Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial

Acronym: **A**scorbic acid, **C**orticosteroids, and **T**hiamine in **S**epsis (**ACTS)** Trial

CLINICAL TRIAL PROTOCOL

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Principal investigator:
Michael W. Donnino, MD
Director of Center for Resuscitation Science
Associate Professor of Medicine, Harvard Medical School
Attending Physician in Emergency and Critical Care Medicine, BIDMC

Beth Israel Deaconess Medical Center
West Clinical Campus 2nd Floor
One Deaconess Road, Boston MA 02215
Phone: 617-754-2295
Fax: 617-754-2350
Email: mdonnino@bidmc.harvard.edu

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SYNOPSIS

The “Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS)” trial is a multi-center, double-blind, randomized clinical trial that aims to determine the impact of Vitamin C, Hydrocortisone, and Vitamin B1 vs. Placebo on organ injury and mortality on participants with sepsis and septic shock. The trial will be conducted in accordance with all applicable national and international laws, regulations, and guidelines The trial and this protocol is developed in accordance with the International Conference on Harmonization (ICH) guidelines[1-3] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[4,5]. The principal investigator wrote the protocol with input from the steering committee. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

TRIAL OVERVIEW

Title	Vitamin C, Hydrocortisone, and Vitamin B1 in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial (The ACTS Trial)

Clinical Trials Number	NCT03389555
Sources of monetary or material support	Open Philanthropy Project (https://www.openphilanthropy.org/)
Study Sites	12-sites in the United States
Condition studied	Sepsis and septic shock
Interventions	Vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6 hours x 4-days), and Vitamin B1 (100mg every 6 hours x 4-days)
Comparator	Placebo
Inclusion criteria	• Adult participant (age ≥ 18 years) • Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection • Receiving vasopressor (norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin, or angiotensin II)
Exclusion criteria	• Member of a protected population (pregnant, prisoner) • Known history of kidney stones within the past 1 year • End stage renal disease (ESRD) requiring dialysis • Known history of G6PD deficiency • Known history of Hemochromatosis • Comfort Measures Only status • Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician) • Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin (<2mg) • Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug • Clinical indication for ascorbic acid supplementation in any form • Clinical indication for vitamin B1 as determined by the clinical team providing this drug • Known allergy to vitamin C, hydrocortisone, or vitamin B1
Study type	Interventional Allocation: Randomized (1:1) Intervention model: Parallel group Masking: Double-blind
Target sample size	200 Participants (100/arm)
Primary outcome	Change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours
Key secondary outcomes	Incidence of renal failure during index ICU stay 30-day mortality

STEERING COMMITTEE

Michael Donnino, M.D.
Associate Professor of Medicine
Director, Center for Resuscitation Science
Beth Israel Deaconess Medical Center
Harvard Medical School

Paul E. Marik, M.D.
Professor of Medicine
Chief, Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School

Ari Moskowitz, M.D.
Attending, Pulmonary and Critical Care Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School

Katherine Berg, M.D.
Assistant Professor of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School

Lars W. Andersen, M.D., MPH, Ph.D
Associate Professor of Medicine
Research Center for Emergency Medicine
Department of Clinical Medicine
Aarhus University and Aarhus University Hospital

Anne Grossestreuer, Ph.D.
Instructor in Emergency Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School

Michael N. Cocchi, MD
Assistant Professor of Emergency Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School

Joseph Miller, MD
Attending, Emergency Medicine
Department of Emergency Medicine
Henry Ford Hospital

Conflicts of interest
The members of the steering committee have no financial conflicts of interest related to the current trial.

TRIAL SITES

Coordinating Center
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215
Site Investigator: Michael W. Donnino, MD

Enrolling Sites*

Hospital Name	Location	Site Principal Investigator
Henry Ford Hospital	Detroit, MI	Bruno DiGiovine, MD
DMC-Detroit Receiving Hospital	Detroit, MI	Rob Sherwin, MD
DMC-Sinai-Grace Hospital	Detroit, MI	Rob Sherwin, MD
Harper Hospital	Detroit, MI	Rob Sherwin, MD
UT Health, The University of Texas Health Science Center	Houston, TX	Pratik Doshi, MD
Mayo Clinic	Phoenix, AZ	Ayan Sen, MD
Beth Israel Deaconess Medical Center	Boston, MA	Ari Moskowitz, MD
Beaumont Hospital	Royal Oak, MI	Ron Otero, MD
Brigham and Women's Hospital	Boston, MA	Peter Hou, MD
Long Island Jewish Hospital Center - Queens	New York, NY	Maksim Korotun, MD; Jonathan Gong, MD
Long Island Jewish Hospital Center – Hyde Park	New York, NY	Ayelet Hilewitz, MD; Jonathan Gong, MD
Mount Auburn Hospital	Cambridge, MA	Jessica McCannon, MD
University of Pittsburgh	Pittsburgh, PA	David Huang, MD
South Shore Hospital	Weymouth, MA	Mark Hershey, MD

*Depending on study progress, sites may be added or removed in the future.

1. BACKGROUND AND SIGNIFICANCE

1.1 Scope of the Problem

The worldwide incidence of sepsis has been estimated at more than 23 million cases[6] and sepsis contributes to more than a third of all hospital deaths in the United States.[7,8] Mortality for those in septic shock with elevated lactate is more than 40%.[9] In addition to high short-term mortality, sepsis is associated with significant post-discharge morbidity and mortality.[10-15] The economic burden for participants suffering from sepsis is staggering with an estimated yearly financial burden of $17 billion.[16] Treatments are generally limited to antibiotics and intravenous fluids while providing support to maintain organ function.[17,18]

1.2 Existing Interventions

To date, numerous interventions have been tested for participants with sepsis and septic shock with limited, if any, success.[19-22] Recently, three large studies found no benefit from early goal directed therapy over usual care in emergency department participants with sepsis.[23-25] Other recent studies focusing on hemodynamics, fluid therapy, and transfusions have also failed to show a significant benefit in this participant population.[26-28] Previous studies focusing on immunomodulary therapies or drotrecogin alfa have likewise shown disappointing results.[29-35]

