, stroke, renal failure, sternal wound infection.

*Cognitive Function*
Cognitive function will be assessed using the abbreviated Montreal Cognitive Assessment total score.

*Physical Function*
Physical function will be defined using the Patient-Reported Outcomes Measurement Information System® Short Form (PROMIS SF) V.1.2—Physical Function 8b final score. This will be assessed at baseline, at 30, 90 and 180 days. The T-score from each standardised metric will be used in analysis.

*General Health*
The global health score will be defined from the PROMIS SF V.1.1—Global Health Short Form. From this assessment the overall score, the mental subscale, and the physical subscale will be analysed and reported. The T-score from each standardised metric subscales will be used in analysis.

*Pain*
Pain will be defined using the pain interference final score from the PROMIS SF V.1.0—Pain Interference 8a instrument. The T-score from each standardised metric will be used in analysis.

*Applied Cognition*
Applied cognition abilities will be reported as the final score with the PROMIS V.1.0—Applied Cognition Abilities SF 8a. The T-score from each standardised metric will be used in analysis.

*Sleep Quality*
Sleep quality is defined as a raw sum score with the PROMIS V.1.0—Sleep Disturbance 4A. The T-score from each standardised metric will be used in analysis.

*Mortality*
Mortality will be assessed by chart review, and/or elicited from family member during follow-up calls. This will occur at 30, 90 and 180 days.

*Patient Demographics and Ancillary Characteristics*
Patient characteristics will be evaluated and described that clearly define the population being examined, including demographic information (e.g., age, gender, race/ethnicity, and education). No information will be reported or displayed that allow identification of the individual participants. Patient characteristics unrelated to basic demographic information that help define the population will also be evaluated (e.g. surgical procedure).

**Sample Size and Statistical Power**

*Sample Size*
The primary objective of this study is to detect a difference in the incidence of ICU delirium between the dexmedetomidine-induced sleep and placebo groups. Assuming a delirium event rate of 15%, a type I error of 0·05, and power of 0·90, a sample size of n = 185 patients per group will enable us to detect an absolute difference of 10% (i.e., 15% versus 5%). With respect to decreased morbidity and healthcare costs, this change represents a clinically meaningful difference. Therefore, we will recruit up to 370 patients total who receive the study intervention on postoperative day 0.

**Interim and Final Analyses**

*Interim Analyses*

There are no planned interim analyses. Confidential review of safety events will be performed by a Data Safety Monitoring Board (DSMB) routinely, and we will not apply stopping rules for futility or superiority.

*Ending the Trial*
Enrolment will cease when the target enrolment is obtained. The final analysis will proceed when all follow-up measurements are completed and the databased is cleaned and locked.

*Analysis Populations*

Modified Intent-To-Treat Analysis Set
The Modified Intent-To-Treat (mITT) set is defined to be the set of all participants who were randomised and were not dropped from the study before the primary outcome assessment (postoperative day 1). The mITT set will be used for the primary analysis.

Safety analysis set
This set consists of any randomised subjects who received any dose of the study drug or placebo at any timepoint. This study sample will be used for secondary analyses.

Per-Protocol Analysis Set
The Per-Protocol (PP) analysis set will consist of the subjects in the mITT population, who received the drug on study day zero.

*Protocol Deviations*
The numbers and proportions of participants with protocol deviations and the numbers and proportions of days in which there are protocol deviations will be summarised by allocated group with details of type of deviation provided.

**Analyses**

*Primary Analyses*
The primary outcome will be evaluated using logistic regression examining the presence or absence of delirium conditional on randomised group assignment (dexmedetomidine vs placebo) and the stratification variable used in randomisation (cardiac versus non-cardiac surgery type).

Hypothesis testing will be two-tailed with statistical significance interpreted at $p < 0{\cdot}05$.

*Secondary Analyses*
The secondary outcomes involve variables with a range of measurement types and expected distributions. The proposed methods are designed using the generalised linear model with estimation conditional on the treatment effect (dexmedetomidine vs placebo) and the stratification variable used in randomisation (cardiac versus non-cardiac surgery type). For binary outcomes, including the chart review definition of delirium and mortality, a binomial distribution with a logit link will be used. For continuously scaled outcomes with at least ordinal measurement properties, including severity of delirium, PROMIS function outcomes, pain, and sleep, a gaussian distribution with either an identity or log link will be used to accommodate deviations from normality. Secondary outcomes will be evaluated at each measurement occasion.

