3. Background

3.1. Introduction

Sepsis is an inflammatory syndrome with life threatening organ dysfunction resulting from a dysregulated host response to infection.[1] The global burden is estimated to exceed 15 million cases annually.[2] In the United States, the incidence is increasing and currently there are more 1,750,000 cases each year, with more than half requiring intensive care unit (ICU) admission.[3-5] Further, sepsis cases account for 30%-50% of all hospital deaths, making it the 3rd leading cause of death in the United States, and is the most expensive reason for hospitalization with annual expenditures exceeding $20 billion.[6-8] Notably, even among those that do survive, many endure significant reductions in physical, emotional and cognitive quality of life.[9,10] New therapeutic approaches to reduce the high morbidity and mortality of sepsis are needed.

3.2. Current Management of Sepsis

Current management strategies focus on early aggressive fluid resuscitation, blood pressure support with vasopressors, early appropriate antibiotics, and the identification and control of infected sites.[11,12] Though outcomes have improved with the bundled deployment of these strategies,[13-16] mortality remains high at 20 – 30%.[5,17] Despite over a hundred phase 2 and phase 3 clinical trials of pharmacological agents with the potential to improve sepsis outcomes, only antibiotics have demonstrated reproducible benefits.[18,19]

3.3. Overview of Combination Therapy

In June of 2017, Marik et al. published the outcomes of 47 patients admitted to the ICU of an academic medical center with severe sepsis or septic shock and a procalcitonin (PCT) level of > 2 ng/mL.[20] All patients were treated with a combination of intravenous hydrocortisone (50 mg every 6 hours), vitamin C (1.5 g every 6 hours), and thiamine (200 mg every 12 hours). The outcomes of the patients were compared to 47 historic controls from their center, 60% of whom received hydrocortisone per the guidelines of the American College of Critical Care Medicine.[21,22] Mortality in the treated group was significantly lower than in the historical control group (8.5% v. 40.4%; $p < 0.001$). In a propensity adjusted analysis, the odds of death in the treated group was 0.13 (95% CI, 0.04 – 0.48; $p = 0.002$). Additional findings included a shorter duration of vasopressor support (18.3h v. 55h; $p < 0.001$), a lower requirement for renal replacement therapy (RRT, $p = 0.02$) and a greater improvement in SOFA score at 72 hours ($p = 0.001$) for the treatment group. Although these results are promising, they require further study and confirmation in a rigorous randomized control trial before such treatment can be advocated broadly. The components of the treatment and the rationale for their inclusion are detailed below:

Vitamin C – Vitamin C is an essential micronutrient not synthesized by humans.[23] Specific actions include its role as an enzymatic cofactor for the synthesis of collagen, carnitine, norepinephrine, and peptide hormones, as well as tyrosine metabolism.[24,25] It also acts as a chemical reductant of iron in the gastrointestinal tract, which in turn facilitates absorption. Importantly, vitamin C is a well-known antioxidant, which reduces oxidative damage of DNA, protein, and low-density lipoprotein. Further, it decreases lipid peroxidation, extracellular oxidants from neutrophils, and endothelium-dependent vasodilatation.[23,24]

5. Endpoints

Primary outcome

The primary outcome for this trial is the number of consecutive days free of vasopressors and mechanical ventilation (VVFD) in the first 30 days after start of the Study Intervention, recorded to the nearest day. Ventilator and vasopressor free days will only accrue from the last date the patient was free of both ventilator and vasopressor support. Patients who die are scored zero VVFD, and patients who return to ventilator support or vasopressor support (as defined in the inclusion criteria) will have the VVFD count reset to zero days.

Secondary Outcomes

Secondary outcomes will be mortality at 30 days, ICU mortality, mortality at 180 days, length of ICU stay, length of hospital stay, and long-term emotional and cognitive outcomes at 180 days.

6. Study Design

6.1. Design Overview

The VItamin C, Thiamine And Steroids in Sepsis (VICTAS) Study is a double-blind, placebo-controlled, adaptive randomized clinical trial designed to investigate the efficacy of the combined use of vitamin C, thiamine and corticosteroids (hereafter "Treatment Protocol" or “TP”) versus indistinguishable placebos (hereafter "Control Protocol" or “CP”) for patients with sepsis. The trial employs a novel endpoint that approximates a patient's risk of death based on the time spent on vasopressors or receiving respiratory support. Time spent on vasopressors or receiving respiratory support captures a patient's speed of recovery. Mortality rate is a key secondary endpoint for the trial.

The trial has a flexible sample size that will be determined adaptively. The trial will have an initial enrollment target of up to 500 subjects to detect a potential mortality difference of 20%, a conservative estimate based on the 32% benefit observed in the study by Marik, et al. However, if the data are indeterminate on mortality at N=200, 300, or 400 subjects, the trial may continue to a larger sample size (up to 2000) using an adaptive “Goldilocks” strategy based on the primary endpoint of VVFD with assessments at 500, 1000, 1500, or 2000 subjects randomized to either the TP or CP. The overall type I error rate for the trial is controlled at 2.5%. The early interim analyses have conservative rules for spending alpha so that 0.1% will be used up to N=400 and the remaining 2.4% is reserved for N=500 (or beyond). For more detail, please see section on Statistical Considerations below (Section 11).

