

# VICTAS

## Vitamin C, Thiamine and Steroids in Sepsis

A multi-center, randomized, placebo-controlled, double-blind, adaptive clinical trial of vitamin C, thiamine and steroids as combination therapy in patients with sepsis.

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## 1. Executive Summary

**Title:** Vitamin C, Thiamine And Steroids in Sepsis: The VICTAS Study

**Objective:** To demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids in reducing mortality and improving organ function in critically ill patients with sepsis.

**Background:** Sepsis is an acute life-threatening illness.

### Hypotheses:

- A. In critically ill patients with sepsis, combination therapy using vitamin C, thiamine and corticosteroids will increase ventilator and vasopressor-free days (VVFD) at 30 days when compared to control patients treated with matching placebos.
- B. In critically ill patients with sepsis, combination therapy using vitamin C, thiamine and corticosteroids will reduce mortality at 30 days when compared to control patients treated with matching placebos.

### Specific Aims

- 1) To demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids to reduce the duration of respiratory and cardiovascular organ dysfunction in critically ill patients with sepsis.
- 2) To demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids to reduce 30-day mortality in critically ill patients with sepsis.

### Study Design

A multi-center, randomized, placebo-controlled, double-blind, adaptive clinical trial of vitamin C, thiamine and steroids as combination therapy in patients with sepsis.

### Intervention

Intravenous vitamin C (1.5 grams every 6 hours), thiamine (100 mg every 6 hours), and hydrocortisone (50 mg every 6 hours), or a matching placebo, will be administered for 4 days or until ICU discharge.

### Eligibility Criteria

#### *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 ( $\text{PaO}_2/\text{FiO}_2 \leq 300$  or  $\text{SpO}_2/\text{FiO}_2 \leq 315$ ) 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  $\text{FiO}_2 \geq 0.40$

**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

*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  $\text{PaO}_2/\text{FiO}_2 > 300$  or  $\text{SpO}_2/\text{FiO}_2 > 315$  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
- i) Chronic hypoxemia requiring supplemental non-invasive oxygen (nasal cannula or NIPPV) or home mechanical ventilation
- j) Chronic cardiovascular failure requiring home mechanical hemodynamic support (e.g., LVAD) or home chemical hemodynamic support (e.g., milrinone)
- k) Known allergy or known contraindication to vitamin C, thiamine, or corticosteroids (including previous history or active diagnosis of primary hyperoxaluria and/or oxalate nephropathy, or known/suspected ethylene glycol ingestion, or known G6PD Deficiency)
- l) Use of vitamin C at a dose of  $\geq 1$ g/day (IV or oral) within the 24 hours preceding first episode of qualifying organ dysfunction during a given ED or ICU admission
- m) Chronic disease/illness that, in the opinion of the site investigator, have an expected lifespan of < 30 days unrelated to current sepsis diagnosis (e.g., stage IV malignancy, neurodegenerative disease, etc.)
- n) Pregnancy or known active breastfeeding
- o) Prisoner or Incarceration
- p) Current participation in another interventional research study\*  
Inability or unwillingness of subject or legal surrogate/representative to give written informed consent

\*Note: Co-enrollment in other interventional research studies requires written permission from the VICTAS Executive Committee in advance of subject identification.

**Study Endpoints (Outcome Variables)**

Primary Outcome: Vasopressor and ventilator-free days (VVFD)

Secondary Outcomes:

1. Mortality at 30 days
2. ICU mortality

3. Mortality at 180 days
3. Length of ICU stay
4. Length of hospital stay
5. Physical, emotional and cognitive outcomes at 180 days

### **Statistical Considerations**

1. An initial target of up to 500 subjects will be enrolled in the VICTAS Study. Subjects will be randomized to study intervention or control in 1:1 fashion. A priori stoppage rules will determine final number of subjects (up to 2000) enrolled based on adaptive design.
2. All randomized subjects will be included in the ITT analysis set. The ITT population will be used for all primary, secondary, and other efficacy analyses. In these analyses, subjects will be classified according to the treatment randomized (not actual treatment received).

## 2. Table of Abbreviations

Abbreviation	Text
ABG	Arterial Blood Gas
AE	Adverse Event
AKI	Acute Kidney Injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
bCAM	Brief Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the ICU
CAPA	Corrective and Preventive Action Plan
CCC	Clinical Coordinating Center
CCP	Central Coordinating Pharmacy
CP	Control Protocol
CRA	Clinical Research Associate
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DCFD	Delirium-free and Coma-free Days
DCR	Data Clarification Request
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FWA	Federal Wide Assurance
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
OD	Organ Dysfunction
PD	Protocol Deviation
PP	Per Protocol
PAAE	Potentially Associated Adverse Event
PCT	Procalcitonin
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SIRB	Single (centralized) Institutional Review Board
SOFA	Sequential Organ Failure Assessment
TP	Treatment Protocol
VVFD	Ventilator and Vasopressor-free Days

## 3. Background

### 3.1. Introduction

Sepsis is an inflammatory syndrome with life threatening organ dysfunction resulting from a dysregulated host response to infection.<sup>1</sup> The global burden is estimated to exceed 15 million cases annually.<sup>2</sup> 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.<sup>3-5</sup> Further, sepsis cases account for 30%-50% of all hospital deaths, making it the 3<sup>rd</sup> leading cause of death in the United States, and is the most expensive reason for hospitalization with annual expenditures exceeding \$20 billion.<sup>6-8</sup> Notably, even among those that do survive, many endure significant reductions in physical, emotional and cognitive quality of life.<sup>9,10</sup> 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.<sup>11,12</sup> Though outcomes have improved with the bundled deployment of these strategies,<sup>13-16</sup> mortality remains high at 20 – 30%.<sup>5,17</sup> 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.<sup>18,19</sup>

### 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.<sup>20</sup> 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.<sup>21,22</sup> 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.<sup>23</sup> Specific actions include its role as an enzymatic cofactor for the synthesis of collagen, carnitine, norepinephrine, and peptide hormones, as well as tyrosine metabolism.<sup>24,25</sup> 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.<sup>23,24</sup>

Oxidative stress is a well-described phenomenon in sepsis and is characterized by the overproduction of reactive oxygen species, including nitric oxide ( $\cdot\text{NO}$ ), superoxide ( $\text{O}_2^-$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), peroxynitrite ( $\text{ONOO}^-$ ), hypochlorous acid ( $\text{HOCl}$ ), and hydroxyl free radicals ( $\cdot\text{OH}$ ).<sup>26,27</sup> These reactive species disrupt endothelial cell function leading to decreased vascular tone and increased permeability.<sup>27,28</sup> Of note, the levels of antioxidants, including vitamin C, are decreased in critically ill patients including those with sepsis.<sup>26,29,30</sup> Moreover, even when circulating levels of vitamin C are in the normal range, the activation of complement-mediated inflammation leads to inadequate tissue concentrations.<sup>31</sup> 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.<sup>32,33</sup> 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.<sup>34,35</sup> 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.<sup>36</sup>