Using the same formulation as above, time-to-event analyses will be used to compare the effects of dexmedetomidine and placebo on mortality, and CSICU and hospital lengths of stay. Cox proportional hazard models will be used for estimation and Kaplan-Meier survival curves will be used for graphical presentation of these time-to-event outcomes, with adjusted hazard ratios will be used to assess these effects. Censoring for CSICU or hospital discharge readiness analyses will occur at time of death or trial withdrawal.

*Missing Data*
Long-CAM assessments for patients who are reintubated for clinical care or for further surgical management will be considered as missing data for the primary analysis.

Due to the nature of the study methods and in-hospital timing of data collection, only small amounts of missing data are expected in the mITT set. If there are greater than 5% missing primary outcome assessments, a sensitivity model will be conducted to examine the impact of missing data on the treatment effect estimate for the primary outcome. A multiple imputation model will be conducted using all prognostic variables as outlined above. Additionally, the secondary outcome of chart review/NLP derived delirium will be used as a predictor in the multiple imputation model. The models will be conducted using multiple imputations by chained equations (MICE), with m = 20 iterations, using predictive mean matching algorithm (PMM). The pooled estimates will be combined using Rubin's rules.

*Sensitivity Considerations*
Several sensitivity models are planned to evaluate the treatment effect estimates under the context of differing assumptions.

The primary models will be re-specified adding a set of prognostic variables that might impact treatment effect. Age, preoperative cognitive function, cardiac condition, surgery duration, and sex will be specified as fixed covariate predictors, as these variables are known to be associated with presence of delirium. The conditional estimates based on this model will be informally compared to that from the primary model with predictions from this model used to estimate treatment effects.

As above, treatment heterogeneity will be examined using interaction terms between cardiac condition, age, sex, preoperative cognitive function, surgery time (morning vs afternoon) and treatment assignment (e.g., age x treatment). Because such interaction terms are difficult to power, and subject to spurious associations, they will be treated as exploratory and used in a hypothesis-generating context.

As above, in order to ensure treatment effects are sufficiently robust, baseline variables that are unexpectedly imbalanced (i.e., ASD > 0·10) will be entered into the models as covariates for the primary outcome model.

As described in the missing data approach, a sensitivity analysis will be triggered if missing data is greater than 5% for the mITT sample.

Although the number of individuals who are randomised but do not receive a study medication is expected to be small, an additional sensitivity analysis will be conducted by including these individuals in the analysis according to their randomisation assignment and imputing missing outcome assessments as described in the multiple imputation models.

*Safety*
The numbers and proportions of participants with death events and date of death, cause of death will be summarised by allocated group with details.

*Statistical Software*
The latest versions of R (R core Team, Vienna, Austria) and RStudio (Boston, MA) will be used to examine all hypotheses and analyse all data.

*Consort (2010)*
A CONSORT Flow Diagram (2010) will be presented illustrating the number of individuals who were screened, were eligible for the trial, who withdrew from the study, and any other information that defines how the total number of participants in the intent to treat and per protocol analyses was generated. Included in this will be those who withdrew, why they withdrew, and at what point in the trial they withdrew. Any publications stemming from the analyses will conform to the CONSORT 2010 reporting guidelines.

**Addendum 1**

12/8/2017 Clinical Trials Registration

The clinical trial registration was updated to reflect a corrected target sample size of 370 patients for the per-protocol sensitivity analysis (it was erroneously listed as N = 300 on clinicaltrials.gov).

**Addendum 2**

On July 15, 2021, an unplanned, *blinded* interim analysis was conducted due to slow recruitment caused by COVID-19. Several simulation studies were conducted using the currently enrolled sample and the overall (i.e., pooled) primary outcome event rate.