6.2. Interim Analyses and Criteria for Study Termination

Early interim analyses focused on detection of a large mortality effect will be conducted as soon as possible following the enrollment of subject numbers 200, 300, and 400. At each of these points, predictive probability of meeting significance on the endpoint of mortality once all currently enrolled subjects have been followed to their final outcome will be calculated. If predictive probability of achieving statistical significance (with one-sided alpha set at 0.001) exceeds 90%, study accrual will be stopped. All currently enrolled subjects will continue and the final analysis will be conducted after all currently enrolled subjects have been followed to their final outcome.

If these conditions are not met, the trial will continue under an adaptive “Goldilocks” strategy with a primary endpoint of VVFD. Interim analyses under this design will be performed as soon as possible following the enrollment of subject numbers 500, 1000 and 1500. Following each of these interim analyses, any one of the following actions may result:

a. Stoppage of the trial for futility on VVFD (6.2.a)
b. Stoppage of accrual for expected success on VVFD and mortality (6.2.b)
c. Stoppage of accrual for expected success on VVFD alone (6.2c)
d. Continuation to the next analysis (6.2.d)

The decision criteria are based on predictive probabilities of meeting statistical significance on VVFD or mortality. Thus, we compute the predictive probability that VVFD (and mortality) will meet statistical significance once all currently enrolled subjects have been followed to their final outcome (30 days after

enrollment). We also compute the predictive probability that VVFD (and mortality) will be significant if the trial continues to its maximum sample size of N=2000. Each of the possible interim actions is described in greater detail below.

a.) Stoppage of the trial for futility

Stoppage of the trial for futility will occur if there is less than 10% predictive probability of ever detecting a statistically significant (alpha = 0.022) beneficial effect on VVFD, even if enrollment continues to 2000 subjects.

b.) Stoppage of accrual for expected success on both VVFD and mortality.

Accrual to the trial may stop for expected success on both the primary endpoint of VVFD and mortality. This requires that predictive probability be greater than 95% for detection of a statistically significant beneficial effect on both VVFD (alpha = 0.022) and mortality (alpha = 0.024) at the current sample size. In order to meet this threshold, the data must already be strongly positive, and furthermore, there must be little risk that the subjects with outstanding data might reverse the success once all data becomes available. If this threshold is reached, then no additional subjects will be enrolled. Follow-up of currently enrolled subjects will continue and the final analysis will be conducted after all currently enrolled subjects have been followed to their final outcome.

c.) Stoppage of accrual for expected success on VVFD alone

Accrual to the trial may also stop for expected success on the primary endpoint of VVFD alone. This requires that predictive probability for detecting a statistically significant beneficial effect (at the current sample size) on VVFD exceeds 95% and predictive probability for detection of such an effect on mortality (at the maximal sample size) is less than 10%. Thus, the data must already be strongly positive for VVFD and indicate a low probability that significance can be achieved on mortality, even with additional sample size. If this early stopping threshold is reached, then no additional subjects will be enrolled. Follow-up of currently enrolled subjects will continue and the final analysis will be conducted after all currently enrolled subjects have been followed to their final outcome.