1.3 The combination of vitamin C, hydrocortisone, and vitamin B1 may improve outcomes

In a before-and-after study exploring the effects of the combination of vitamin C, hydrocortisone, and vitamin B1 in a cohort of participants with sepsis and septic shock, Marik et. al. found a remarkable improvement in time to shock reversal (18.3 ± 9.8 hours vs. 54.9 ± 28.4 hours), organ injury (ΔSOFA 4.8 ± 2.4 vs. 0.9 ± 2.7), and mortality (8.5% vs. 40.4%) following implementation of the drug 'cocktail' as compared to before implementation even after adjusting for potential confounders.[36] This study joins other promising trials of individual elements of this drug combination. In a trial of vitamin B1 in septic shock, there was a substantial reduction in mortality and organ injury (particularly kidney injury) in those with vitamin B1 deficiency and septic shock who were given vitamin B1 as compared to placebo.[37,38] In addition, several studies of vitamin C alone have shown promise in critically ill populations[39-42] and a recent meta-analysis of corticosteroids in sepsis suggests potential benefit.[43]

1.4 Physiologic Rationale

The combination of vitamin C, hydrocortisone, and vitamin B1 is hypothesized to improve outcomes in sepsis through a number of mechanisms.[36] Vitamin C is an important contributor to endothelial integrity and severe deficiency states (e.g. scurvy) can result in endothelial breakdown with resultant vascular leak and edema.[44,45] In addition, vitamin C is a potent anti-oxidant and is integral to endogenous vasopressor synthesis.[36] Hydrocortisone, a potential adjunctive therapy in septic shock[46,47], may act synergistically with vitamin C.[48,49] Vitamin B1, a key cofactor of pyruvate dehydrogenase, is a critical component of metabolic dysfunction without which a shift towards anaerobic energy production occurs.[50] Vitamin B1 is also a necessary component of the pentose phosphate pathway, which plays a role in reducing oxidative stress.[51,52] While the physiologic effects of these drugs given in combination is not entirely known, we hypothesize that there will be synergistic effects with respect the metabolic resuscitation of sepsis.

2. TRIAL DESIGN

2.1 Overview

This will be an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vitamin C, hydrocortisone, and vitamin B1 vs. placebo in participants with sepsis and septic shock. A total of 200 adult participants will be enrolled. The primary outcome will be the change in SOFA score between enrollment and 72-hours. Key secondary outcomes include the incidence of renal failure during the index ICU stay and survival at 30 days.

2.2 Allocation

Participants will be randomized in a 1:1 ratio to either the combination of vitamin C, hydrocortisone, and vitamin B1 or placebo in blocks with random sizes of 2 or 4. The randomization will be stratified according to site.[53] An independent statistician will create the randomization list using a random number generator. The complete list will only be shared with an independent pharmacy consultant, who will not be involved in clinical care. The pharmacy consultant and the independent statistician will both store the randomization list. The research pharmacy at each enrolling site will receive a site-specific randomization list.

2.3 Intervention

2.3.1 Vitamin C, Hydrocortisone, and Vitamin B1

The study drugs will consist of vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6 hours x 4-days), and vitamin B1 (100mg every 6 hours x 4-days).

2.3.2 Placebo

The placebo will consist of matching volumes of normal saline (0.9% NaCl). See below section 4.4 for specifics of drug and placebo preparation.

2.4 Blinding

The trial will be double-blind; participants, investigators, and the clinical team will be blinded to the allocation. Only the pharmacy providing the study drug will be aware of the allocation. The pharmacy will not be involved with clinical care or outcome evaluation.

As vitamin C possess a yellow tinge, the bags containing the vitamin C/placebo will be covered with light-protective bags. In testing, after dilution there is not distinguishing characteristics of the vitamin C vs. placebo in the IV tubing. Vitamin C, hydrocortisone, and vitamin B1 are not known to have distinctive rapid effects which could lead to unblinding.

The decision to unblind will be at the complete discretion of the treating physician and clinical team. If a clinical team wishes to unblind a participant (e.g. if anaphylaxis occurs), they will contact the research pharmacy who will reveal the study group to the clinical team (but the research team will remain blinded). However, we do not expect many scenarios where emergency unblinding will be necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report form. The patient will no longer receive study medications, but will be followed for outcomes.

2.5 Regulatory Issues

An Investigational New Drug (IND) application was submitted to and approved by the Food and Drug Administration (FDA) for the study of vitamin C, hydrocortisone, and vitamin B1 in sepsis and septic shock (IND # 136882).

The trial has been registered on ClinicalTrials.gov: NCT03389555

3. SETTING AND PARTICIPANT POPULATION

3.1 Setting

The trial will be conducted at approximately 13 hospitals in the United States. Additional sites might be recruited if needed.

3.2 Inclusion criteria

Inclusion criteria:

1) Adult participant (age ≥ 18 years)
2) Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection
3) Receiving (continuous infusion) vasopressor (norepinephrine, phenylephrine, epinephrine, dopamine, angiotensin II, or vasopressin)
    a. Hypotension related primarily to sepsis as opposed to another cause of hypotension (e.g. bleed, cardiogenic shock)

3.3 Exclusion criteria

Exclusion criteria:

1) Member of a protected population (pregnant, prisoner)
2) Known history of kidney stones within the past 1 year (not including incidentally noted stones noted on imaging studies)
3) End stage renal disease requiring dialysis (hemodialysis or peritoneal dialysis)
4) Known history of G6PD deficiency
5) Known history of Hemochromatosis
6) Comfort Measures Only status
7) Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)
8) Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin (<2mg)
9) Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug
10) Clinical indication for ascorbic acid supplementation in any form
11) Clinical indication for vitamin B1 as determined by the clinical team providing this drug
12) Known allergy to vitamin C, hydrocortisone, or vitamin B1

Justification of Inclusion and Exclusion Criteria: The inclusion criteria were chosen to isolate a septic participant population with high risk of organ injury and death. The exclusion criteria were chosen to minimize the risk of potential harm and to ensure that participants enrolled do not already have chronic end-stage renal failure with a high likelihood of early need for renal replacement therapy. By evaluating this high-risk population (i.e., most likely to die), we will target those most likely to benefit and therefore increase the probability of showing efficacy.[19]

3.4 Pregnancy

Hydrocortisone is considered pregnancy class C on the basis of animal studies showing an association between prenatal parenteral hydrocortisone use and risk of cleft-palate. In addition, there are concerns about effects of hydrocortisone on fetal growth and the possibility of neonatal adrenal insufficiency. The effects of high-dose vitamin C and thiamine in pregnancy are not entirely known. As such, participants who are pregnant will be excluded from the study. Prior to enrollment, all participants of potentially child-bearing potential (women aged <45 years[54]) will be required to have a negative serum or urine HCG test (generally performed as standard-of-care).