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.<sup>37</sup> Patients receiving vitamin C required significantly less fluid resuscitation in the first 24 and 48 hours, exhibited better  $\text{PaO}_2/\text{FiO}_2$  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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>12</sup> 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”.<sup>20</sup> 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.<sup>21,22,40-44</sup> 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.<sup>45</sup> Glucocorticoids in turn enhance the transport of vitamin C into cells, thereby making it available for intracellular use.<sup>46</sup> 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.<sup>47</sup>

**Thiamine** – Thiamine is another essential micronutrient and cofactor for many human enzymes including those in the Krebs Cycle and pentose phosphate pathway.<sup>48</sup> Because of its key roles in these pathways, deficiency disrupts aerobic metabolism and, if severe enough, can lead to lactic acidosis and death. Of note, thiamine deficiency is not uncommon in sepsis.<sup>49</sup> In a recent study, patients with septic shock were randomized to receive 200 mg thiamine twice daily vs. placebo for seven days.<sup>50</sup> Patients treated with thiamine who were found to be thiamine deficient on presentation were observed to have significantly lower levels of serum lactate at 24 hours. Further, there was a reduction in mortality among this group compared to thiamine deficient patients who were randomized to receive placebo.

In addition to the putative benefits of thiamine repletion in septic patients, thiamine is a cofactor for the enzyme glyoxylate aminotransferase, which converts glyoxylate to carbon dioxide. Without this enzyme, glyoxylate would be converted to oxalate, which can deposit in the kidneys and cause oxalate nephropathy (see risks/benefits section below).<sup>51,52</sup>

### 3.4. Rationale for the Study

Though the reduction in mortality from 40.4% to 8.5% observed in the Marik study is notable, and has generated significant excitement in the lay press, to date there are no examples of therapeutics that improve survival as a result of modifying the inflammatory cascade of sepsis.<sup>19</sup> Indeed, numerous well-designed research trials in critical care have failed to reproduce the beneficial results observed in smaller preliminary studies.<sup>19,53-58</sup> In a non-scientific survey of intensivists working in multiple high-volume academic and non-academic medical center throughout the U.S., it was observed that the use of the Marik therapy combination is rare or absent, primarily as a result of queried clinicians wanting a more robust assessment of the value of this therapeutic regimen prior to adoption.

The purpose of the current study is therefore to determine (or confirm) the efficacy of the combination therapy described in the Marik publication in the management of patients with circulatory and/or respiratory dysfunction resulting from sepsis. This subset of sepsis patients has been chosen because they are easily identified, have a high mortality, and consume significant critical care resources. As such, any improvements in outcomes attributed to effective therapies would be of great value to patients, as well as their care providers and healthcare systems. Further, because the promulgated therapies are composed of three inexpensive and readily available drugs, its efficacy would have important implications the management of sepsis in both well and poorly resourced settings worldwide.

### 3.5. Risk/Benefit Assessment

#### **Vitamin C**

High dose intravenous vitamin C has been in clinical use for more than half a century,<sup>59,60</sup> and is known to have few toxic or adverse effects.<sup>23,61</sup> In one study of 9,227 patients receiving an average of 24 g intravenous vitamin C every four days, only 59 adverse events were reported.<sup>62</sup> Among these, the most common were lethargy and fatigue. Others included irritation at the infusion site, nephrolithiasis, hyperglycemia, nausea, two cases of hemolysis, and one case of renal failure in a patient with pre-existing kidney disease and cancer metastatic to the kidneys.

Other adverse effects that have been reported are also rare, and are mild with two exceptions: oxalate nephropathy and hemolysis. Oxalate is a metabolite of vitamin C. At high concentrations, it can deposit in the kidneys leading to oxalate nephropathy. This has been reported among individuals who either (1)

received grams per hour of intravenous vitamin C,<sup>63-66</sup> or (2) received moderate to high doses of oral vitamin C for weeks to months.<sup>67-71</sup> Despite these case reports, three recent studies of high dose intravenous vitamin C have showed either similar or reduced renal failure event rates among patients with sepsis or burn injury, compared to patients that did not receive vitamin C.<sup>20,37-39</sup> Acute hemolysis in the setting of high dose intravenous vitamin C administration is also rare and is only known to occur in patients with G6PD-deficiency.<sup>72-74</sup>

Because oxalate nephropathy and hemolysis are rare events, and because patients with primary hyperoxaluria, previous or current oxalate nephropathy, and those with known G6PD-deficiency will be excluded from the study, we do not view these potential adverse events as significant risks to enrolled patients. Moreover, given the high prevalence and mortality associated with sepsis, the benefit of identifying an effective pharmacologic therapy for the sepsis syndrome justifies the small risk that one of these rare adverse events could occur.

Lastly, it should be noted that falsely elevated glucose levels have been observed when measurements are made using point of care glucometers during the administration of very high dose intravenous vitamin C to burn patients (66 mg/kg/hour).<sup>75,76</sup> Treatment of falsely elevated glucose could result in potentially harmful hypoglycemic events. Two studies comparing glucose levels measured by point of care devices versus central laboratory measurements show that some devices (Accu Chek by Roche Diagnostics, Indianapolis, IN, USA) overestimate actual glucose levels as serum vitamin C concentration increased up to or above 851  $\mu\text{M}$ .<sup>77,78</sup> In the phase I study by Fowler et al, patients received 50 mg/kg/day in 4 divided doses.<sup>39</sup> For a 70 kg man, this is equivalent to 3.5 g/day intravenous vitamin C. In that study, the average day 4 vitamin C trough level was 331  $\mu\text{M}$  (range: 101 - 806). Hypoglycemic events were not reported, but glucose was measured in a central laboratory. In the Marik study, 6 g/day of intravenous vitamin C was administered in 4 divided doses (as is planned for this study), and no episodes of clinically significant hypoglycemia were reported.<sup>20</sup> Further, Marik et al, measured glucose levels using the Accu-Chek Inform glucometer (Roche Diagnostics, Indianapolis, IN, USA) at the end of vitamin C infusion, and found similar glucose values as those measured in the central laboratory.<sup>79</sup> They concluded the fictitious hyperglycemia was not a clinically significant problem at the doses of vitamin C used in their study (and those that will be used in VICTAS).<sup>75</sup> However, the Marik protocol also refers to a strategy of “permissive hyperglycemia” in which insulin was not given unless glucose exceeded 220 mg/dl.<sup>80</sup>

Given the serum vitamin C concentrations observed in the study by Fowler et al, it is reasonable to consider that some patients in the current study may develop vitamin C concentrations that could interfere with some point of care glucometers. Only one point of care glucometer has been approved by the FDA for use in the critical care setting.<sup>81</sup> The accuracy of this device has been validated to vitamin C concentrations we will not approach, as well as many other interfering substances encountered in the critical care setting. As a safety measure, we will require that participating centers only use this point of care glucometer, or validated central or critical care laboratory devices to measure glucose in study participants.