Below are summary data for context:

- Total Randomised Cohort = 465 patients
- Intention to Treat Cohort = 391 patients
    - Day 1 Delirium = 5·6% (primary outcome; lower than the 10% expected)

*Simulation results for ITT analysis based on the observed event rate:* Using the ITT cohort to date, and assuming a two-tailed alpha = 0·05, and a 1:1 randomisation ratio, the study is powered to detect a difference of ± 3·2% from the marginal event rate of 5·6% for the two groups. This would suggest adequate power to detect a difference in proportions if the group delirium rates were 8·8% and 2·4% (or more extreme). Enrolling and randomising approximately 100 additional patients would provide power to detect a ± 2·9% difference from the pooled rate (e.g., 8·5% vs 2·7%).

Based on the results of simulations, it was concluded by the PI and study team that continuing to recruit patients into the MINDDS study posed diminishing returns in relation to the value of the added statistical power when compared to additional recruitment time and costs. Given that the observed event rate is lower than anticipated and that enrolling additional patients is unlikely to remediate the statistical power in relation to the original effect size assumptions, the study PI asked the statistical team to engage with the DSMB to ensure that there are no fundamental concerns to closing the study. Following approval from the DSMB, the study was closed to enrolment on July 29, 2021.

**SUPPLEMENTARY APPENDIX 5. Planned Sensitivity Models**

**Prespecified Sensitivity Analyses for Primary Outcome**

| | N | Odds Ratio[a] (95% CI) |
|---|---|---|
| **Modified Intention to Treat Cohort** | | |
| Model 1 (Primary): *Adjusted for Cardiac Randomisation Strata Only* | 364 | 0·32 (0·10, 0·83) |
| Model 2 (Prognostic): *Adjusted for Age, Preoperative Cognitive Function, Cardiac Strata, Surgery Duration, and Sex* | 364 | 0·31 (0·09, 0·88) |
| Model 3 (Multiple Imputation): *Multiple Imputation Based on Delirium Keywords Chart Review and Prognostic Variables* | 394 | 0·33 (0·12, 0·91) |
| **Per Protocol Cohort** | | |
| Model 1 (Primary): *Adjusted for Cardiac Randomisation Strata Only* | 312 | 0·23 (0·03, 0·91) |
| Model 2 (Prognostic): *Adjusted for Age, Preoperative Cognitive Function, Cardiac Strata, Surgery Duration, and Sex* | 312 | 0·25 (0·04, 1·05) |
| Model 3 (Multiple Imputation): *Multiple Imputation Based on Delirium Keywords Chart Review and Prognostic Variables* | 334 | 0·23 (0·05, 1·08) |

[a]*Effect estimates are reported comparing the dexmedetomidine group to the placebo group (reference).*
*Abbreviations: CI (confidence interval), N (Number of Observations)*

**SUPPLEMENTARY APPENDIX 6. Post Hoc Sensitivity Analysis of the Primary Outcome Assuming Different Imputation Strategies and Utilising Fisher's Exact Test**

| | **Placebo** N = 206 | **Dexmedetomidine** N = 188 | **P-Value** |
|---|---|---|---|
| Delirium on postoperative day one (as assessed) | 16/189 (8·5) | 5/175 (2·9) | 0·035 |
| Coded missing data on postoperative day one as negative for delirium | 16/206 (7·8) | 5/188 (2·7) | 0·039 |
| Coded missing data on postoperative day one as negative for delirium | 33/206 (16·0) | 18/188 (9·6) | 0·078 |
| Coded missing data on postoperative day one as positive for delirium if delirium was present on postoperative day two | 17/190 (9·0) | 6/176 (3·4) | 0·046 |
| Coded missing data on postoperative day one as positive for delirium if delirium was present on postoperative day two, and negative for delirium if delirium was absent on day two | 17/196 (8·7) | 6/184 (3·3) | 0·043 |
| Coded missing data on postoperative day one as positive for delirium if delirium was present on postoperative day two or if data were missing on day two | 27/200 (13·5) | 10/180 (5·6) | 0·013 |
| Coded missing data on postoperative day one as positive for delirium if delirium was present on postoperative day two or if data were missing on day two, and negative for delirium if delirium was absent on day two. | 27/206 (13·1) | 10/188 (5·3) | 0·012 |

*The resulting p-values for Fishers Exact Test p-values were calculated by doubling the exact one-tailed probability.*