We will additionally inform all women of child-bearing potential who are randomized in this study that we recommend they remain abstinent or use two forms of birth control during the study period and for a period of 48-hours after the last dose of study drug.

4. TRIAL PROCEDURES

4.1 Participant Identification

Screening will be performed in the emergency department and intensive care units (ICUs) with the assistance of electronic screening mechanisms . Detailed screening logs, with reason(s) for exclusion will be kept at each site and reported in the final publication.

We anticipate that all patients, as part of standard-of-care for the septic patient, will have a urine or serum HCG test performed (if a female of child-bearing age). If this test is not sent as part of standard-of-care, it should be sent prior to consent.

4.2 Consent procedures

Informed, written consent will be obtained for all participants prior to enrollment.

After it is determined that they meet all inclusion criteria and no exclusion criteria, the participant (or legally authorized representative [LAR] if the participant is not able to provide consent) will be approached for written informed consent by a physician co-investigator from the team. The investigator will provide the participant/representative information regarding the background and significance of the study, eligibility criteria, and a description of the protocol. To ensure we are correctly identifying the potential participant's LAR, we communicate with members of the clinical team. The consent process may need to be modified based on site-specific IRB recommendations.

The name of the study investigator obtaining consent will be clearly documented, and this person will sign the informed consent document and provide the date and time of their signature. If a physician is performing remote consent, then a copy of the consent form will be signed as soon as he/she is physically present. Signed copies of the consent form will be given to the participant/surrogate, and the original consent document will be stored in the secure study file. In obtaining and documenting informed consent, each investigator will comply with the applicable regulatory requirements and adhere to the ethical and Good Clinical Practice principles that have their origin in the Declaration of Helsinki.

4.3 Randomization

After consent is obtained, the research team will notify the local research pharmacy. The research pharmacy will be in possession of the randomization list and will determine which arm (intervention vs. placebo) the participant will be enrolled in.

Patients should be randomized, consented, and enrolled in the study as soon as possible after meeting inclusion criteria. Patients should not be *consented* if it has been >24hours since the patient met inclusion criteria (i.e. start of vasopressors). At the time of randomization and study drug administration, the patient should still be receiving a vasopressor. The patient should not be given study drug if the vasopressor has been stopped (e.g. patient met inclusion criteria overnight but could not be consented for logistical reasons and then improves to the point of no longer requiring a vasopressor). In this scenario, the paitent will be entered into the dabase as consented but not enrolled.

4.4 Drug preparation and administration

The vitamin C and vitamin B1 will be mixed together in 100ml of normal saline and administered intravenously over 45-60 minutes. The hydrocortisone will be given intravenously as a push-dose in 1ml of saline over 1-2 minutes. The placebo will be given using techniques and volumes matching those of the study medications.

All study medications will be continued for 4-days or until the participant expires or leaves the intensive care unit.

4.4.1 Contingencies and Participant Withdrawal

- In the unlikely event that a participant is discharged alive from the hospital prior to 4 days after enrollment, all study medications will be stopped.The participant will remain in the study and will be followed for outcomes.
- Hydrocortisone is occasionally used for refractory septic shock. If the clinical team opts to provide a participant hydrocortisone, the hydrocortisone will be given open-label but the vitamin C/B1 will remain randomized and blinded. In this case, the research team will ensure that study hydrocortisone/placebo is replaced by open-label hydrocortisone. The participant will remain in the study and will be followed for outcomes.
- If the clinical team decides to give the participant vitamin B1 for clinical purposes, the study drug will be continued (including thiamine) as long as the total maximum dose of vitamin B1 is ≤1,500mg/day. 1,500mg day is a standard dose for Wernicke's encephalopathy at many institutions and has not been associated with any increased harm.
- If the clinical team decides to give the participant vitamin C for clinical purposes, further administration of study meds will be stopped. The participant will remain in the study and will be followed for outcomes.
- If a participant withdraws from the study, further administration of study meds will be stopped. Data collected prior to withdrawal will be maintained but additional data will not be collected.

4.5 Specimen collection procedures

4.5.1 Timing and volume of blood draw

All participants will have a blood samples collected at four time-points and urine samples at two time-points (if not already available as part of routine clinical care). Blood will be obtained by venipuncture, or from an existing venous or arterial catheter. Urine will be collected via clean catch urine or via catheter.

Specimen Collection Time Points

1. T1=0 hrs (just before study drug administration)
2. T2=24 hrs (+/- 2 hrs)
3. T3=72 hrs (+/- 2 hrs)
4. T4=120hrs (+/- 12hrs)

4.5.2 Specimen samples

At the T1, T2, T3, and T4 time points, blood will be sent for complete blood count (including hemoglobin, white blood cell count, platelet count), a serum chemistry (including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatining, glucose, aspartate transaminase, alanine transaminase, and total bilirubin), and a venous blood gas to measure lactate. These tests will be performed by the clinical laboratory at each site. As many of these laboratory tests are commonly obtained for clinical purposes, these tests do not need to be repeated if a result is available from the clinical care of the participant within 2 hours of the time point (or within 12 hours of the T4 time-point).

