Maximizing trEatment of Neurological Dysfunction using INtravenous Guanfacine (MENDING) study

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Title	**Maximizing trEatment of Neurological Dysfunction using INtravenous Guanfacine (MENDING): A Randomized Placebo-Controlled Trial**
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INTRODUCTION

This document serves as the Statistical Analysis Plan (SAP) for Aims 1 and 2 of the **Maximizing trEatment of Neurological Dysfunction using INtravenous Guanfacine (MENDING)** Trial. It accompanies version 1.5 of the protocol (dated 9/12/2023). This SAP has been completed prior to the completion of enrollment, unblinding of data, and the analyses of the outcomes.

1. METHODS AND DESIGN

1.1. TRIAL DESIGN AND AIMS

The MENDING trial is a phase II proof-of-concept trial of IV guanfacine vs. placebo for the treatment of critical illness delirium. The aims of the trial are the following:

Aim 1: To determine whether IV guanfacine twice a day will increase the number of days alive without delirium and coma (delirium/coma-free days, DCFDs) over 14 days relative to placebo.

Aim 2: To evaluate whether IV guanfacine twice a day will increase days alive and free of mechanical ventilation (ventilator-free days, VFDs) and days alive and free of the ICU (ICU-free days, IFDs) over 28 days relative to placebo.

1.2. RANDOMIZATION AND BLINDING

The trial aims to randomize 50 patients with delirium in the ICU in a 1:1 ratio to IV guanfacine or placebo. A computer-generated randomization scheme (with permuted block sizes) was created by the study's primary biostatistician and uploaded directly into REDCap's randomization module [1-2]. Investigators, patients, and clinicians will be blinded for the duration of the study until the database is locked.

1.3. POWER ANALYSIS AND SAMPLE SIZE

Prior to beginning enrollment, our goal was to enroll and randomize 100 participants. We estimate that the participants in the placebo group will have 6.9±5.2 delirium/coma-free days (DCFDs) during the 14-day interventional study period based on the results from the recently completed Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients (MENDS2) study that used similar entry criteria [3]. Enrolling 100 patients would provide us at least 80% power to detect a 3 DCFDs

difference between the treatment groups over 14-day period for Aim 1. For Aim 2, we estimate that the participants in the placebo group will have 15.4±10.9 ventilator-free days (VFDs) and 13±10 ICU-free days (IFDs) based on the results from our MENDS2 study. Enrolling 100 patients would provide us at least 80% power to detect a 6 VFDs and 5.6 IFDs difference between the treatment groups over 28-day period.

Due to low enrollment and, given that this is a phase II proof-of-concept trial to guide safety and preliminary efficacy for future work, our final enrollment target was reduced from 100 to 50 with approval from the National Institute of Health and the Data and Safety Monitoring Board.

By analyzing 50 patients, we will have 80% power to detect a difference of 4.2 DCFDs over 14 days between the IV guanfacine and placebo groups. By analyzing 50 patients, we will have 80% power to detect a difference of 8.8 VFDs and 8.1 IFDs over 28 days between the IV guanfacine and placebo groups.

2. OUTCOMES

2.1. PRIMARY OUTCOME

The primary outcome is delirium/coma-free days (number of days alive without delirium or coma) for 14 days starting on the day of randomization.

2.2. SECONDARY OUTCOMES

The secondary outcomes are:

- Ventilator-free days (number of days alive and free of mechanical ventilation) for 28 days starting on the day of randomization.
- Intensive care unit (ICU)-free days (number of days alive and free of ICU) for 28 days starting on the day of randomization.

For VFDs, both invasive and non-invasive ventilation will be taken into account. To account for terminal extubation for comfort care measures, successful ventilator (invasive or non-invasive) discontinuation will be defined as being alive and free of ventilation for 48 hours following discontinuation. For example, if a patient was discontinued from MV and ventilation was initiated again within the next 48 hours or the patient died within the next 48 hours, then the time (<48 hours) that was off ventilation did not count as a ventilator-free day. Similarly, for ICU-free days, successful ICU discharge will be defined as being alive and free of ICU stay for 48 hours following ICU discharge.

2.3. EXPLORATORY OUTCOMES

The exploratory outcomes are:

1. Hospital-free days (number of days alive and free of hospital) for 28 days starting on the day of randomization.
2. 90-day mortality starting on the day of randomization.