**SUPPLEMENTARY APPENDIX 7. Post Hoc Sensitivity Analysis Utilising Exact Logistic Regression for Outcomes with Low Event Rates in the Modified Intention-to-Treat Cohort**

| | **Effect Estimate** [c] (95% CI) | **P Value** |
|---|---|---|
| **Univariate Models** | | |
| Postoperative Day 1 Delirium *(Primary Outcome)*[a] | 0·32 (0·09, 0·94) | 0·036 |
| Postoperative Delirium Days 1 to 3[b] | 0·58 (0·27, 1·22) | 0·17 |
| Surgical Site Infection | 0·73 (0·06, 6·43) | 1·00 |
| Reoperation for Bleeding | 0·55 (0·01, 10·57) | 1·00 |
| Renal Failure | 3·32 (0·26, 175·35) | 0·56 |
| In Hospital Mortality | 3·32 (0·26, 175·35) | 0·56 |
| 30 Day Mortality | 3·32 (0·26, 175·35) | 0·56 |
| 90 Day Mortality | 4·44 (0·43, 220·52) | 0·32 |
| 180 Day Mortality | 1·10 (0·20, 5·98) | 1·00 |
| **Models Conditional on Randomization Strata** | | |
| Postoperative Day 1 Delirium *(Primary Outcome)*[a] | 0·32 (0·09, 0·94) | 0·036 |
| Postoperative Delirium Days 1 to 3[b] | 0·58 (0·27, 1·22) | 0·17 |
| Surgical Site Infection | 0·69 (0·06, 6·17) | 1·00 |
| Reoperation for Bleeding | 0·54 (0·01, 10·39) | 1·00 |
| Renal Failure | 3·29 (0·26, 173·55) | 0·56 |
| In Hospital Mortality | 3·29 (0·26, 173·55) | 0·56 |
| 30 Day Mortality | 3·29 (0·26, 173·55) | 0·56 |
| 90 Day Mortality | 4·43 (0·43, 219·64) | 0·32 |
| 180 Day Mortality | 1·11 (0·20, 6·03) | 1·00 |

[a]A total of 30 participants (13 in dexmedetomidine group and 17 in the placebo group) were missing the primary outcome, incidence of delirium on postoperative day 1. [b]A total of 57 participants (28 in dexmedetomidine group and 29 in the placebo group) had missing delirium assessments through postoperative day three. No other data was missing unless specified. [c]Effect estimates are reported as odds ratios comparing the dexmedetomidine group to the placebo group (reference).

**SUPPLEMENTARY APPENDIX 8. Hypnotics, Analgesics, and Other Relevant Medications**

| | **Placebo** N = 206 | | **Dexmedetomidine** N = 188 | | **P Value** |
|---|---|---|---|---|---|
| | *N Received* | *Dose* | *N Received* | *Dose* | |
| **Intraoperative Medications** | | | | | |
| **Midazolam,** *mg* | 145 | 2 [2, 4] | 127 | 2 [2, 4] | 0·64 |
| **Propofol,** *mg* | 174 | 687 [345, 1226] | 157 | 704 [332, 1222] | 0·83 |
| **Fentanyl,** *mcg* | 175 | 500 [500, 750] | 158 | 500 [500, 750] | 0·38 |
| **Hydromorphone** | 134 | 1·0 [0·5, 1·5] | 124 | 1·0 [0·5, 1·5] | 0·78 |
| **Etomidate** | 5 | 16 [15, 18] | 6 | 20 [20, 20] | 0·16 |
| **Morphine,** *mg* | 23 | 10 [10, 20] | 10 | 10 [10, 20] | 0·31 |
| **Administered After Extubation Until 6PM on Postoperative Day 1** | | | | | |
| **Fentanyl,** *mcg* | 11 | 50 [25, 150] | 11 | 100 [50, 200] | 0·39 |
| **Haloperidol** | 11 | 1·00 [0·50, 1·50] | 8 | 1·00 [0·75, 1·75] | 0·93 |
| **Oxycodone** | 118 | 30·0 [20·0, 45·0] | 120 | 37·0 [25·0, 47·5] | 0·44 |
| **Ketorolac** | 12 | 30 [30, 60] | 14 | 30 [30, 60] | 0·89 |
| **Lorazepam** | 3 | 0·50 [0·25, 1·00] | 2 | 0·50 [0·50, 0·50] | 1·00 |
| **Tylenol** | 155 | 1950 (1300, 2275) | 135 | 1950 (1300, 2600) | 0·19 |