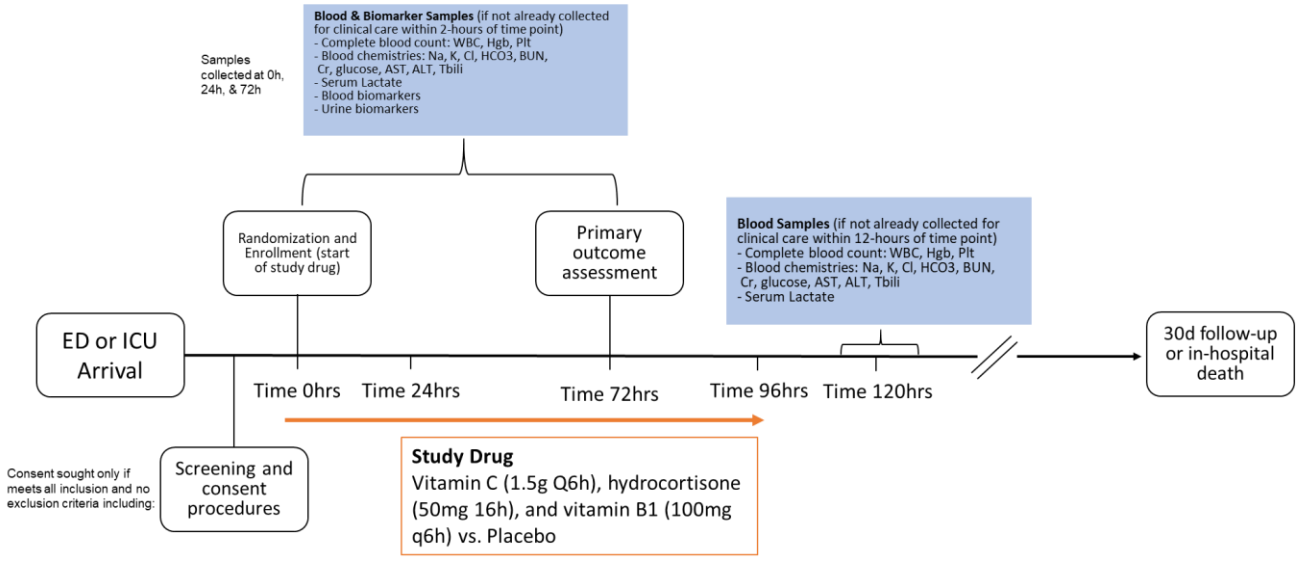
In addition to traditional clinical markers, blood will be obtained for future biomarker analysis (including inflammatory biomarkers, markers of endothelial function, and markers of mitochondrial function), and measurement of vitamin C, vitamin B1, and cortisol levels. The total volume of blood that may be drawn for a participant at each time point will not exceed 60mls. Levels of vitamin C, vitamin B1, and cortisol will be measured at time T1 and time T3 only. 20ml of urine will be collected for future biomarker analysis at T1, T2, and T3.

If performed as part of standard-of-care, results of urinalysis and urine sediment testing will be collected prior to enrollment.

4.5.3 Biomarker tube initial processing and shipping
Please see accompanying blood collection standard operating procedure for full details. In brief, 15ml of blood will be drawn into EDTA tubes and 10ml of blood will be drawn into a corvac tube. From one of the EDTA tubes, 3ml of whole blood will be initially drawn and separated into 3x 1ml aliquots. Plasma will then be isolated from the EDTA tube(s) and aliquoted into cryovials as follows: 4x 0.5ml aliquots and the remainder in 1ml aliquots. Serum will then be isolated from the corvac tube, and separated into 1ml aliquots. Cryovials will be protected from light and frozen at -80°C until processing. An additional 20ml of urine will also be collected, centrifuged, and separated into 1ml aliquots then frozen at -80°C until processing.

Sites will be expected to ship frozen samples to the coordinating center after every 5 enrollments. The coordinating center will assist with all shipping procedures.

4.6 Study flow diagram



4.7 General Sepsis Management
Investigators should follow local sepsis management guidelines. No specific sepsis bundle is required by this study, however the early administration of antibiotics, maintenance of a mean arterial pressure ≥65mmHg with a combination of volume resuscitation and vasopressors, and early source control are recommended—as detailed in the Suriving Sepsis Guidelines.[55] Elements of sepsis care should be reported on the online case report form (CRF).

4.8 Glucometer use during the study period

High dose vitamin C has been shown to falsely elevate glucose level readings when measured with certain point-of-care glucometers employing glucosedehydrogenase-pyrroloquinoline quinone amperometric methods[56]. Some commonly used glucometer brands using this approach include Accu-Chek (Roche Diagnostic) and Optium (Abbott Diabetes Care) (but not StatStrip; Nova Biomedical). While the effects of high-dose vitamin C on glucometer readings have been seen primarily at higher doses of vitamin C than are intended for use in this trial,[56] we recommend that sites explore what glocumeters are in use in local ICUs. If locally used glucometers may be impacted by high serum concentrations of vitamin C (as determined by the manufacturer), we recommend that clinical teams caring for enrolled participants be alerted to the possibility of falsely elevated blood-glucose levels when measured by glucometer. If there is a clinical concern about a glucose reading obtained via glucometer, a serum glucose should be obtained which will not be impacted by vitamin C. In the event of an emergency related to suspected hypoglycemia, glucose should be immediately given while a serum glucose level is pending.

5. OUTCOMES

5.1 Definitions

5.1.1 Primary Outcome

The primary outcome will be the absolute change in the Sequential Organ Failure Assessment (SOFA]) score from enrollment (time=0) to 72 hours after drug administration. The SOFA score will be defined using a modification in which the SaO2/FiO2 ratio is substituted for the PaO2/FiO2 ratio as has been previously described.[57,58] This modified score will be used so that participants without an existing arterial catheter can be spared arterial puncture.

Points	SaO2*/FiO2§	Blood Pressure	GCSǁ	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10^{3}µL)
1	<400	< 70 mm/Hg	13–14	1.2–1.9	1.2 – 1.9	<150
2	<326	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	<236 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 5µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP†<500ml/day	<50
4	<151(and receiving invasive or non-invasive mechanical ventilation)	dopamine > 15, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	>12	> 5.0 UOP†<200ml/day Or receiving renal replacement therapy	<20

*SaO2=Oxygen saturation (%); § = Fraction of inspired oxygen (%); ǁ = Glasgow Coma Scale; † = Urine Output

Fio2 will be determined by using either the set FiO2 (for patients receiving invasive or non-invasive mechanical ventilation) or by adding 3% FiO2 for each liter/minute of supplemental oxygen added up to 100% FiO2 (for patients not receiving mechanical ventilation). Patients with an SaO2/FiO2 ratio <236 who are not receiving invasive or non-invasive mechanical ventilation, will be assigned a score of 2.