### **Thiamine**

Thiamine rarely causes any side effects when given orally or intravenously (as planned in this study).<sup>82</sup> However, rarely reported side effects are injection site reactions (such as irritation or redness) and hypersensitivity reactions (the only contraindication to thiamine use). In a study of 989 consecutive

patients who received 100 mg intravenous boluses of thiamine (1070 doses), a total of 12 adverse reactions were reported (1.1%).<sup>82</sup> Eleven were local injection site reactions and considered minor. One was more severe and was characterized as generalized puritis.

### **Hydrocortisone**

Hydrocortisone has been shown to cause hyperglycemia and hypernatremia in some patients with septic shock, though these observations have not been shown to cause significant adverse effects on patient outcomes.<sup>12,83</sup> Steroids in general, and when given over weeks and months, have been associated with the development of gastric ulcers, and a slight increased risk of infection in hospitalized patients. Other side effects that have been reported include difficulties with wound healing. Rare, but serious side effects of steroids include fluid retention, thinning of the skin, muscle weakness, and acute mental status changes. Though these potential adverse effects are recognized, they are rare and relate to chronic steroid use at higher doses. They are not anticipated when steroids are given in the setting of sepsis, where the dose is relatively low, and the duration short (as is planned in the current study).<sup>12,84,85</sup>

## 4. Objectives and Hypotheses

**Primary Objective:** To demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids to reduce the duration of respiratory and cardiovascular organ dysfunction in critically ill patients with sepsis.

**Primary Hypothesis:** In critically ill patients with sepsis, combination therapy using vitamin C, thiamine and corticosteroids will increase vasopressor and ventilator-free days (VVFD) at 30 days when compared to control patients treated with matching placebos.

**Secondary Objective:** To demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids to reduce mortality in critically ill patients with sepsis.

**Secondary Hypothesis:** In critically ill patients with sepsis, combination therapy using vitamin C, thiamine and corticosteroids will reduce mortality at 30 days when compared with control patients treated with matching placebos.

## 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 (6.2.c)
- 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.

## 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 ( $\text{PaO}_2/\text{FiO}_2 \leq 300$  or  $\text{SpO}_2/\text{FiO}_2 \leq 315$ ) 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  $\text{FiO}_2 \geq 0.40$
  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  $\text{PaO}_2/\text{FiO}_2 > 300$  or  $\text{SpO}_2/\text{FiO}_2 > 315$  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

- i) Chronic hypoxemia requiring supplemental non-invasive oxygen (nasal cannula or NIPPV) or home mechanical ventilation
- j) Chronic cardiovascular failure requiring home mechanical hemodynamic support (e.g., LVAD) or home chemical hemodynamic support (e.g., milrinone)
- k) Known allergy or known contraindication to vitamin C, thiamine, or corticosteroids (including previous history or active diagnosis of primary hyperoxaluria and/or oxalate nephropathy, or known/suspected ethylene glycol ingestion, or known G6PD Deficiency)
- l) Use of vitamin C at a dose of > 1g/day (IV or oral) within the 24 hours preceding first episode of qualifying organ dysfunction during a given ED or ICU admission
- m) Chronic disease/illness that, in the opinion of the site investigator, have an expected lifespan of < 30 days unrelated to current sepsis diagnosis (e.g., stage IV malignancy, neurodegenerative disease, etc.)
- n) Pregnancy or known active breastfeeding
- o) Prisoner or Incarceration
- p) Current participation in another interventional research study\*
- q) Inability or unwillingness of subject or legal surrogate/representative to give written informed consent

\*Note: Co-enrollment in other interventional research studies requires written permission from the VICTAS Executive Committee in advance of subject identification.

### 7.3. Screen Failures

All patients with suspected infection and sepsis should be screened after presenting to a study site hospital (please see section 9.2: Screening and Informed Consent). Sites will maintain an electronic screen failure log that includes all patients with a diagnosis of sepsis or septic shock who are not randomized into VICTAS. Sites will document the primary reason for exclusion or failed enrollment.

Subjects who have been consented and subsequently determined to violate eligibility criteria, due to newly available data prior to randomization, will be excluded and documented as screen failures. Such events are expected to be rare, but may occur when study team becomes newly aware of historical data, such as chronic dependence on supplemental oxygen.

### 7.4. Study Completion and Discontinuations

Study procedures should not delay clinical care. All randomized subjects will be included in the intention-to-treat (ITT) analysis. Randomized subjects are expected to complete the trial.

Subjects have the right to withdraw from the trial for any reason at any time. If the subject (or the patient's legally authorized representative) withdraws consent, for any reason, such an act prematurely stops the subject's participation in the trial, and all scheduled trial-related interventions, assessments and laboratory testing will be stopped. All data collected prior to withdrawal will remain in the database but data obtained after the patient has withdrawn his/her consent will not be entered into the database. However, results from assessments and blood samples collected prior to the withdrawal of the consent but not analyzed at the time of the withdrawal will be entered into the database, unless the patient requests that these be removed.

Subjects or their legally authorized representatives may opt to discontinue the study intervention without full withdrawal of participation in research. Additionally, the site investigator, Co-PIs (Sevransky, Rothman and Wright) and/or DSMB may determine to prematurely discontinue the study intervention for safety or potential contraindications to study intervention. Subjects whose study intervention is terminated prematurely, but who have not withdrawn from the study will continue with all planned follow-up and study related assessments.

Subjects will only receive study drug while admitted to the ICU or in the ED while awaiting transfer to the ICU. If a subject's level of care changes prior to final dose of study drug, study intervention will be discontinued upon physical transfer from the ICU to another level of care (i.e., transferred to step-down or intermediate care, telemetry, med-surg, outside facility, home, etc.). Patients who have been downgraded, but physically remain in the ICU, will continue to receive study drug for 4 days or as long as they are physically in the ICU (whichever comes first).

#### 7.5. Inclusion of Minorities, Women and Children

Subjects will not be excluded based upon race, ethnicity or gender. Pregnant patients will be excluded. Pediatric patients (<18 years of age) will be excluded due to differing diagnostic criteria, care pathways, and protocols in sepsis.