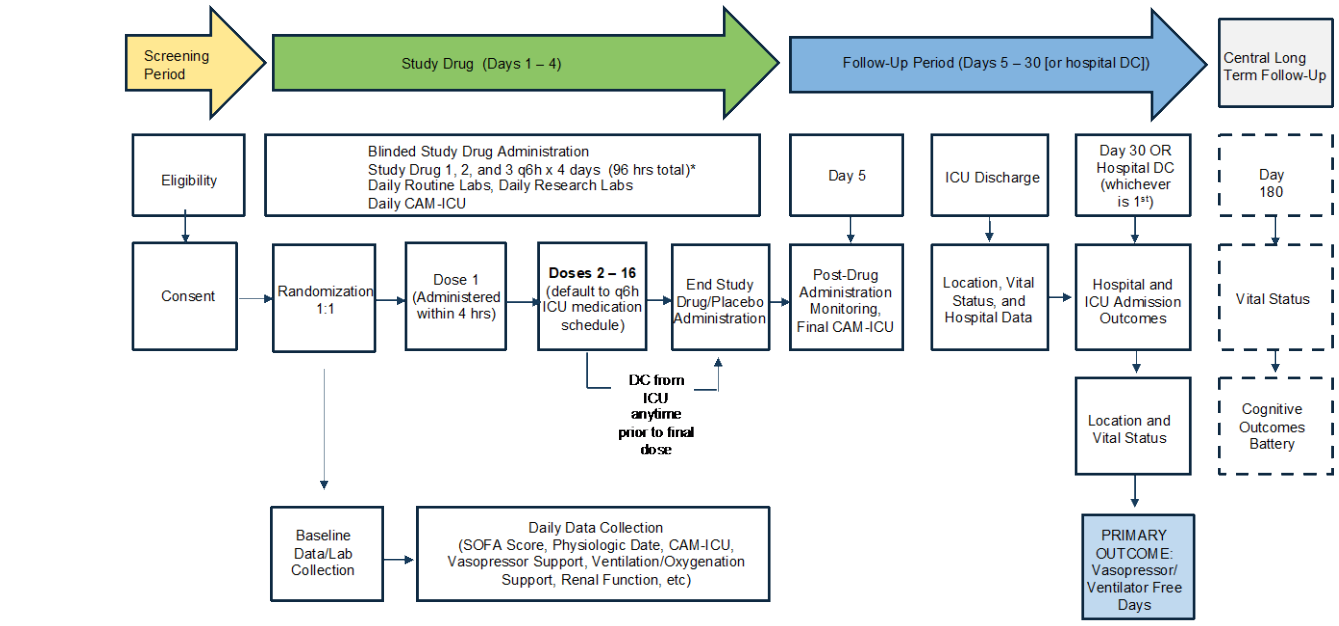
d.) Continue to the next analysis

If no condition for stopping accrual is met at the interim, then the trial will continue accrual to the next analysis time (either the next scheduled interim, or to full enrollment and final analysis). For more detail, please see section on Statistical Considerations below (Section 11).

6.3. Number of Subjects

There is an initial enrollment target of 500 subjects, with a maximum of 2000 subjects to be enrolled in the VICTAS Trial. Subjects will be randomized to study invention or control in 1:1 fashion. *A priori* stoppage rules will determine final number of subjects enrolled based on the adaptive study design.

The diagram below illustrates the individual subject progression for the trial.



*Note: 96h can occur over 5 calendar days

9.2. Screening and Informed Consent

Potentially eligible subjects will be initially screened by several methods including clinical team referrals, electronic health record reviews (see HIPPA form 4) or predictive analytic methods (at site where those methods are available). When sepsis is suspected the research team on-call will be immediately notified (using systems established at local sites). The study team will determine if the patient meets the *basic inclusion* criteria for presumptive eligibility (detailed above).

The investigator or designee will respond to the ED or ICU in order to verify patient eligibility based on the full inclusion/exclusion checklist. If the patient meets the basic inclusion criteria, the investigator or designee will review the enrollment criteria with the clinical care team to confirm eligibility. All screen failures will be recorded on the Screen Failure Log. To maintain compliance with recruitment procedures, sepsis admissions should be reviewed weekly by a research team member to determine if any eligible cases were missed and to identify local barriers to enrollment.

It is anticipated that each site will enroll on average 2 subjects per month.

Eligibility Verification: The eligibility CRF must be completed prior to randomization to ensure all inclusion and exclusion criteria have been confirmed. If eligibility questions arise, the CCC/National Hotline should be contacted immediately for clarification.

Informed Consent: Informed consent must be obtained before any study specific procedures are done. The investigator (or designee) will give the subject or subject's legally authorized representative (LAR) information about the trial in a form that they can read and understand. The consent process and date of informed consent given by the subject or the subject's LAR will be documented in the subject's files and carried out in accordance with state and institutional regulations. In the case where the subject is unable

10.2. Schedule of Events

In this section, the study day terminology does not correspond to calendar days, but reflects how the data is organized in the electronic data capture (EDC) system.

SCHEDULE OF EVENTS	Enrollment & Randomization	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	ICU D/C	HOSP D/C	DAY 30	DAY 180
Procedure										
Eligibility Verification	X									
Informed Consent	X									
Randomization	X									
Study Drug Admin[a]	X	X	X	X	X					
Demographics	X									
Anthropometrics	X									
Source of Admission	X									
History and Physical[b] (including comorbidity)	X									
Respiratory support[b]	X	X	X	X	X	X	X	X	O	
Vasopressor Use (each agent and dose)[b]	X	X	X	X	X	X	X	X	O	
APACHE II[c]	X									
SOFA Score[c]	X	X	X	X	X	X				
Vitals[b]	X	X	X	X	X	X				
GCS	X	X	X	X	X	X				
RASS[d]	X	X	X	X	X	X				
CAM-ICU[d]	X	X	X	X	X	X				
Hematology (platelets)	A	A	A	A	A	A				
Chemistry (T.bili, creatinine)	A	A	A	A	A	A				
Lactate	A	A	A							
Coagulation	A									
Pregnancy Test[e]	X									
Central Research Labs[f]	X	X	X	X	X					
Antimicrobial Therapy[b]	X						X	X	O	
Infection Source Data[b]	X						X	X		
Healthcare Location	X	X	X	X	X	X	X	X	O	C
Adverse Event Monitoring										
Potentially Associated	X	X	X	X	X	X	X	X	O	
Serious	X	X	X	X	X	X	X	X	O	
Subject Completion and Follow-up										
Vital Status							X	X	O	C
Renal Replacement Free Days								X	O	
VVFD								X	O	
Neuro-psychological Battery										C

X = Performed by study site
A = Collect if available
O = Only performed by study site if patient remains hospitalized at 30 days
C = Performed by Central Long-Term Outcomes Team