5.1.2 Key Secondary Outcomes

Incidence of Acute Renal Failure – Renal failure will be defined as the development of Kidney Disease Improving Global Outcomes [KDIGO] Stage 3 acute kidney injury during the index ICU stay after study enrollment.[58]

KDIGO Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	**Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 µmol/l] with an acute increase of at least 0.5 mg/dl [44 µmol/l])**	**Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours OR New renal replacement therapy (RRT)**

30-Day Mortality – Mortality at 30-days. This will be assessed by review of the medical records if the participant remains in the hospital or if the participant expired while in the hospital. If the participant was discharged, 30-day mortality will be assessed by contacting the participant by phone or by searching the National Center for Health Statistics (NCHS) National Death Index (NDI) consistent with a recent multicenter phase III trial in sepsis.[23] Phone calls will be made by the research team at each site.

5.2 Rationale for Outcomes

Change in SOFA score: Organ failure is highly associated with mortality[60] and improvement in organ function is a key goal for critical care physicians. In the study by Marik et al.[36], participants who received the 3-drug regimen had substantial improvements in the trajectory of organ failure over the first 72-hours of their ICU stay. If the combination of vitamin C, hydrocortisone, and vitamin B1 can improve organ function in the first 72-hours following ICU admission, we believe that clinicians will likely quickly adopt this safe and inexpensive therapy. Importantly, this outcome can be measured early in the hospital stay and is therefore less likely to be affected by other potential elements of hospital care that can affect more distal outcomes (e.g., mortality).

Kidney Injury: Renal failure has been estimated to occur in 23% of participants with sepsis and over 50% of participants with septic shock.[61] In studies of participants with septic shock, there is a step-wise increase in mortality with worsening acute kidney injury (AKI).[62] In addition, many participants who experience renal injury during septic shock do not recover renal function prior to hospital discharge and may require long term dialysis. As both data from the study by Marik et. al.[36] and a separate study of vitamin B1 in septic shock[38] have shown substantial improvements in renal outcomes, kidney failure is a natural secondary outcome and one that could change practice independently from other factors – in other words, many clinicians would likely provide this therapy if they knew that kidney function could be protected, since this organ is vital to long-term health.

Mortality: Finally, we will measure 30-day mortality. We anticipate that the combination of vitamin C, hydrocortisone, and vitamin B1 will reduce mortality in this high-risk population.

5.3 Additional Secondary Outcomes

5.3.1 Additional secondary outcomes

Additional secondary outcomes will include length of ICU stay, length of hospital stay, ventilator-free days over the first 7-days after enrollment, shock-free days over the first 7-days after enrollment,

and the incidence of delirium on day #3 of the ICU stay (as assessed using the Confusion Assessment Method [CAM-ICU] system).[63] Sites at which the CAM-ICU is performed daily as part of standard-of-care should assess whether delirium occurs on any day during the initial ICU stay. See Appendix #2.

5.3.2 90-day follow-up for Quality of Life assessment

Sites may choose to participate in a long-term outcomes substudy exploring the effects of ascorbic acid, hydrocortisone, and thiamine vs. placebo on quality of life following sepsis. If a site chooses to participate, a trained research assistant/investigator at the site (who is blinded to treatment arm) will contact all participants who were alive at 30-days, and perform the SF-36 at day 90 following enrollment. The SF-36 is a 36-Item Short-Form Health Survey (SF-36), a validated survey of general quality of life in adults, can be administered in person or over the telephone by research personnel. It measures eight different dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions, as well as one question asking about perceived changes in health. The telephone version of the 36-Item Short-Form Health Survey has been validated[64,65] and used in sepsis.[66-69]

5.4 Safety

5.4.1 Definitions

The following definitions will be used[70]:

Adverse event: any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment

Serious adverse event: any untoward medical occurrence that at any dose requires inparticipant hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death

Unexpected serious adverse event: a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

5.4.2 Specific adverse event data collection

To assess specific amd potentially serious adverse events that may be related to the combination of the study medications, we will collect data on the following:

Serious Adverse Event	**Definition**
Hyperglycemia	Serum glucose >300mg/dl in the first 120-hours after enrollment
Hypernatremia	Serum sodium (> 150 mmol/L) occurring in the first 120-hours after enrollment
New Infection	As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics.
Catheter-site	
Lung	
Gastrointestinal	
Urinary tract	
Other	
Serious allergic reaction	Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Allergic reaction should be related (or suspected to be related) to the study medicaiton
Renal calculus	Development of a renal calculus between enrollment and 30-day follow-up (based on question asked during follow-up phone call).

5.4.3 Adverse Event Reporting

All unexpected serious adverse events thought to be related to the study drug, and any unexpected fatal or life-threatening adverse events thought to be related to the study drug will be recorded in the online CRF, reported directly to the coordinating center, and reported to the appropriate IRB shortly following the event per local protocol. In addition, unexpected serious adverse events related to the study drug will be undergo expedited reporting to the DSMB within 7 days of the coordinating center becoming aware of the event. The DSMB will additionally review all adverse events in aggregate after every 50 patients are enrolled.

Adverse events will additionally be reported to the FDA as outlined in 21CFR312.32 and summarized below:

a. All unexpected fatal or life-threatening adverse events thought to be related to the study drug will be reported to the FDA within 7 calendar-days of when the ACTS team is made aware of the event.
b. All unexpected serious adverse events thought to be related to the study drug will be reported to the FDA within 15 calendar-days of when the ACTS team is made aware.
c. All serious unexpected adverse events, and any unexpected fatal or life-threatening events thought to be related to the study drug, will be reported back to all site investigators within 15 calendar-days of the event.
d. The ACTS team will periodically review all published information relating to the safety of each element of the drug combination. Any concerning safety information obtained from this review, or otherwise obtained (e.g. from unpublished scientific papers), will be reported to the FDA within 15 calendar-days.