## 8. Pharmacologic Intervention

### 8.1. Agents

The three agents being studied include:

- Agent 1: Vitamin C
  - Route: Intravenous infusion over 30 minutes
  - Dose: 1.5 grams
  - Frequency: every 6 hours
  - Duration: 96 hours
  
- Agent 2: Thiamine
  - Route: Slow intravenous push over 2 – 3 minutes
  - Dose: 100 mg
  - Frequency: every 6 hours
  - Duration: 96 hours
  
- Agent 3: Hydrocortisone
  - Route: Slow intravenous push over 2 – 3 minutes
  - Dose: 50 mg
  - Frequency: every 6 hours
  - Duration: 96 hours

### 8.2. Rationale

Daily recommended dietary allowances for vitamin C are in the range of 75 to 110mg/daily.<sup>86,87</sup> This is meant to exceed a mean dietary intake of 46 mg daily needed to prevent scurvy. Normal serum levels of ascorbic acid are variable, but in the range of 50-70  $\mu\text{M}$  in healthy, fasting adults.<sup>88</sup> Levels of approximately 60 – 90  $\mu\text{M}$  are achieved following maximal repletion by oral vitamin C intake.<sup>89,90</sup> Data in septic and critically ill cohorts demonstrate that serum levels are commonly < 20  $\mu\text{M}$  (5). Oral delivery of vitamin C is commonly used to restore serum levels to normal in deficient patients, however, high dose oral delivery of vitamin C does not increase serum vitamin C to therapeutic levels needed for sepsis.<sup>23,89,90</sup> Rather, they generally plateau at < 100  $\mu\text{M}$  even in studies using very high dose oral regimens.

The use of intravenous vitamin C allows for rapid increases in serum levels many fold higher than oral dosing allows. At intravenous doses of ~2g daily in critically ill patients, mean serum levels of approximately 100  $\mu\text{M}$  were achieved and maintained.<sup>91</sup> At intravenous doses of 10g daily, serum levels plateaued at an approximate mean value of 500  $\mu\text{M}$ . Prompt restoration of normal to elevated serum levels of Vitamin C were also demonstrated with administration of 3g doses of intravenous vitamin C in critically ill patients. In the same study, doses of 300mg and 1g daily, both resulted in persistently low vitamin C serum levels after 2 days.

As detailed in the Background above, preliminary data suggest a benefit of vitamin C administration in critically ill patients, ARDS, and sepsis. The doses used in these populations have varied substantially. In sepsis, simply repleting vitamin C to normal serum levels may confer some benefit; however, the pluri-potent therapeutic effects may require levels 3-4 times normal. Rapid repletion of vitamin C levels is only

possible with IV administration. High dose oral administration to deficient, hospitalized adults did not result in normal serum levels for weeks to months.<sup>89</sup> We have chosen 1.5g every six hours based on preliminary data suggesting efficacy at this dose or similar dosing regimens.<sup>20,39</sup> Of note, dosing regimens that raise serum vitamin C levels to 10-15 times normal (1-5mM) are believed to trigger cytotoxic effects on malignant cells.<sup>92</sup> However, such high levels have been associated with harmful side effects (e.g. renal failure, hemolytic anemia, disruption of accurate glucose measurements) and are not thought to be of value in the treatment of sepsis. We aimed for a dose that achieves serum level adequate to confer benefits by rapidly repleting Vitamin C deficiency in patients.

The rationale for thiamine supplementation in critical care and sepsis is detailed in the Background. At a dose of 200mg twice daily, septic patients with a concurrent thiamine deficiency were demonstrated to have improved clearance of lactate and decreased mortality.<sup>50</sup> Thiamine deficiency is common among critically ill populations. Oral administration of thiamine can replete thiamine stores and return subjects to adequate serum levels, but requires chronic supplementation.<sup>49,50</sup> In the acute setting, when it is believed that severe thiamine deficiency contributes to defects in aerobic metabolism, higher doses of intravenous thiamine are required to adequately replete thiamine levels quickly.<sup>93</sup> Thiamine is poorly absorbed after oral ingestion, with a maximal GI absorption from single oral dosing of approximately 4-5mg in healthy volunteers.<sup>93</sup> Absorption is likely lower in alcoholics or the critically ill, further necessitating intravenous administration. Some professional societies recommend doses as high as a total of 1500mg daily for patients with suspected Wernicke's encephalopathy - a disease that results directly from thiamine depletion. The optimal dose for suspected thiamine deficiency is not known. Dose recommendations range from 200mg daily to 1500mg daily for patients with suspected deficiency.<sup>94,95</sup> Based on the findings of Donnino et al, we believe the beneficial effect of intravenous thiamine is predominantly a result of the rapid resolution of deficiency, rather than a separate pharmacologic mechanism at higher doses.

Administration of intravenous thiamine has been shown to be extremely safe. At bolus doses of greater than 200mg there have been reports of anaphylactoid reactions, although those reactions are rare.<sup>96,97</sup> A prospective study of 989 patients receiving a dose of 100mg in bolus form showed no significant adverse reactions.<sup>82</sup> The safety of 100mg intravenous bolus dosing, the signal of a positive clinical effect by Donnino et al when giving a total dose of 400mg daily,<sup>50</sup> and the short half-life of serum thiamine supported the 100mg q6h hour dosing strategy outlined above.

The rationale for the use of hydrocortisone in patients with septic shock is detailed in the Background. The dosing strategy for hydrocortisone in the VICTAS trial is based on current guidelines for the treatment of patients with septic shock. Surviving Sepsis Campaign guidelines recommend:

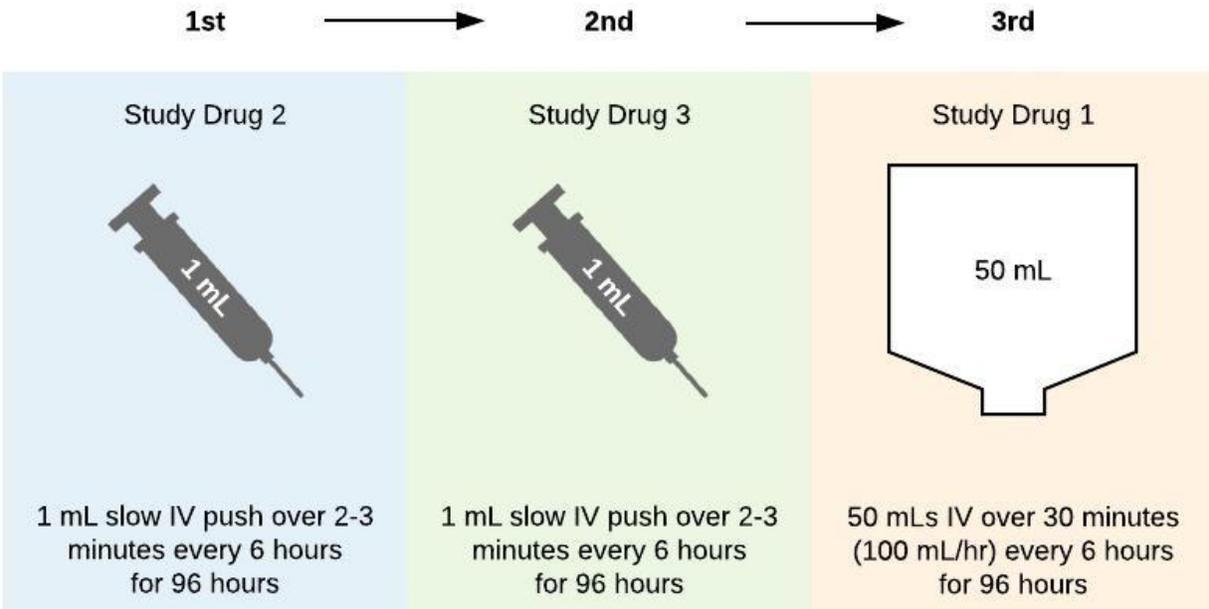
*“We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).”*

### 8.3. Treatment and Study Drug Administration

Randomized subjects will receive either active agents or placebos, labeled as VICTAS Study Drug 1, VICTAS Study Drug 2, and VICTAS Study Drug 3. The table below details these three active agents or matching placebos.