[a] *Note: patients that receive ≤ 3 administrations of study drug/placebo on Enrollment & Randomization day, will complete the last dose(s) on day 4 (if they remain in the ICU that long)*
[b] *Data will be abstracted from Electronic Medical Record (EMR). Abstracted data will include baseline data, and daily data. For baseline data, use most abberant elements from the 24 hours preceding the time of randomization. For daily values, use data from as close to 8 a.m. as is possible up to day 5 or ICU discharge (whichever occurs first). Vasopressor doses will only be recorded at time of randomization. After randomization day, only report the use of vasopressors or not (yes/no).*
[c] *Data elements collected via REDCap; score calculated centrally.*
[d] *Performed by research staff, at time of randomization and days 1-5 or ICU discharge (whichever occurs first).*
[e] *Pregnancy test (serum or urine), documentation of surgical sterilization or menopausal required for eligibility. If not performed as standard of care, patient will not be eligible*
[f] *Central Research Labs will only be collected at designated site*

10.3. Laboratory assessments

Though specific laboratory data or results are not required for eligibility, it is **expected** that various laboratory tests will routinely be performed by the treating clinical team. When available, recorded lab data should be from values as close to 8 a.m. daily up to day 5 or ICU discharge (whichever occurs first, see schedule of events). These tests include, but are not limited to: complete blood count including platelets with or without differential, chemistry including creatinine and total bilirubin, serum lactate, coagulation studies, blood cultures, procalcitonin (PCT), C-reactive protein (CRP), urinalysis, and arterial or venous blood gas.

Note, women of child bearing age who have not undergone a sterilization procedure cannot be considered for enrollment unless the clinical teams has demonstrated they are not pregnant via a negative pregnancy test as part of routine care.

Due to the potential for errors in some point of care glucometers in the setting of high serum vitamin C concentrations (see section 3.5), participating sites will be required to measure glucose using a point of care device that has been validated for use in the setting of high vitamin C concentrations [81], or use devices validated for high vitamin C concentrations[81] in their critical care or central laboratory. If glucose is measured in a critical care of central laboratory, approximately one milliliter of blood will be obtained from an artery or vein. The number of blood draws will depend on each patient's needs and the number of glucose measurements clinical care providers order. For sites that do not have a valid point of care glucometer, and do not want to use their critical care or central laboratory, Nova Biomedical has agreed to loan sites two Nova StatStrip devices, a charging station, and test strips. Nova Biomedical will also provide on-site training in the use of the devices. Of note, use of loaned devices in this study will require the use of venous or arterial (approximately one drop of blood per measurement) samples and NOT fingersticks. The number samples will depend on each patient's needs and the number of glucose measurements clinical care providers order. Loaned StatStrip glucometers will be validated on site as detailed in the "Procedure Manual" uploaded with this application. Sites that already use a glucometer that has been validated for use in the setting of high vitamin C concentrations should measure glucose according to their usual protocol.

10.4. Clinical Assessments and Procedures

Baseline Data - At enrollment, basic information about disease characteristics and the subject, including common sepsis and research related variables will be collected. Examples include:

- Demographics
  - Age
  - Race/Ethnicity
  - Gender
  - Education
- Anthropometrics
- Source of Admission
- Comorbidities and Medical History
- History and Physical (brief physical exam findings)
- APACHE II (ICU mortality) – using the most aberrant data from the 24 hours preceding the time of randomization

- SOFA Score
- Vasopressor requirements
- Respiratory and ventilator support requirements
- Total volume of fluid resuscitation
- Presumed infection source and organism
- Initial antimicrobial therapy
- CAM-ICU

Daily Measurements and Physiologic Data:

Use data that is obtained as close to 8 a.m. each day while the patient is in the ICU up to day 5.

- Vital Signs (MAP, HR, RR, and Temp)
- CAM-ICU Score
- SOFA Score
- Study Drug Compliance

Additional Measures to be determined and collected at time of ICU discharge and/or Hospital Discharge:

- Daily Vasopressor Requirements
- Daily Ventilator / Respiratory Support Requirements
- Antimicrobial therapy
- Final infectious source data
- Location and/or disposition

Outcome Assessments – The primary outcome measure is VVFD at 30 days (+/-3 days) after randomization. Vasopressor and ventilator-free days will be determined by recording all start and stop days of these measures. Additional measures will include renal replacement therapy (RRT) free days and determination of subject's vital status. These will be assessed at ICU discharge, and hospital discharge or day 30 (whichever comes first). The final study visit for individual sites will be the time of hospital discharge or day 30 (whichever comes first). For patients discharged prior to day 30, status at discharge will be assumed to reflect outcome at day 30.