5.4.5 Safety Monitoring Labs

As detailed above, safety monitoring labs will be obtained at 120-hours, after completion of the study protocol.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

The study has been powered to have at least 80% power for the primary outcome and all key secondary outcomes as follows:

SOFA Score: Based on preliminary data[36], we conservatively anticipate a decrease in SOFA score of 6 (standard deviation [SD]: 4) in the treatment group and 4 (SD: 2) in the placebo group. With these estimates, enrollment of **200 participants (100/arm)** at an alpha of 0.05 and using a t-test with unequal variance, the trial will provide > 99% power to detect a statistical significant difference between groups.

Kidney Injury: Based on preliminary data from our study of vitamin B1 in septic shock,[38] we anticipate that 30% of participants in the treatment group and 55% in the placebo group will have renal failure which will result in a 94% power for this outcome. This calculation and following calculation were performed using the Fisher's exact test.

Mortality: Based on preliminary data[36,37,71], we anticipate that the control group will have a mortality of 40%. We estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the treatment group. With these estimates, 182 participants will lead to 80% power. To further increase

the trial's power and due to potential loss-to-follow-up, we will aim to enroll 200 participants. These estimates are conservative compared to the Marik et al. study which found a treatment effect corresponding to a risk ratio of 0.21 which persisted in adjusted analysis.[36]

Sample Size Adjustment

If after 100 patients are enrolled, the overall change in SOFA score is less than anticipated in the above power analysis and/or the renal failure event rate or mortality rate is lower than predicted, the enrollment target of 200 patients may be adjusted accordingly so as to improve power for the primary outcome and all key secondary outcomes at the end of the trial period. Specifically, we will aim to maintain ≥90% power to detect a 2-point difference in ΔSOFA score (using variance seen for the full cohort) and ≥80% power to detect a 50% treatement effect on mortality. Whether to increase the study sample size, and the degree of sample size increase, will be decided on by the blinded Steering Committee who will not have access to data stratified by treatment group. The Steering Committee will take into account logistical and financial considerations when updating the enrollment target.

6.2 Statistical analysis plan

6.2.1 General considerations

The statistical analyses and reporting will adhere to the CONSORT guidelines.[72,73] All tests will be two-sided, a p-value < 0.05 will be considered significant, and all confidence intervals will have 95% coverage. All analyses will be conducted on a modified intention-to-treat basis only including participants receiving at least the first dose of the study medications. In a double-blind trial, this approach is unbiased while increasing precision.[74] The two groups will be compared in relation to baseline characteristics using descriptive statistics.

The persons conducting the statistical analysis will be blinded to the randomized allocation. Groups will be designated as "A" and "B" until all pre-specified analyses are performed and shared with all authors and the Data Safety Monitoring Board.

6.2.2 SOFA score and renal failure

The change in SOFA score will be calculated and compared between groups using the Wilcoxon Rank Sum test (if the change is not normally distributed) or by a t-test if the change is approximately normally distributed. Fisher's exact tests will be used to compare the incidence of renal failure during the index ICU stay.

If a participant expires prior to the 72-hour time point, SOFA scores will be imputed based on a pre-defined plan as follows. If a participant expires before 24-hours has elapsed, a 20% increase from baseline will be imputed. If a participant expires between 24-hours and 48-hours, a 15% increase from the 24-hour time point will be imputed. If a participant dies between 48-hours and 72-hours, a 20% increase from the 24-hour time point will be imputed. Sensitivity analyses will be performed using various other imputation techniques. Specifically, we will perform 1) a sensitivity analysis in which the worst possible SOFA score (score of 24) is imputed for those participants who expire, 2) a sentivity analysis in which the last SOFA score for participants who expire will be carried forward, and 3) a sensitivity analysis in which only those patients who survive to 72-hours are included. These sensitivity analyses were chosen to model 'worst-possible' and 'best-possible' scenarios. For the secondary outcome of renal failure, participants who expire during their ICU stay will be assessed to have developed renal failure if they demonstrated any degree of unresolved KDIGO acute kidney injury prior to death. If there was no evidence of acute kidney injury prior to death or if kidney injury had fully resolved, these participants will be assessed as not having developed renal failure.

6.2.3 30-day mortality
Survival until 30 days will be analyzed using survival analysis. Participants lost to follow-up will be censored and the censoring will be assumed non-informative. Results will be presented with Kaplan-Meier curves and the groups compared using the log-rank test.[75] Hazard ratios with 95% confidence intervals will be obtained using Cox's proportional hazards models.[76] The proportional hazards assumption will be verified by visual inspection of the Kaplan-Meier curves and statistically by including a product term (i.e. "interaction") between the treatment group variable and the natural logarithm of time in the model.[77] If the proportional hazards assumption is not met, only the Kaplan-Meier curves and the p-value from the log-rank test will be presented.

Adverse events and other binary outcomes will be presented and analyzed like renal failure.

6.2.4 Additional Secondary Analyses
Both ICU and hospital length of stay will be compared using Wilcoxon Rank Sum tests. Ventilator and shock free days over the first 7-days after enrollment will likewise be compared using the Wilcoxon Rank Sum given that the data will likely be not normally distributed. In these latter two analyses, patients who expire prior to 7-days will be assessed to have 0 ventilator or shock free days if they had died while on a ventilator or vasopressor respectively. The incidence of delirium will be compared using the Fisher's exact test. For the quality-of-life outcome (i.e. 90-day SF-36), the primary analysis will only include patients with available data. As a secondary analysis, multiple imputation will be used to estimate SF-36 scores in all patients not known to be dead at 90 -days.

6.2.5 Subgroup analyses
The analysis will include three pre-defined subgroup analyses for the primary and key secondary outcomes according to 1) participants with initially high SOFA scores (≥9). This cut-off was chosen to represent a population with a ≥50% predicted likelihood of mortality[78] 2) baseline vitamin B1 deficiency and 3) baseline adrenal insufficiency. We will not plan to perform a subgroup analysis according to vitamin C deficiency, as prior work has shown that the vast majority of participants with septic shock have vitamin C levels below the reference range.[36] Vitamin B1 deficiency will be defined as a plasma vitamin B1 level ≤ 7 nmol/L as has been previously described.[37] Adrenal insufficiency will be defined as a cortisol level <10μg/dL.[43] The trial is not powered to detect subgroup differences and these will be considered exploratory and hypothesis generating.