	VICTAS Study Drug 1		VICTAS Study Drug 2		VICTAS Study Drug 3	
Intervention	Vitamin C	Placebo	Thiamine	Placebo	Hydrocortisone	Placebo
Active Agent	Ascorbic acid	N/A	Thiamine hydrochloride	N/A	Hydrocortisone sodium succinate, powder	N/A
Carrier / Reconstitute	Dextrose 5%	Normal Saline in Dextrose 5%	Monothiol-glycerol, 0.5% v/v; water for injection	Normal Saline	Sterile Water or Normal Saline	Normal Saline
Strength	25000 mg in 50 ml	N/A	200 mg in 2 mL	N/A	100 mg in 2 mL	N/A
Dose	1.5 grams	N/A	100 mg	N/A	50 mg	N/A
Volume and rate to be administered	50 mL over 30 minutes (100 mL/hour)	50 mL over 30 minutes (100 mL/hour)	1 mL over 2-3 minutes	1 mL over 2-3 minutes	1 mL over 2-3 minutes	1 mL over 2-3 minutes
Expiration	24 hours refrigerated and protected from light		24 hours		24 hours	
Route	Intravenous (IV)					
Frequency	Every 6 hours					
Duration	96 hours while physically in the ICU					

**Administration** – Randomized subjects will receive VICTAS Study Drugs 1, 2, and 3, via intravenous administration every 6 hours up to 96 hours. The first dose should be administered as soon as possible but no longer than 4 hours from randomization. All subsequent doses should default to the local institution every 6 hour routine dosing schedule. All three study drugs should be administered within +/- 2 hours of their scheduled time. Missed doses should be treated via the “Treatment Compliance and Discontinuation” section of this protocol (page 27). All three study drugs should be administered separately and should not be infused or administered with any other medications or study drugs. We recommend that study drugs 2 and 3 be administered first since they are IV push and study drug 1 is administered over 30 mins. *For subjects already prescribed open-label corticosteroids at the time of randomization, or for patients prescribed corticosteroids after randomization, see section below on steroid management.*



The total number of individual study drug administrations is 48 (3 study drugs per administration x 4 administrations per day x 4 days). The total number of study drug administration time points per day is 4 (3 study drugs per administration).

**Steroid Management** – See table below. For patients without clinically prescribed corticosteroids, VICTAS Study Drug 3 will always be administered. If treating physicians believe there is an indication for steroids, (i.e., continued shock after adequate fluid resuscitation and vasopressor therapy, etc.), they are permitted to initiate open-label corticosteroid therapy based on local practice and international guidelines. If treating physicians place an active order prescribing at least 200 mg or greater of daily hydrocortisone, or equivalent (see APPENDIX A), then VICTAS Study Drug 3 (hydrocortisone or placebo) will NOT be administered (see table below). The research team, investigational pharmacy, and clinical teams should monitor at least daily for new, or discontinued, corticosteroid orders for randomized patients. When new corticosteroid orders are discovered, the study team and pharmacy will discontinue VICTAS Study Drug 3 (as soon as possible). If treating physicians discontinue clinically prescribed corticosteroids, or reduce the total daily dose to less than 200 mg of hydrocortisone daily (or equivalent), VICTAS Study Drug 3 will be restarted (as soon as possible) if this occurs within the first 96 hours following randomization, and the patient remains in the ICU.

<b>Provider Orders During 96 Hours After Randomization</b>	<b>Study Drug 3 Delivered</b>
No Systemic Steroids	Yes
Systemic Steroids < 200 mg Hydrocortisone (or equivalent)	Yes
Systemic Steroids $\geq$ 200 mg Hydrocortisone (or equivalent)	No

#### 8.4. Study Drug Packaging and Preparation

The FDA approved commercial products of each study medication will be procured from McGuff Pharmaceuticals and shipped to the central coordinating pharmacy (CCP) at Vanderbilt University Medical Center. Matching placebos will be procured by the CCP from a manufacturer, distributor, and/or supplier. All three study drugs and placebo supplies will be tagged as investigational product and coded with unique identification numbers linking each vial to the matching kit.

#### STUDY DRUG HANDLING

All commercial products and placebos will arrive to the CCP in their commercial formulation and packaging directly from a manufacturer, distributor, and/or supplier. All three study drugs and placebos will be tagged as investigational product and coded with unique identification numbers. Study drugs and placebos will be packed into study kits. The exterior of kits will be blinded and identical in size, shape, and color. Each kit will be identified with a unique code (i.e., randomization number) and the kits contents will have matching codes. After unsealing study drug kits, site pharmacists will be UNBLINDED to randomization assignment. Site pharmacists are **prohibited** from informing anyone of study drug assignment.

Overview of CCP labeling and packaging process for study drugs:

1. Receive medication / placebo
2. Visual inspection of medication to ensure vial integrity
3. Label study drug (active agent or placebo) with appropriate identification and coding (i.e., randomization number and/or kit number) and label product for investigation use only
4. Package study drugs in appropriate kits
5. Label and seal exterior of kit
6. Ship study drug kits to sites in appropriate shipping containers (see storage and temperature control)
7. Ensure drugs are received by local site pharmacies

The CCP will be responsible for restocking sites with study drug kits to maintain an acceptable par level.

The CCP will **NOT** perform any compounding of medications.

Final verification of all study drugs will be completed by the research pharmacist or designee to ensure that the site maintains correct inventory.

Local sites pharmacies will compound and dispense medications as required and as outlined below.

**VICTAS Study Drug 1:** Blinded, multi-dose vials of either 25,000 mg / 50 mL of commercial ASCOR (ascorbic acid, McGuff pharmaceuticals) or 50 mLs of dextrose 5% will be distributed to sites and stored at 2-8 degrees Celsius. After randomization, site pharmacies will locate the specified kit using the unique identification code. Three (3) mLs will be removed from the study drug vial and compounded into a 50 mL infusion bag of dextrose 5%. The site pharmacy will label the compounded drug as investigational product and place in light protected bag. The study drug vials will expire four (4) hours after first puncture. Site pharmacies will prepare up to four (4) doses from one (1) study drug vial as determined by local investigational drug guidelines. The compounded infusion bags may be stored for up to 24 hours at 2-8 degrees Celsius. If more than one (1) infusion bag is compounded from the same study drug vial and stored for subsequent doses, the site will be responsible for maintaining appropriate accountability for the investigational product.