Long Term Outcome Assessments Sub-Study - Explicit subject consent for participation in long term telephone follow-up will be sought for all patients at all sites. Participation in long term outcome assessments is not required for participation in other aspects of the VICTAS study. Subjects who participate will be compensated fifteen dollars. In these participants a diverse array of neurocognitive outcomes will be assessed approximately 6 months after patient discharge. Evaluations will be done using a specially-designed battery of tests that evaluates key aspects of functioning and behavior and will be administered via phone by the Vanderbilt Long-Term Outcomes team, which will serve as the coordinating center for these follow-up assessments. The battery, which takes about 40 minutes to complete, will assess cognition, mental health (depression and PTSD), quality of life, and employment - all of which have been shown to be adversely affected in between one third and two thirds of survivors of sepsis. This battery has been successfully used by researchers in multiple studies at Vanderbilt Medical Center and elsewhere - it is well tolerated by patients, easy to administer and to understand, and is very sensitive to the detection of even minor difficulties. Tests comprising the battery (*by domain and name*) are as follows:

- Complications related to ICU procedures
- Death
- Arrhythmia
- Delirium
- Bowel ischemia
- Ileus
- Leukopenia or leukocytosis
- Anemia or thrombocytopenia
- Coagulopathy (DIC)
- Hypoglycemia
- Electrolyte abnormalities

In addition, planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial, or before randomization, will also not be considered study related AEs. None of these expected adverse events will be considered study related AEs, unless the events:

(1) Are felt by the Investigator to be related to Investigational Product (See Table Below), *or*
(2) Lead to discontinuation of Investigational Product.

Potentially Associated Adverse Events (PAAE): Based on the reported potential risks of vitamin C, thiamine, and/or hydrocortisone, several important risks have been identified that could be associated with administration of one or all three drugs and have been labeled as "potentially associated adverse events" (PAAE). All PAAEs occurring following randomization through the initial hospital stay will be recorded on the AE page in the EDC portal. Identified PAAEs include but are not limited to nephrolithiasis, hemolysis, (refer to **Section 13.5 Table** for a detailed list).

Serious Adverse Event: A serious adverse event (SAE) is an AE that occurs during the study (ie, after randomization through to hospital discharge or day 30 follow-up [whichever occurs first]), that fulfills one or more of the following criteria:

1. Results in death (for the purposes of this trial, deaths will be captured as clinical outcomes and only recorded as an SAE if deemed related to the investigational product)
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of an existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect; OR
6. Is an important and significant medical event. (Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition).

Serious and Unexpected Adverse Event

Serious Adverse Events (see above) that are **Unexpected** (i.e. not consistent with the natural history of the disease under study) and deemed to be definitely or possibly study-related will be reported in an expedited manner to the DSMB (see **Reporting Rules** below).

Relationship to Investigational Product

11.4.4. Safety Endpoints

Complete listings and summary tables for all safety information will be presented for subjects who are included in the Safety analysis set. Descriptive statistics (number and percentage) for adverse events and serious adverse events will be presented by treatment arm. No formal statistical analysis will be performed.

11.5. Interim Analyses

Interim analyses of mortality will be conducted at N=200, 300, and 400. If the predictive probability of achieving $p<0.001$ on mortality exceeds 90%, the trial will stop accrual and all current patients will be followed until completion. When all subjects are complete, the primary analysis will consist of determining if the p-value on mortality is less than 0.001.

If the data are indeterminate on mortality at N=200, 300, or 400 subjects, the trial may continue to a larger sample size (up to 2000) using an adaptive strategy based on the primary endpoint of VVFD with assessments at 500, 1000, 1500, or 2000 subjects randomized to either the TP or CP. At each interim, we will compute the predictive probability that VVFD will be significant if the trial continues follow up with the currently enrolled sample size, and if the trial continues to its maximum sample size of N=2000. Stopping rules will be based on these predictive probabilities as described in Section 6: Study Design.

11.5.1. Statistical Models for the Interim Analysis

At the time of each interim analysis, there will be subjects for whom the final outcome is unknown (e.g. subjects who are enrolled but whose data is not yet available, or future subjects not yet enrolled). To make decisions regarding sample size selection, Bayesian predictive distributions are employed for the multiple imputation of outcomes for such subjects. These models will play no role in the final analysis, but rather are only used to facilitate the early stopping rules at the interims.

Predictive Probabilities for Mortality

To compute predictive probabilities for the mortality endpoint alone, we rely on a Beta-Binomial model, with independent non-informative Beta(0.5, 0.5) priors on each q_j, where q_j is the mortality rate on arm j. Based on this model, we compute:

- PP_{mort} (current N): the predictive probability of success on the mortality endpoint (Chi square test) if enrollment stops at the current sample size, and all currently enrolled subjects are followed to their primary outcome.
- PP_{mort} (max N): the predictive probability of success on the mortality endpoint (Chi square test) if enrollment continues to the maximum sample size (N=2000), and all subjects are followed to their primary outcome.

Similarly, we compute predictive probabilities for the VVFD endpoint using a model based on an exponential family (additional details of the model may be found in a separate document entitled *VICTAS Trial Adaptive Design Report*):

- PP_{VVFD} (current N): the predictive probability of success on the VVFD endpoint (Wilcoxon test) if enrollment stops at the current sample size, and all currently enrolled subjects are followed to their primary outcome.
- PP_{VVFD} (max N): the predictive probability of success on the VVFD endpoint (Wilcoxon test) if enrollment continues to the maximum sample size (N=2000), and all subjects are followed to their primary outcome.