*Data is presented as median [quartile 1, quartile 3. The p-values compares the dose of each medication among those who received it in each group.*

**SUPPLEMENTARY APPENDIX 9. Participant Characteristics at Baseline in the Per-Protocol Cohort**

| | **Placebo** N = 175 | **Dexmedetomidine** N = 159 |
|---|---|---|
| **Demographics** | | |
| Age, *years* | 69·0 [65·0, 74·0] | 67·0 [63·0, 73·0] |
| Male Sex | 128 (73·1) | 122 (76·7) |
| Height, *centimetres* | 175·3 [167·6, 180·3] | 175·3 [167·6, 180·3] |
| Weight, *kilograms* | 86·0 [72·6, 95·5] | 85·3 [77·1, 97·5] |
| Body Mass Index, *kg/m²* | 27·62 [25·13, 30·96] | 28·19 [25·13, 31·99] |
| Self-Reported Race | | |
| White | 171 (97·7) | 153 (96·2) |
| Asian | 2 (1·1) | 5 (3·1) |
| American Indian or Alaskan Native | 0 (0·0) | 1 (0·6) |
| Other | 1 (0·6) | 0 (0·0) |
| Unknown | 1 (0·6) | 0 (0·0) |
| Ethnicity | | |
| Hispanic or Latino | 1 (0·6) | 1 (0·6) |
| Not Hispanic of Latino | 166 (94·9) | 152 (95·6) |
| Not Documented | 8 (4·6) | 6 (3·8) |
| Marital Status at Enrolment | | |
| Married | 134 (76·6) | 116 (73·0) |
| Divorced | 14 (8·0) | 18 (11·3) |
| Single | 12 (6·9) | 10 (6·3) |
| Widowed | 14 (8·0) | 13 (8·2) |
| Other | 0 (0·0) | 2 (1·3) |
| Unknown | 1 (0·6) | 0 (0·0) |
| Highest Level of Education | | |
| 8$^{th}$ Grade but Less than High School Graduate | 0 (0·0) | 3 (1·9) |
| High School Graduate, GED | 26 (14·9) | 27 (17·0) |
| Some College, Associate's Degree | 36 (20·6) | 32 (20·1) |
| Bachelor's Degree | 52 (29·7) | 46 (28·9) |
| Master’s Degree | 35 (20·0) | 24 (15·1) |
| Doctoral Degree | 26 (14·9) | 26 (16·4) |
| Unknown | 0 (0·0) | 1 (0·6) |
| **Comorbidities and Past Medical History** | | |
| Diabetes | 33 (18·9) | 36 (22·6) |
| Hypertension | 134 (76·6) | 123 (77·4) |
| Heart Failure[a] | 46/170 (27·1) | 50/157 (31·8) |
| Prior Myocardial Infarction | 15 (8·6) | 17 (10·7) |
| Previous Cardiac Intervention | 48 (27·4) | 49 (30·8) |
| Peripheral Arterial Disease | 11 (6·3) | 14 (8·8) |
| Cerebrovascular Disease | 21 (12·0) | 16 (10·1) |
| Liver Disease | 7 (4·0) | 7 (4·4) |

| | **Placebo** N = 175 | **Dexmedetomidine** N = 159 |
|---|---|---|
| Syncope | 7 (4·0) | 3 (1·9) |
| Sleep Apnoea | 44 (25·1) | 32 (20·1) |
| Chronic Lung Disease | 29 (16·6) | 22 (13·8) |
| **Baseline Neurocognitive and PROMIS Scores** | | |
| Delirium at Baseline | 0 (0·0) | 0 (0·0) |
| Abbreviated MoCA | 19·0 [18·0, 20·0] | 19·0 [17·0, 20·0] |
| PROMIS Scores[b] | | |
| Global Health – Physical | 50·8 [44·9, 57·7] | 50·8 [44·9, 57·7] |
| Global Health – Mental | 56·0 [48·3, 62·5] | 56·0 [50·8, 62·5] |
| Physical Function | 46·4 [40·1, 59·7] | 45·5 [39·4, 52·5] |
| Pain Interference | 40·7 [40·7, 51·2] | 40·7 [40·7, 55·0] |
| Applied Cognition | 51·7 [45·9, 62·7] | 53·0 [45·9, 62·7] |
| Sleep Disturbance[c] | 50·5 [43·8, 54·3] | 50·5 [43·8, 56·1] |