6.2.6 Statistical stopping criteria
Since the primary outcome is not mortality, there will be no formal stopping criteria for efficacy. There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow for detection of efficacy in subgroups or in other outcomes even if the primary outcome is negative.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data collection process
Data collection will be the responsibility of the individual site investigators with oversite from the trial coordinating center. Most variables (i.e. demographics, sepsis characteristics and laboratory results) will be obtained prospectively from the electronic medical record. 30-day follow-up regarding safety and mortality end-points will be obtained via telephone call post-discharge (unless the participant remains in the hospital at 30-days). Data will be entered directly into the online database software (see below).

7.2 Variables
Will be provided on the online CRF. A PDF version is available upon request.

7.3 Data quality and validity
Data quality and validity will be optimized by using a detailed data dictionary which will be distributed to all sites. Data quality will be monitored both centrally by the coordinating site and locally by each site principal investigator.

7.4 Data storage and security
The database application we will use is REDCap Cloud (https://www.redcapcloud.com/). REDCap Cloud is a professional database that provides a user-friendly interface. The REDCap Cloud data management system is secure, fully compliant with all regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, participant confidentiality will be safeguarded. All members of the research team will be required to complete standardized training in REDCap cloud, which will be documented within the software.

The consent form and other trial documents for each participant will initially be stored in a secure, locked place at the individual sites. Participating sites will be responsible for maintaining their own trial documents and study materials (e.g. signed ICFs, site logs etc). Trial documents generated at the Coordinating Center will be maintained the Coordinating Center. Following completion of the trial, documents will be maintained for a period of at least 2-years at each site per FDA regulations (or longer depending on local IRB guidelines).

8. ETHICAL CONSIDERATIONS
8.1 Risks and Benefits
8.1.1 Potential benefits

Potential Benefits to Individual Participant: Assuming our hypothesis is correct and our results are comparable to those previously published[36], individual participants enrolled in our study and randomized to the treatment arm will benefit from a better trajectory of organ failure and improved mortality. As many participants who survive an initial episode of sepsis will have a future admission for sepsis, participants participating in this study but randomized to the placebo arm may see a future benefit from knowledge gained.

Potential Benefits to Society: Septic shock remains a highly morbid clinical condition for which there is no specific therapy. Our study, assuming our hypothesis is confirmed, will provide strong support for the widespread adoption of vitamin C, corticosteroids, and vitamin B1 for participants with septic shock. This, in turn, will significantly improve participant outcomes and reduce the global burden of death related to septic shock. Thus, even if participants are randomized to the placebo arm, their involvement with this study has tremendous potential benefits for society as whole. If vitamin C, corticosteroids, and vitamin B1 are found to be neutral or harmful (the latter being highly unlikely), society will benefit as the study will likely prevent the widespread dissemination of an ineffective medication combination.

8.1.2 Potential harms

Study Drug

Vitamin C – Ascorbic acid is a water-soluble essential vitamin that is safe even at high doses. Nevertheless, adverse effects related to high-dose ascorbic acid have been described. These adverse effects include diarrhea/abdominal bloating, increased oxalate excretion, iron overload in participants with hemochromatosis, and hemolysis in participants with G6PD deficiency.[79] We exclude participants with known renal failure, known G6PD deficiency, or known hemochromatosis to limit these potential risks. We will additionally exclude participants with known allergy to ascorbic

acid. Ascorbic acid has additionally been used in at least 3 clinical trials in critically-ill populations without major associated adverse effect.[40-42]

Hydrocortisone – Hydrocortisone is a well-established medication for the treatment of refractory shock in sepsis. Some studies (e.g. CORTICUS) have found an increased incidence of secondary infection in participants with septic shock who receive steroids.[46] This finding has not been replicated in other large trials of corticosteroids for sepsis.[47] Additional hypothetical risks to the administration of hydrocortisone to participants with septic shock (e.g. increased gastro-intestinal bleeding, muscle weakness, and delirium) have not been found in clinical trials of corticosteroids in sepsis.[46,47] Finally, hydrocortisone may increase the risk of hyperglycemia and hypernatremia.

Hydrocortisone will not be tapered in this study as prior studies have shown benefit with corticosteroids in septic shock without a taper.[80] In addition, a recent large trial of corticosteroids in septic shock (ADRENAL, NEJM 2018) randomized patients to 7-days of corticosteroids or placebo and did not include a taper. In that trial there was no reported difference in rates of recurrent shock.

Vitamin B1 – The only potential serious side effect that has been reported from vitamin B1 administration is an extremely rare anaphylactic reaction (1:250,000 cases) and this might not even be of issue with the current manufactured version of vitamin B1 in the United States. The risk of an anaphylactic reaction was associated with a vitamin complex dispensed in Europe, and whether vitamin B1 was the actual offending agent remains unknown; however, this 0.0004% theoretical chance of an adverse reaction is incredibly low. In a series of 989 participants in the United States who received intravenous vitamin B1, none had an anaphylactic reaction and the only reported side effects were minor consisting of transient local irritation or in one case pruritus (0.093%).[81] Further safety data comes from the clinical use of intravenous vitamin B1 at our coordinating site. At Beth Israel Deaconess Medical Center (BIDMC, coordinating center) vitamin B1 is provided liberally for participants with nutritional deficiency – for example, BIDMC has administered intravenous vitamin B1 in over 8,000 separate participant encounters from 2002 until present. Despite this heavy usage, no adverse reactions were reported in any of the 8,000 participant encounters.

The combination of vitamin C, hydrocortisone and vitamin B1 – To date, the only study of the combination of vitamin C, hydrocortisone and vitamin B1 was the above referenced study by Marik et. al.

All procedures will take place at the study site. All research procedures and monitoring will be conducted by experienced personnel, and participants will be in the ICU given critical illness. This permits closer observation and more detailed monitoring by clinicians familiar with the care of participants experiencing and resuscitated from septic shock.