11.5.2. Decision Criteria for Stopping Accrual

The decision criteria are summarized in the table below.

Sample Size	Interim Decision	Condition for Decision
N < 500	Futility	*may be recommended by DSMB*
	Expected success (mortality)	PP_{mort} (current N) > 0.90
	Continue	PP_{mort} (current N) < 0.90
N >=500	Futility	*PP_{VVFD} (max N) < 0.10*
	Expected success (both endpoints)	*PP_{VVFD} (current N) > 0.95 AND PP_{mort} (current N) > 0.95*
	Expected success (VVFD only)	*PP_{VVFD} (current N) > 0.95 AND PP_{mort} (max N) < 0.10*
	Continue	*otherwise*

Oxidative stress is a well-described phenomenon in sepsis and is characterized by the overproduction of reactive oxygen species, including nitric oxide (·NO), superoxide (O), hydrogen peroxide (H2O2), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and hydroxyl free radicals (·OH).[26,27] These reactive species disrupt endothelial cell function leading to decreased vascular tone and increased permeability.[27,28] Of note, the levels of antioxidants, including vitamin C, are decreased in critically ill patients including those with sepsis.[26,29,30] Moreover, even when circulating levels of vitamin C are in the normal range, the activation of complement-mediated inflammation leads to inadequate tissue concentrations.[31] For these reasons, the pharmacologic repletion of vitamin C in the setting of sepsis is of clinical interest. Indeed, in animal models of sepsis, intravenous vitamin C repletion has demonstrated the beneficial effects of improved arteriolar responsiveness to vasoconstrictors, better capillary blood flow, and decreased microvascular permeability.[32,33] In mouse models of lung injury, vitamin C has been demonstrated to improve epithelial barrier function and alveolar fluid clearance, as well as attenuate microvascular coagulation abnormalities and thrombosis in the lung.[34,35] Lastly, it has been shown that mice with adequate or repleted vitamin C levels are less likely to experience organ dysfunction in the setting of sepsis.[36]

High dose intravenous vitamin C has been used in a variety of inflammatory conditions. In an unblinded study, patients with $\geq$ 30% total body surface area burns were randomized into vitamin C (66 mg/kg/hr) and control groups.[37] Patients receiving vitamin C required significantly less fluid resuscitation in the first 24 and 48 hours, exhibited better PaO_2/FiO_2 ratios, and required significantly fewer days on mechanical ventilation. In another study, 595 critically ill surgical patients were randomized to either enteric alpha-tocopherol (1000 IU every 8 hours) and intravenous vitamin C (1g every 8 hours) or standard care.[38] Although there was no difference in progression to pneumonia or acute lung injury (the combined primary outcome), the development of organ failure was significantly lower and ICU length of stay was shorter in patients that received alpha-tocopherol and vitamin C.

More recently, Fowler et al. completed a phase I safety trial of intravenous vitamin C on patients with severe sepsis or septic shock.[39] In this study, patients were randomized 1:1:1 to low dose intravenous vitamin C (50 mg/kg/24 h), high dose intravenous vitamin C (200 mg/kg/24h), or placebo. Importantly, no adverse events due to vitamin C at either dose were observed. The pro-inflammatory markers C-reactive protein (CRP) and procalcitonin (PCT) were significantly reduced in patients randomized to receive vitamin C, as was thrombomodulin, a measure of vascular endothelial injury.

Hydrocortisone – The 2016 Surviving Sepsis Campaign Guidelines recommend the use of moderate dose corticosteroids for patients with septic shock who remain hemodynamically unstable after fluid resuscitation and vasopressor initiation.[12] In the pilot study by Marik et al., moderate dose corticosteroids were added to vitamin C and thiamine to capitalize on "the multiple and overlapping effects of all three agents as compared with drugs that target a single molecule or pathway".[20] Indeed, vitamin C and hydrocortisone both play important roles in numerous physiologic functions relevant to patients with septic shock including modulation of inflammatory mediators, catecholamine synthesis, endothelial function, and vasopressor sensitivity.[21,22,40-44] Importantly, it has been demonstrated that oxidation of the glucocorticoid receptor alters ligand and DNA binding sites, which diminish the effects of glucocorticoids. The antioxidant effect of vitamin C restores these binding sites to their normal conformation.[45] Glucocorticoids in turn enhance the transport of vitamin C into cells, thereby making it available for intracellular use.[46] Lastly, the integrity of vascular endothelial cells exposed to endotoxin is greater when bathed in a combination of vitamin C and glucocorticoid, than with placebo or either agent by itself.[47]

6.4. Study Initiation and Expected Trial Duration

The VICTAS Study is expected to begin enrollment in the spring of 2018. Enrollment of 500 subjects is predicted to require approximately 36 months after the first subject is enrolled. A minimum of 20 sites will participate in subject recruitment and enrollment.