2Data is presented as mean (standard deviation), median [quartile 1, quartile 3], or n (%) depending on variable type and distribution. [a]History of heart failure was missing for seven participants, including two in the dexmedetomidine group and five participants in the placebo group. [b]All PROMIS scores are translated to T-scores for reporting. [c]Baseline PROMIS sleep disturbance scores were introduced after enrolment began, therefore sleep disturbance scores are missing in the first ten enrolled participants (six in the placebo group and four in dexmedetomidine group). No other data was missing unless specified. *Abbreviations: GED (General Educational Development), MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System)*

**SUPPLEMENTARY APPENDIX 10. Surgical Characteristics and Study Drug Administration in the Per-Protocol Cohort**

| | **Placebo** N = 175 | **Dexmedetomidine** N = 159 |
|---|---|---|
| **Surgical Characteristics** | | |
| Cardiopulmonary Bypass Time, *minutes* | 128·0 [95·0, 162·0] | 125·0 [93·0, 162·0] |
| Cross Clamp Time[a], *minutes* | 88·0 [70·0, 115·0] | 90·0 [73·0, 116·0] |
| Strata at Randomisation: Isolated CABG Surgery | 35 (20·0) | 35 (22·0) |
| Procedure Type Performed | | |
| Isolated CABG | 34 (19·4) | 33 (20·8) |
| AV Replacement + CABG | 23 (13·1) | 13 (8·2) |
| AV Replacement + MV Replacement | 3 (1·7) | 1 (0·6) |
| AV Replacement | 40 (22·9) | 35 22·0) |
| MV Repair | 29 (16·6) | 37 (23·3) |
| MV Repair + CABG | 4 (2·3) | 3 (1·9) |
| MV Replacement + CABG | 1 (0·6) | 2 (1·3) |
| MV Replacement | 4 (2·3) | 2 (1·3) |
| Other | 37 (21·1) | 33 (20·8) |
| Afternoon Surgery | 28 (16·0) | 18 (11·3) |
| **Study Drug Administration** | | |
| Received the Study Drug (Ever) | 175 (100·0) | 159 (100·0) |
| Received the Study Drug on POD 0 | 175 (100·0) | 159 (100·0) |
| Number of Days Receiving the Study Drug | | |
| 0 | 0 (0·0) | 0 (0·0) |
| 1 | 147 (84·0) | 131 (82·4) |
| 2 | 17 (9·7) | 18 (11·3) |
| 3 | 10 (5·7) | 10 (6·3) |
| 4 | 1 (0·6) | 0 (0·0) |

Data is presented as mean (standard deviation), median [quartile 1, quartile 3], or n (%) depending on variable type and distribution. [a]Cross clamp time was missing for one participant in the dexmedetomidine group who did not have their aorta clamped. *Abbreviations: AV (aortic valve), MV (mitral valve), CABG (coronary artery bypass graft), POD (postoperative day)*

**SUPPLEMENTARY APPENDIX 11. Outcomes and Clinical Characteristics of the Per-Protocol Cohort Conditional on the Randomisation Strata**