VICTAS Study Drug 1 should be light protected during storage and compounded bags should have be protected from light using the provided opaque bag after compounding and while being administered. Light protected tubing is not required during administration. Each dose will be administered over 30 minutes through a dedicated IV line (i.e., infused separately and should not administered concurrently with any other medications or study drugs) at the frequency and dose described above.

**VICTAS Study Drug 2:** Blinded, single-dose, light-protected vials of either thiamine 200 mg / 2 mLs or 2 mL normal saline solution for placebo will be provided to sites and stored at 15-30 degrees Celsius. After randomization, site pharmacies will locate the specified vial using the unique identification code. One (1) mL of thiamine or placebo will be withdrawn into a syringe using standard IV drug preparation techniques. The syringe will be labeled as investigational product (VICTAS Study Drug 2) and administered via slow IV push over 2-3 minutes at the frequency and dose as described above. One (1) mL of thiamine or placebo will be wasted.

**VICTAS Study Drug 3:** Blinded, single-dose vials of hydrocortisone 100 mg powder or vials of saline solution for placebo will be provided to sites and stored at 20-25 degrees Celsius. After randomization, site pharmacies will locate specified vial using the unique identification code. Using a standard IV drug preparation and reconstitution technique, 2 mLs of diluent (sterile water or saline) will be added to the hydrocortisone powder, agitated and allowed proper time to reconstitute. One (1) mL of hydrocortisone or placebo will be withdrawn via syringe, labeled as investigational product (VICTAS Study Drug 3) and dispensed to the bedside. Study drug 3 will be administered via slow IV push over 2-3 minutes at the frequency and dose as describe above.

#### 8.5. Investigational New Drug (IND)

The VICTAS Trial received an IND exemption from the FDA on 1/11/2018, which applies to all three VICTAS study drugs. *The official FDA letter has been uploaded a part of the IRB application.*

This is a clinical evaluation of the FDA-approved drugs: ASCOR (ascorbic acid), thiamine hydrochloride (thiamine), and Solu-cortef (hydrocortisone), for an off-label indication and accordingly meets regulatory criteria (21 CFR Sec. 312.2(b)(1)) for an exemption, which has been granted by the FDA. Exemption is based on the following criteria: (1) the drug products are lawfully marketed in the United States, (2) the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the

drugs, (3) in the case of prescription drugs, the investigation is not intended to support a significant change in the advertising for the drugs, (4) the investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug products, (5) the investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent, and (6) the investigation is not intended to promote or commercialize the drug products.

## Treatment Compliance and Discontinuation

Interruptions of study drug administration should be avoided as much as possible. Missed doses of VICTAS study drugs may be administered up to 3 hours after the scheduled administration time (one additional hour from + 2 hours window), but should be administered as soon as possible after the scheduled time. Any study drug interruptions will be recorded, including the reason for the interruption.

When a research subject is discharged from the ICU prior to completing the full 96 hour study treatment period, all future study drug administrations will be discontinued.

In the case of a significant safety concern related to any of the three drugs administered as part of the VICTAS study, the local site PI should evaluate the situation and determine if discontinuing the study intervention or any individual component of the study intervention is warranted. Since there is no specific antidote for hydrocortisone, thiamine, or vitamin C, in almost all cases simply discontinuing the study drug is appropriate. For this reason, **the study medication blind shall not be broken, as breaking the blind will not provide increased safety.** The local site PI and clinical treating team has ultimate discretion to discontinue study intervention if they believe the study intervention is having untoward effects with significant safety concern for the subject. The study teams should contact the 24/7 Trial Physician Phone Line for safety concerns or questions regarding complete or partial study intervention termination. The date, time, and reason for early intervention discontinuation will be provided and documented. Subjects will not be withdrawn from the study and should be followed per protocol.

The local site PI will inform the DCC of all possible reactions when discovered by study staff. The DCC will prepare reports of these incidents as needed for communication to the CCC who will then report to the SIRB, and/or the DSMB.

### 8.6. Concomitant Therapies

Any patient currently participating in another trial of a pharmacologic agent for sepsis will not be eligible for enrollment in the VICTAS trial. Any patient enrolled in another trial that requires administration of vitamin C, thiamine or hydrocortisone will not be eligible for enrollment in the VICTAS trial.

Subjects may receive Vitamin C, thiamine, or hydrocortisone during the course of the study at the discretion of their treating physicians with the following stipulations:

#### Vitamin C

- May be given for known or suspected vitamin C deficiency (i.e. scurvy).
- May not be given at doses greater than 1g daily (total daily dose) – either orally or intravenously.
- Any administration of vitamin C outside of study protocol will be recorded and registered.

#### Thiamine

- May be given for known or suspected thiamine deficiency (e.g., prevention of Wernicke's encephalopathy in chronic alcoholics or malnourished patients).

#### Hydrocortisone

- As detailed previously, the use of hydrocortisone will be allowed at the discretion of the primary clinical teams. Refer to section discussing steroid management for further detail.
- The use of other steroid agents will be allowed, and will be converted to hydrocortisone equivalent doses for the purposes of determining the details of Study Drug 3 (see APPENDIX A). Subjects on chronic steroids will not be excluded from enrollment.

### 8.7. Drug Storage, Accounting and Disposal

**Storage** – All study drugs will be stored on site and are expected to remain stable for months under the pre-specified temperature control. Expiration dates and shelf life for study drugs will be determined and amended based on stability testing. Study drug(s) will be sent to sites prior to the expiration dates.