7. Study Population

Any patients admitted to a study site hospital who have or subsequently develop sepsis or septic shock associated with cardiovascular or respiratory failure will be considered for enrollment. The site is responsible for screening patients and selecting those who are appropriate for the study based on the defined inclusion and exclusion criteria (section 7.1). Subjects must be randomized within 24 hours of the onset of organ failure (i.e., cardiovascular or respiratory support).

7.1. Inclusion Criteria

a) Suspected or confirmed infection as evidenced by ordering of blood cultures and administration of at least one antimicrobial agent
b) Anticipated or confirmed intensive care unit (ICU) admission
c) Acute respiratory and/or cardiovascular organ dysfunction attributed to sepsis as evidenced by at least one of the following requirements:
    1. **Respiratory Support Requirement** – Acute hypoxemic respiratory failure defined as persistent hypoxemia ($PaO_2/FiO_2 \leq 300$ or $SpO_2/FiO_2 \leq 315$) requiring (1) intubation and mechanical ventilation, or (2) positive pressure ventilation via tight-fitting face mask (i.e. CPAP or BIPAP) or (3) high flow nasal cannula $\geq$ 40 LPM flow and $FiO2 \geq 0.40$
    2. **Vasopressor Requirement** – Continuous infusion of norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine or other vasopressor agents at any dose for greater than 1 hour and required to maintain a mean arterial pressure $\geq$ 65 mm Hg despite intravenous crystalloid infusion of at least 1000cc

7.2. Exclusion Criteria

a) Age < 18 years of age
b) Weight < 40 kg
c) Prior enrollment in VICTAS
d) Qualifying organ dysfunction no longer present at the time subject would be randomized (does not require either (1) respiratory support as defined above to maintain $PaO_2/FiO_2 > 300$ or $SpO_2/FiO_2 > 315$ or (2) vasopressor infusion to maintain a mean arterial pressure $\geq$ 65 mm Hg)
e) Cardiovascular or respiratory organ failure caused by an illness other than sepsis
f) First episode of qualifying organ dysfunction during the current ED or ICU admission occurred > 24 hours before subject could be randomized (patients may be reconsidered for enrollment during a subsequent ED or ICU admission)
g) Limitations of care (defined as refusal of cardiovascular and respiratory support modes described in inclusion criteria 7.1.b) including “do not intubate” (DNI) status
h) Current hospitalization > 30 days at time of randomization

to provide consent, the subject's LAR (in accordance with applicable law) may provide consent for the patient.

Subjects will be assessed regularly during trial participation for return of cognitive function and their ability to provide informed consent. The subject will be informed about the trial if and when he/she becomes able to provide informed consent, and the subject will be given the opportunity to continue trial participation or withdraw. If the subject consents to continue in the trial, the subject will be requested to sign a consent form. If consent is denied by the subject, he/she will be withdrawn from the trial however, data obtained under LAR consent will be retained. If a subject dies before becoming able to consent, then the rights to trial data will remain with the LAR. The consent process should be clearly documented in the subject's medical record.

9.3. Enrollment and Randomization

Subjects are considered enrolled in the trial after informed consent and a randomization code (kit number) is provided. To enroll and randomize a patient, the enrolling investigator or designee confirms eligibility criteria is met and enters the required data into the Electronic Data Capture (EDC) portal. After all required data for entry is entered and no violations are present, the EDC will provide a randomization code / kit number.

9.4. Subject Tracking and Loss to Follow-up

The local study team will collect extensive contact information on each subject from multiple sources to facilitate future attempts to contact the individual by phone for long-term outcomes assessment. To attain a high rate of long-term follow up (>90%), the study team will request multiple phone numbers (home, cell phones, pagers, etc) and addresses from the subject and his/her relatives, friends, primary doctor (if available), clergy and clinics. At the time of consent and enrollment, proxy respondents will be asked to provide the telephone number of the place where the subject will likely reside following discharge. At the time of hospital discharge, each subject's disposition will be noted (nursing home, rehabilitation facility, another acute care hospital, subject's home, relative's home, etc) so plans can be made for long-term outcomes telephone follow-up. Date of birth (used for death records and tracking patients) will also be obtained and kept with the secure subject ID key.

Subjects cannot be deemed "Lost to Follow-Up" (LTF) without Clinical Coordinating Center (CCC) approval. The site investigator or long-term outcomes assessment team must present a case to the CCC that includes the efforts exerted to locate the study subject. Investigator may be asked to continue their efforts prior to approval.

Cognition: Attention (Digit Span), Delirium (Telephone Confusion Assessment Method), Executive Functioning (Hayling Test), Language (Controlled Oral Word Association Test or COWA), Memory (Paragraph Recall from the Wechsler Memory Scale IV), Orientation (Telephone Interview for Cognitive Status), Reasoning (WAIS-IV Similarities)
Functioning: Activities of Daily Living (Katz ADL), Employment (Employment Questionnaire), Instrumental Activities of Daily Living (Functional Activities Questionnaire)
Mental Health: Mental Health: Depression (PROMIS Depression 6), PTSD (Posttraumatic Stress Disorder - 8)
Quality of Life: EuroQol, 5 dimension (EQ5D)

10.5. Efficacy Measures

All patients who are randomized will be included in the ITT analysis population. Patients will be analyzed as randomized. The ITT analysis will be the primary efficacy analysis population (see study design and statistical considerations).