| | **Placebo** N = 175 | **Dexmedetomidine** N = 159 | **Effect Estimate** [g] (95% CI) | **P Value** |
|---|---|---|---|---|
| **Delirium Outcomes** | | | | |
| Postoperative Day 1 | | | | |
| Delirium *(Primary Outcome)*[a] | 9/162 (5·6) | 2/150 (1·3) | 0·23 (0·03, 0·91) | 0·036 |
| Delirium Severity [b] | 3·0 [2·0, 4·0] | 3·0 [2·0, 4·0] | 0·97 (0·89, 1·06) | 0·50 |
| Postoperative Days 1 to 3[c] | | | | |
| Delirium | 16/152 (10·5) | 9/135 (6·7) | 0·60 (0·25, 1·39) | 0·25 |
| Delirium Severity [b] | 3·0 [2·0, 4·5] | 3·0 [2·0, 4·0] | 0·97 (0·90, 1·05) | 0·52 |
| Delirium Free Days to Day 3[c] | | | 1·73 (0·76, 4·21) | 0·20 |
| 0 | 0/158 (0·0) | 0/157 (0·0) | | |
| 1 | 5/168 (3·0) | 3/157 (1·9) | | |
| 2 | 11/168 (6·5) | 6/157 (3·8) | | |
| 3 | 152/168 (90·5) | 148/157 (94·3) | | |
| **Hospital Clinical Characteristics** | | | | |
| Length of Hospital Stay, *days* [b] | 6·0 [5·0, 7·0] | 6·0 [5·0, 8·0] | 1·02 (0·94, 1·10) | 0·63 |
| Length of ICU Stay, *hours* [b] | 25·2 [23·0, 32·6] | 26·0 [23·0, 45·0] | 1·07 (0·95, 1·21) | 0·24 |
| Readmitted to the ICU | 4 (2·3) | 6 (3·8) | 1·68 (0·47, 6·67) | 0·43 |
| Total Postoperative Ventilation Time, *hours* [b] | 4·80 [3·90, 6·50] | 4·70 [3·80, 6·20] | 0·96 (0·85, 1·08) | 0·46 |
| Discharged to Home[d] | 141/174 (81·0) | 139/157 (88·5) | 1·80 (0·98, 3·40) | 0·06 |
| **Clinical Characteristics Within 30 Days Postoperatively** | | | | |
| Readmitted [e] | 14/174 (8·0) | 13/155 (8·4) | 1·04 (0·47, 2·29) | 0·93 |
| Surgical Site Infection | 3 (1·7) | 2 (1·3) | 0·69 (0·09, 4·28) | 0·69 |
| Reoperation for Bleeding | 2 (1·1) | 0 (0·0) | NA | 1·00 |
| Stroke | 1 (0·6) | 0 (0·0) | NA | 1·00 |
| Renal Failure | 1 (0·6) | 1 (0·6) | 1·13 (0·04, 28·78) | 0·93 |
| Atrial Fibrillation | 74 (42·3) | 57 (35·8) | 0·77 (0·49, 1·19) | 0·24 |
| **Mortality** | | | | |
| In Hospital Mortality | 1 (0·6) | 2 (1·3) | 2·19 (0·21, 47·34) | 0·53 |
| 30 Day | 1 (0·6) | 2 (1·3) | 2·19 (0·21, 47·34) | 0·53 |
| 90 Day | 1 (0·6) | 3 (1·9) | 3·33 (0·42, 67·77) | 0·30 |
| 180 Day | 3 (1·7) | 3 (1·9) | 1·11 (0·20, 6·07) | 0·90 |
| **Neurocognitive and PROMIS Scores at Follow Up** | | | | |
| Number Assessed at Follow Up | | | | |
| 30 Days | 118 | 116 | --- | --- |
| 90 Days | 108 | 98 | --- | --- |
| 180 Days | 105 | 106 | --- | --- |