Blood Collection
Most participants will have existing venous or arterial catheters in place and we will be able to collect blood from these ports, essentially eliminating the risks associated with blood collection. In the very rare case that a participant does not have an indwelling line, the risk of venipuncture is extremely low, and will not exceed the risk of clinical blood draws the participant will already be receiving.

Loss of Confidentiality
All measures will be taken to ensure that no confidential information is released. All participant information will be stored in a password protected database to which only study investigators will

have access. Additionally, all hard copies of study data will be kept in a locked office accessible only to study investigators. Thus, the risk of loss of confidentiality is very low.

9. MONITORING

9.1 Institutional Review Board (IRB)

The study will be reviewed and approved by the IRB at each participating site.

9.2 Data Safety and Monitoring Board (DSMB)

The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will consist of three clinicians with critical care experience in the management of septic participants. An independent biostatistician/epidemiologist will prepare all DSMB reports. The DSMB members will be chosen such to avoid any financial or intellectual conflicts of interest. The DSMB will review deidentified data after every 50 participants are enrolled to assess for safety; unless there are group differences necessitating unblinding (as determined by the DSMB), the DSMB will be blinded to treatment groups. The trial will continue while the DSMB review data. After each review, the DSMB will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. Criteria for recommending termination will be at the discretion of the DSMB and there will be no formal statistical criteria for termination due to efficacy or safety. A detailed charter for the DSMB will be provided.

DSMB Members

Clifton Callaway, MD, PhD
University of Pittsburgh
400A Iroquois
Pittsburgh, PA 15260
(412) 647-8287
callawaycw@upmc.edu
Professor (tenured) of Emergency Medicine; Executive Vice-Chair of Emergency Medicine; UPMC Professor of Emergency Medicine Research
Expertise: Cardiac Arrest/Clinical Trials

Taylor Thompson, MD
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114
(617) 724-7823
tthompson1@partners.org
Professor of Medicine, Harvard Medical School
Director, Critical Care Translational Research, Pulmonary/Critical Care Unit, MGH
Medical Director, ARDS Network Clinical Coordinating Center
Expertise: Sepsis/Clinical Trials

Shahzad Shaefi, MD MPH [DSMB Chair]
Beth Israel Deaconess Medical Center
One Deaconess Raod
Boston, MA 02115
(617) 355-6286
sshaefi@bidmc.harvard.edu
Attending Physician, Department of Anesthesia, Critical Care and Pain

Expertise: Critical Care Medicine

10 CLINICAL MONITORING PLAN

The detailed clinical monitoring plan has been developed and is available from the Coordianting Center upon request.

11. TIMELINE AND ENROLLMENT

11.1 Timeline

11.2 Screening & Enrollment

Enrollment at each site will be continuously monitored by the site investigator and the principal investigator. Each site will be expected to maintain a screening log including all participants who meet all eligibility criteria at that site. A standardized screening log will be provided to each site via RedCap Cloud—thus allowing for continuous updating of the screening log and will allow capture of all screening failures.

Enrollment will be competitive (i.e. without specific enrollment caps). Number of enrollments at each site will be shared with all sites on a monthly basis. Sites will be expected to complete all elements of the online CRF within 48-hours of each time point. In the case that a site continuously underperforms despite troubleshooting and feedback, the steering committee will evaluate whether enrollment will continue at that site.

12. FUNDING

Funding for the present trial is provided by the Good Ventures Foundation (http://www.goodventures.org/). The funding agency will have no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

13. PUBLICATION

The manuscript will adhere to the CONSORT guidelines.[72,73] The principal investigator will be responsible for assigning authorship position and will follow authorship guidelines from the International Committee of Medical Journal Editors.[82] At a minimum, all members of the Steering Committee and all site Principal Investigators (for sites enrolling at least 10 participants) will be included in the primary author list. The main results will be presented at an international conference. The trial results will be shared with participating sites and via press releases but not directly with the participants.

14. DATA SHARING

Six months after the publication of the last results, all de-identified individual participant data will be made available for data sharing.[83] Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data. All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent ethics review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Interested parties will be able to request the data by contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors[82] and might or might not include authors from the steering committee depending on the nature of their involvement.

15. TASKS AND RESPONSIBILITIES

Principal investigator and sponsor: Overall responsibility for protocol development, funding, budget overview, data dictionary development, ethical approval, trial registration, daily management, trial oversight and collection of adverse events, contact to the pharmacy, contact to Good Clinical Practice monitoring unit and the data and safety monitoring board, assessment of overall recruitments, potential recruitment of additional sites, data analysis, and dissemination and presentation of results.

Steering committee: Protocol development, funding, budget overview, data dictionary development, trial oversight, dissemination of results, responsibilities as principal investigator for short time periods.

Site investigators: Responsible for site-specific enrollment, evaluation of eligible patients not included, education of personnel at participating sites, reporting of site-specific issues or challenges to the principal investigator, participant consent for data collection, collecting and reporting data regarding adverse drug events.

Clinical team: Administration of the study drug, participant consent for data collection.

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Appendices

Appendix 1: Abbreviations

ICH……..International Conference on Harmonization
SPIRIT……..Standard Protocol Items: Recommendations for Interventional Trials
ACT……..Ascorbic Acid, Corticosteroids, and Thiamine
ESRD……..End Stage Renal Disease
SOFA……..Sequential Organ Failure Assessment
IND……..Investigational New Drug
FDA……..Food and Drug Administration
ICU……..Intensive Care Unit
SaO2……..Oxygen Saturation
FiO2……..Fraction of Inspired Oxygen
GCS……..Glasgow Coma Scale
UOP……..Urine Output
RRT……..Renal Replacement Therapy
CAM……..Confusion Assessment Method
NCHS…….. National Center for Health Statistics
NDI……..National Death Index
AKI……..Acute Kidney Injury
SD…….. tandard deviation
CRF……..Case Report Form
BIDMC……..Beth Israel Deaconess Medical Center (Coordinating Center)
IRB……..Institutional Review Board
DSMB……..Data Safety and Monitoring Board

Appendix 2: CAM-ICU Form

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU **Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive**		
	Criteria Met →	☐ **CAM-ICU Positive** (Delirium Present)
	Criteria Not Met →	☐ **CAM-ICU Negative** (No Delirium)