



STATISTICAL ANALYSIS PLAN

**A Phase II Double-blind Randomized Controlled Trial of Intravenous Hydroxocobalamin
in Septic Shock**

Clinical Trials.gov Number: NCT03783091

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Statistical considerations

1.1 Study Design

This is a single site, prospective, randomized, phase II study.

1.2 Randomization

Patients will be randomized utilizing OnCore by Forte Clinical Trial Management Software. Patients will be randomized with a 1:1 ratio with a block scheme randomization.

1.3 Sample Size and Power Estimate

Using the variability values from ATHOS-3 trial,⁴² if we assume a standard deviation of 15% in percent change in blood pressure from baseline to 3 hours, then with 13 patients per group the study would have 80% power to detect a 15 percentage point difference in the percent change of norepinephrine at 3 hours between the two groups at a one-sided 5% significance level.

1.4 Replacement Policy

Patients will only be replaced if they were consented into the trial but failed to receive study drug for any reason. Patients who began treatment but were unable to complete the infusion will be included in the analysis with intent to treat.

1.5 Interim Analyses and Stopping Rules

No interim analysis is planned at this time.

After each 25% increment in completed enrollment, the study will be reviewed by the DSMB. The DSMB will provide a recommendation to either continue the study or stop early.

1.6 Analyses Plans

Appropriate descriptive statistics such as median, mean, standard deviation, range, and proportions reported with 95% confidence interval will be used to summarize the demographic and clinical characteristics of our patient population. Time-to-event outcomes, such as length of stay, time to 50% reduction in vasopressors, will be presented using cumulative incidence curves with in-hospital mortality as a competing risk. The primary outcome, the reduction in norepinephrine dose at 3 hours, will be compared between the groups using the Wilcoxon rank-sum test. In addition to the primary unadjusted analysis, regression-based approaches will be used to explore the effect of the prognostic covariates such as age, co-morbidities, APACHE scores, etc. on the outcomes of interest. All analyses will be on an intention-to-treat basis, utilizing all patients randomized.

Statistical support will be provided by Aniko Szabo, PhD. She is an Associate Professor of Biostatistics and Director of Biostatistics Consultation at the Medical College of Wisconsin in Milwaukee, WI.