| | | | | |
|---|---|---|---|---|
| Abbreviated MoCA [b] | | | | |
| 30 Days | 20·0 [19·0, 21·0] | 20·0 [18·0, 21·0] | 0·98 (0·95, 1·01) | 0·22 |
| 90 Days | 20·0 [19·0, 21·0] | 20·0 [19·0, 21·0] | 1·01 (0·98, 1·03) | 0·73 |
| 180 Days | 21·0 [19·0, 22·0] | 20·5 [19·0, 21·0] | 0·98 (0·94, 1·02) | 0·25 |
| PROMIS Global Health – Physical [f] | | | | |
| 30 Days | 47·7 [42·3, 54·1] | 50·8 [44·9, 54·1] | 0·5 (-1·7, 2·7) | 0·66 |
| 90 Days | 54·1 [47·7, 57·7] | 54·1 [47·7, 61·9] | 0·4 (-2·1, 2·9) | 0·75 |
| 180 Days | 54·1 [50·8, 61·9] | 57·7 [50·8, 61·9] | -0·4 (-2·8, 2·0) | 0·76 |
| PROMIS Global Health – Mental [f] | | | | |
| 30 Days | 56·0 [50·8, 67·6] | 59·0 [50·8, 67·6] | 0·8 (-1·5, 3·2) | 0·48 |
| 90 Days | 62·5 [56·0, 67·6] | 59·0 [53·3, 67·6] | -0·4 (-2·8, 2·0) | 0·75 |
| 180 Days | 62·5 [53·3, 67·6] | 62·5 [53·3, 67·6] | -0·4 (-2·7, 1·9) | 0·75 |
| PROMIS Physical Function [f] | | | | |
| 30 Days | 39·1 [35·5, 44·6] | 40·8 [36·8, 46·4] | 1·1 (-0·9, 3·0) | 0·28 |
| 90 Days | 47·5 [43·7, 52·5] | 48·8 [44·6, 59·7] | 0·7 (-1·6, 3·0) | 0·54 |
| 180 Days | 50·4 [46·4, 59·7] | 50·4 [45·5, 59·7] | -0·5 (-2·8, 1·7) | 0·63 |
| PROMIS Pain Interference [f] | | | | |
| 30 Days | 51·2 [40·7, 56·6] | 49·9 [40·7, 55·8] | -0·5 (-2·8, 1·7) | 0·65 |
| 90 Days | 40·7 [40·7, 49·9] | 40·7 [40·7, 51·2] | 0·7 (-1·4, 2·8) | 0·53 |
| 180 Days | 40·7 [40·7, 40·7] | 40·7 [40·7, 47·9] | -0·3 (-2·0, 1·4) | 0·76 |
| PROMIS Applied Cognition [f] | | | | |
| 30 Days | 53·0 [47·7, 62·7] | 54·6 [48·2, 62·7] | 1·0 (-1·1, 3·1) | 0·34 |
| 90 Days | 54·6 [47·7, 62·7] | 53·0 [49·5, 62·7] | 0·3 (-2·1, 2·8) | 0·80 |
| 180 Days | 53·0 [48·6, 62·7] | 53·8 [47·7, 62·7] | -0·5 (-2·7, 1·7) | 0·64 |
| PROMIS Sleep Disturbance [f] | | | | |
| 30 Days | 50·5 [43·8, 56·1] | 50·5 [43·8, 56·1] | -1·2 (-3·7, 1·3) | 0·35 |
| 90 Days | 48·4 [41·1, 54·3] | 48·4 [43·8, 52·4] | 0·2 (-2·1, 2·5) | 0·87 |
| 180 Days | 46·2 [41·1, 50·5] | 46·2 [41·1, 50·5] | -0·5 (-2·9, 1·9) | 0·70 |

Data is presented as mean (standard deviation), median [quartile 1, quartile 3], or n (%) depending on variable type and distribution. [a]A total of 22 participants (9 in dexmedetomidine group and 13 in the placebo group) were missing the primary outcome, incidence of delirium on postoperative day one. [b]Values were log transformed for analysis, with resulting effect estimates presented as a ratio of geometric means. Effect estimates can be interpreted as the percent increase (or decrease) in for every one-unit increase (e.g. 1.02 corresponds to a 2% increase in the dexmedetomidine group). [c]A total of 47 participants (24 in dexmedetomidine group and 23 in the placebo group) had missing delirium assessments through postoperative day three. One additional participant was assessed as delirious but the delirium severity score was missing. [d]Discharge status was missing for 3 participants (2 in dexmedetomidine group and 1 in the placebo group). [e]Readmission status was missing for 5 participants (4 in dexmedetomidine group and 1 in the placebo group). No other data was missing unless specified. [f]All PROMIS scores are translated to T-scores for reporting. [g]Effect estimates are reported as odds ratios (binary outcomes) or mean difference (continuous outcomes) comparing the dexmedetomidine group to the placebo group (reference). *Abbreviations: ICU (intensive care unit), MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System)*

**SUPPLEMENTARY APPENDIX 12. Kaplan Meier Curve in the Modified Intention-to-Treat Cohort**