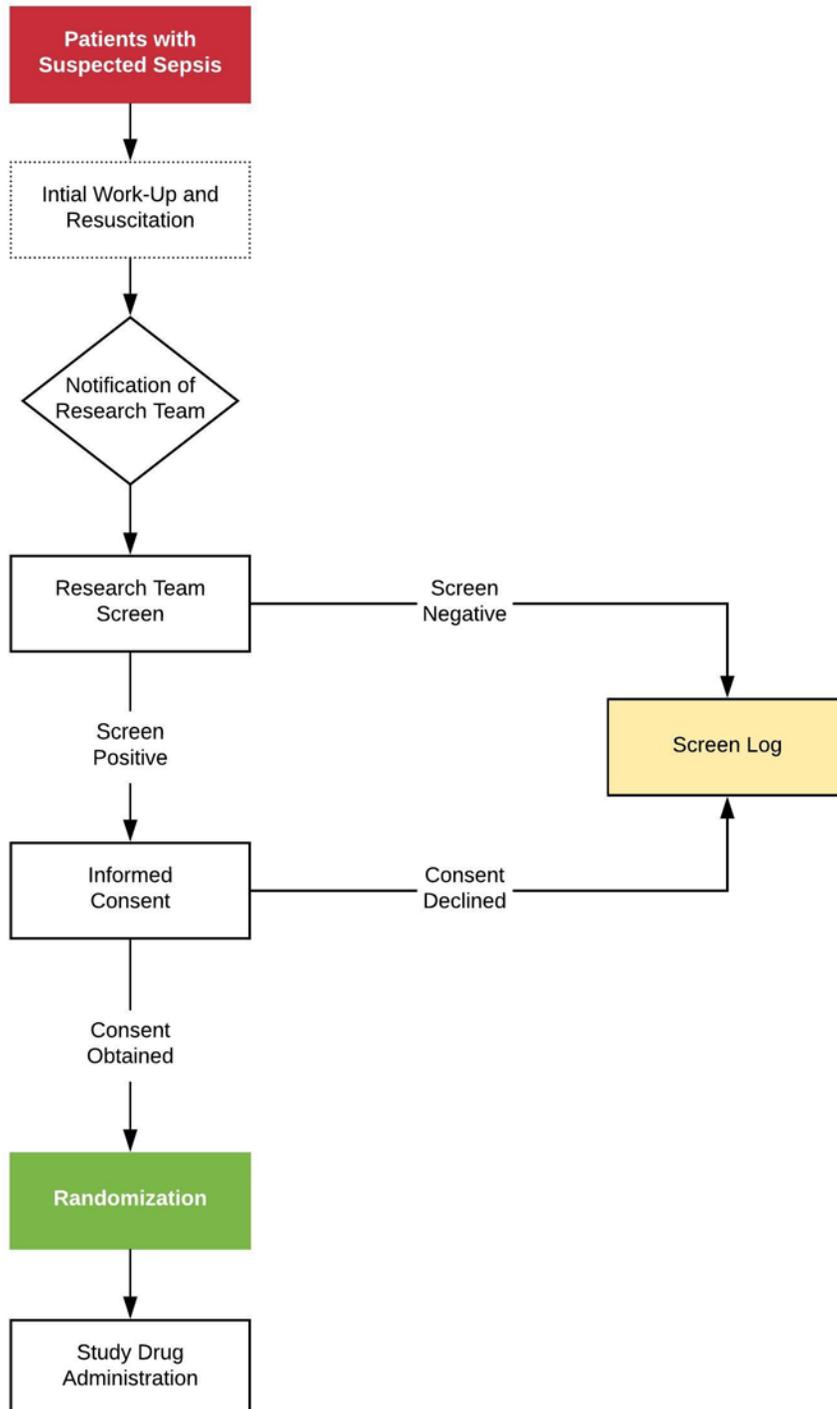
**Accountability** – The CCC and Central Pharmacy will provide management of ensuring appropriate amount of study drug is at each site. Sites will maintain appropriate and accurate drug accountability.

**Drug Disposal** – Any expired drug kits must be destroyed per the institutions disposal policies and documented on the accountability record. Study drugs that are administered and have left over product requiring wasting do not require documentation on the accountability record.

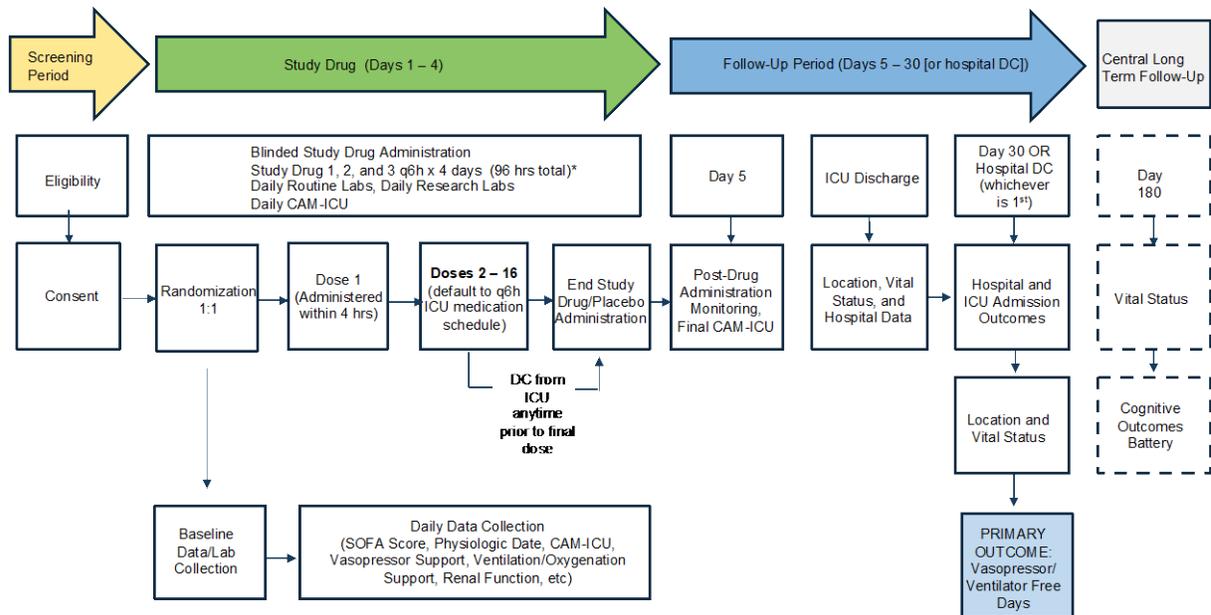
## 9. Study Screening and Enrollment

### 9.1. Study and Subject Progression Flow Chart

The diagram below illustrates the screening and enrollment process for the trial.



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

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.

## **10. Study Procedures, Assessments and Data Collection**

### **10.1. Data Collection and Timelines**

The Data Coordinating Center (DCC), CCC or its designee will instruct the study site regarding data capture procedures on electronic and/or paper Case Report Forms (CRFs). At each site, it is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each patient. Source documentation supporting the data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete data entry as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data. The Investigator must sign and date the Investigator's Statement that will be supplied to endorse the recorded data.

## 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
<b>Procedure</b>										
Eligibility Verification	X									
Informed Consent	X									
Randomization	X									
Study Drug Admin <sup>a</sup>	X	X	X	X	X					
Demographics	X									
Anthropometrics	X									
Source of Admission	X									
History and Physical <sup>b</sup> (including comorbidity)	X									
Respiratory support <sup>b</sup>	X	X	X	X	X	X	X	X	O	
Vasopressor Use (each agent and dose) <sup>b</sup>	X	X	X	X	X	X	X	X	O	
APACHE II <sup>c</sup>	X									
SOFA Score <sup>c</sup>	X	X	X	X	X	X				
Vitals <sup>b</sup>	X	X	X	X	X	X				
GCS	X	X	X	X	X	X				
RASS <sup>d</sup>	X	X	X	X	X	X				
CAM-ICU <sup>d</sup>	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 <sup>e</sup>	X									
Central Research Labs <sup>f</sup>	X	X	X	X	X					
Antimicrobial Therapy <sup>b</sup>	X						X	X	O	
Infection Source Data <sup>b</sup>	X						X	X		
Healthcare Location	X	X	X	X	X	X	X	X	O	C
<b>Adverse Event Monitoring</b>										
Potentially Associated	X	X	X	X	X	X	X	X	O	
Serious	X	X	X	X	X	X	X	X	O	
<b>Subject Completion and Follow-up</b>										
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

<sup>a</sup> 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)

<sup>b</sup> Data will be abstracted from Electronic Medical Record (EMR). Abstracted data will include baseline data, and daily data. For baseline data, use most aberrant 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).