For hospital-free days, successful hospital discharge will be defined as being alive and free of hospital stay for 48 hours following hospital discharge.

2.4. DESCRIPTIVE OUTCOMES

Among others, the following outcomes will be reported as descriptive statistics.

1. Co-administration of sedatives, analgesics, and antipsychotics (frequency and quantity of administration) for 14 days starting on the day of randomization.
2. Hypotension (refractory systolic blood pressure < 90 mm Hg or mean arterial blood pressure < 65 mm Hg despite ongoing ICU therapies) for 14 days starting on the day of randomization.
3. Bradycardia (heart rate < 60 beats per minute despite ongoing ICU therapies) for 14 days starting on the day of randomization.
4. Mental status (new, acute neurologic disturbances such as blurred vision, dizziness, weakness, or vertigo) for 14 days starting on the day of randomization.

3. STATISTICAL ANALYSIS

3.1. STATISTICAL PRINCIPLES

The statistical analyses for all the aims will be conducted as per this SAP and follow the statistical principles described below.

Participant flow diagram of this trial will be reported as specified by the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [4]. The flow diagram will display all stages of the trial such as screening, exclusions, enrollment, randomization, death, and study withdrawal.

Demographic information, clinical characteristics at baseline and study outcomes will be presented for each treatment group. Median and interquartile range (IQR) will be used for describing continuous variables, and frequency (%) will be used for describing categorical variables.

No hypothesis testing for the differences in baseline characteristics between the treatment groups will be conducted as recommended by the CONSORT 2010 guidelines for reporting parallel group randomized clinical trials [4-5].

Statistical significance level will be set at 5% for all outcomes. 95% confidence intervals will be reported with all effect estimates. No multiple comparison adjustments will be made for secondary and exploratory outcomes following the standard practice of analyzing multiple, prospective clinical trial outcomes [6-9]. No subgroup analyses will be conducted.

Missing data will be imputed, and the imputation process will be reported in detail. Since the percentage of missing data is anticipated to be lower than 5%, single imputation is planned to be used.

3.2. ANALYSIS POPULATION

Analysis population will be based on the modified intent-to-treat (ITT) principle for all outcomes. The analysis cohort will include patients who were randomized and received study drug for all the primary, secondary and exploratory outcomes unless otherwise specified in this SAP.

3.3. ANALYSIS METHODS AND MODEL ASSUMPTIONS

All outcomes will be analyzed using regression models. Since this is a phase II proof-of-concept randomized controlled trial, unadjusted analyses will be the primary analyses, where the models will only have the treatment variable and will not be adjusted for any covariates.

Proportional odds logistic regression (POLR) will be used for modeling skewed continuous outcomes [10-11]. Proportional odds assumptions will be checked graphically using multiple cutoffs of the outcome, i.e., binary logistic regression models will be fitted using different cutoffs of the outcome, and the log odds ratios (estimated coefficients) will be plotted against cutoffs to check proportionality assumption [10]. Odds ratios along with 95% confidence intervals will be reported for POLR models.

Simple linear regression will be used for continuous outcomes that are normally distributed and satisfy the other assumptions. Assumptions will be checked graphically using residuals versus fitted values plots and quantile-quantile plots. Regression coefficients along with 95% confidence intervals will be reported for linear regression.

For 90-day mortality, Kaplan-Meier survival curve stratified by the treatment groups will be reported. Patients alive at 90-day will be censored at 90-day. Patients whose death information is unknown will be censored at their last known date alive.

Adjusted analyses will be conducted as sensitivity analyses. For adjusted analyses, all outcomes will be modeled using multivariable regression methods adjusting for the following covariates: age and severity of illness (measured by SOFA score) at randomization. If we have sufficient degrees of freedom in the model, interaction of age and treatment will be evaluated using an interaction term in the model. Otherwise, descriptive statistics will be generated by subgroups. For multivariable regression models, depending on the distribution of the variable, non-linear relationships between the outcome and the continuous covariates will be incorporated into the statistical models using restricted cubic splines with 3 knots when appropriate.

For the sensitivity analyses, redundancy analysis will be performed before modeling using an adjusted R^2 cutoff of 0.7 to evaluate for multicollinearity. Covariates that are highly correlated will be dropped from the model based on the rank order specified above. If the model is overfit, covariates will be reduced based on the rank order listed above.

4. SOFTWARE

Statistical software R version 4.2.3 (or above) will be used for all analyses [12].

5. REFERENCES

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