For the ITT population, missing primary or secondary endpoints due to death will be imputed as failure for the primary efficacy endpoint. Secondary endpoints will be assigned the worst possible values for all analyses.

10.6. Adverse Event Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators and study sponsors. For the purposes of this study, adverse events will be defined and reported using the ***Terms and Classifications*** and ***Adverse Event Reporting Rules*** outlined and summarized in a diagram below:

Terms and Classifications:

Adverse Event: An adverse event (AE) is considered any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

Expected Adverse Events
It is recognized that the patient population with sepsis, septic shock and related forms of critical illness who require ICU care will experience a number of common abnormalities in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. Examples of these expected events include, but are not limited to:

- Respiratory failure
- Heart failure
- Pneumonia or other / new infection
- DVT or PE

Determination of the relationships between AEs and administration of Investigational Product is a clinical decision based on all available information at the time of the completion of the EDC. Research relatedness will be evaluated according to the following definitions:

UNRELATED	The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
UNLIKELY	**Must have both of the following** 2 conditions, but may have reasonable or only tenuous temporal relationship to intervention: 1. Could readily have been produced by the subject's clinical state, or environmental or other interventions. 2. Does not follow known pattern of response to intervention.
REASONABLE POSSIBILITY	**Must have at least 2** of the following 3 conditions: 1. Has a reasonable temporal relationship to intervention. 2. Could not readily have been produced by the subject's clinical state or environmental or other interventions. 3. Follows a known pattern of response to intervention.
DEFINITE	**Must have all 3** of the following conditions: 1. Has a reasonable temporal relationship to intervention. 2. Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions. 3. Follows a known pattern of response to intervention.

Adverse Event Reporting Rules

All research-related AEs, PAAEs and SAEs will be submitted electronically through the EDC.

A. Timing of reporting and duration of tracking:

AE reporting: All research-related non-serious AEs will be recorded up to the first 5 days after enrollment (up to 4 days of drug infusion and 1-day post infusion) and will be reported on the AE page of the EDC, and will be summarized at quarterly intervals for DSMB review and summarized and reported for the annual IRB continual renewal.

PAAE reporting: All non-serious PAAEs occurring following randomization through the acute hospital stay will be reported on the AE page of the EDC, and will be summarized at quarterly intervals for DSMB review and summarized and reported for the annual IRB continual renewal. PAAEs deemed to be serious will be reported as per the SAE reporting process below.

SAE reporting: All SAEs occurring following randomization through the acute hospital stay or 30-days after enrollment, whichever comes first, that are unexpected and deemed to be study related will be

12.Data Management

Data management will be handled by the Data Coordinating Center (DCC) at Vanderbilt University Medical Center (VUMC). All activities will be conducted in coordination with the study PI, the sites and VICTAS Executive Committees. The data validation procedure will be implemented on two levels: first, automated checks will display warnings for invalid data, and second, the DCC team will verify individual data fields and query discrepancies. More information can be found in the Monitoring Plan.

12.1. Investigator Responsibilities for Data Management

The Investigator will allow direct access to source data/documents for trial related monitoring, auditing, IRB/EC review, and regulatory inspection. Also, the investigator will allow auditing of their clinical investigational procedure(s). Source documents are defined as original documents, data and records. For the duration of the study, the Investigator will maintain complete and accurate documentation including but not limited to medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, drug accountability records, correspondence with the CCC, DCC, IRB, and DSMB, adverse event reports, and information regarding subject discontinuation or completion of the study.

12.2. Data Collection and Handling

The entire study will be conducted using an electronic data acquisition method where all research related data on enrolled subjects will be entered (single-keyed) by the site personnel. This web-based data management system entitled Research Electronic Data Capture (REDCap) system, provides a user-friendly and easy-to-navigate interface. The latest version of each electronic case report form (eCRF) and source document worksheets (as applicable) will be available as a PDF file on the REDCap website for use by study personnel. This web-based database housing the eCRFs has been designed for the study, which will improve efficiency, lower cost of the study, and expedite publication of the results. Use of drop-down selection lists, radio buttons, checkboxes, and validation checks will be incorporated to aid the speed, accuracy and consistency of data entry. The database will be backed up regularly.

12.3. Data Acquisition and Central Study Database

Each site will be required to have a local coordinator who will be responsible for entering the study information into the web-based database and uploading the non-redacted, identifiable source documents/medical records associated with the study information. In order to verify data entered into the study database, source documentation containing protected health information will be uploaded for cross-reference and source verification. This will include medical records containing clinical information for the purposes of screening up until the participant's last day on the study that is relevant to the research study.

The web-based Randomization Module will be used by authorized site personnel for the purpose of randomizing eligible patients. The Study Coordinator (or other appropriate study team member) will log onto the REDCap system using a unique username and confidential password. When a subject is deemed eligible, a unique subject ID and record will be generated in REDCap. Once the Study Coordinator has entered the required subject information and clicked “Randomize”, the computer program will display the