<sup>c</sup> Data elements collected via REDCap; score calculated centrally.

<sup>d</sup> Performed by research staff, at time of randomization and days 1-5 or ICU discharge (whichever occurs first).

<sup>e</sup> 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

<sup>f</sup> 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<sup>81</sup>, or use devices validated for high vitamin C concentrations<sup>81</sup> in their critical care or central laboratory. If glucose is measured in a critical care or 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:

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

- 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**

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:

<b>UNRELATED</b>	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)
<b>UNLIKELY</b>	<b>Must have both of the following 2 conditions</b> , 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.
<b>REASONABLE POSSIBILITY</b>	<b>Must have at least 2 of the following 3 conditions</b> : 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.
<b>DEFINITE</b>	<b>Must have all 3 of the following conditions</b> : 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

reported by the Investigator or designee to the DCC by entering the event on the AE page of the EDC without delay.

These events (both PAAEs and SAE) will be followed (by the site PI) for outcome until resolution/stabilization or until 30 days from enrollment whichever comes first.

## B. Reporting Procedures

### i. General Reporting Guideline:

The site investigator, study coordinator, or designee is responsible for entering all AEs and SAEs and updating the information (e.g., date of resolution, action taken) in a timely manner. SAEs meeting criteria should be submitted within 72 hours.

AE, PAAE and SAE reports will include, but are not limited to: the adverse event term, subject identifier, description of the event, concomitant medication used to treat the adverse event, Investigator assessment of causal relationship to the Investigational Product and/or research participation and any other relevant information.

### ii. Reporting of SAEs to the DCC:

The Investigator or designee will complete an electronic SAE Report Form, assess the causal relationship to study procedure/intervention, and enter the information in the EDC system. This initial report should describe whether the SAE has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation.

The DCC will review all site submitted SAEs to determine if the event is indeed an SAE. In some cases, submitted SAEs may be downgraded to a PAAE. Such PAAEs will not be forwarded to the Medical Monitor or CCC, but instead be reviewed in aggregate along with other PAAEs at quarterly intervals for DSMB review and summarized and reported for the annual IRB continual renewal.

The DCC will then contact the Medical Monitor at the CCC for review of the electronic SAE Report Form and the supporting source documents. The CCC will report to the DSMB chair for review per the DSMB charter. If an ongoing SAE significantly worsens in its intensity or the relationship to study drug changes significantly, follow-up information will be provided by the site Investigator or designee within 72 hours of knowledge of this new information using the same procedure as described for transmitting the initial report. Based on reports delivered to the DCC, the CCC will report SAEs following SIRB criteria.

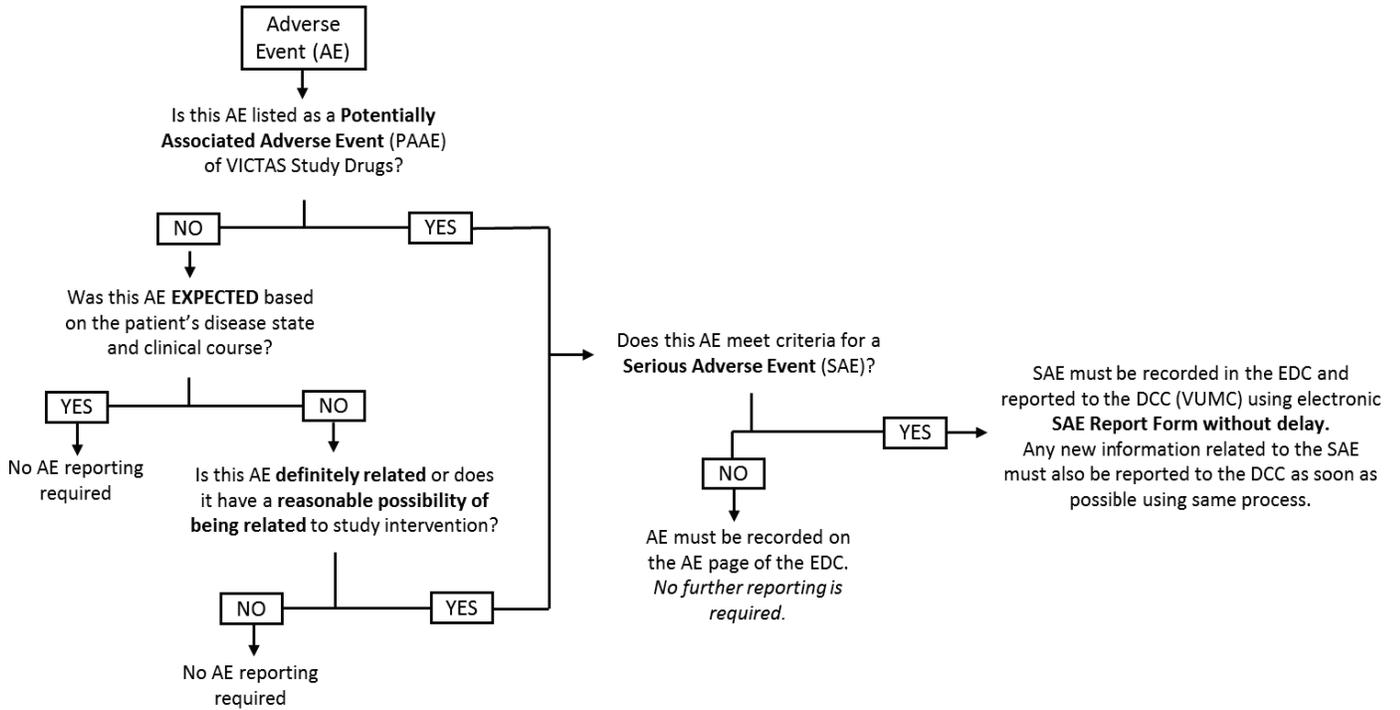
### iii. Reporting to the IRB:

All PAAEs and SAEs will be reported as described above to the JHU SIRB in accordance with SIRB reporting requirements and may be reported locally, as determined to be required by each relying site.

If IRB reporting is determined to be required by the relying site, the Investigator or designee will inform their local IRB of the SAE and provide them with all relevant initial and follow-up information. If only limited information is available during the initial 72-hour reporting time frame, then follow-up information will be provided promptly when it becomes available. If an ongoing SAE significantly

worsens in its intensity or relationship to study drug or if new information becomes available regarding an SAE, the follow-up information will be provided within 72 hours of knowledge of this new information using the same procedure for transmitting the initial report.

**The diagram below illustrates decision-making guidance and process flow for reporting of AEs by individual sites:**



## 10.7. Central Laboratory Testing

**Biomarkers and Pharmacokinetic Sampling** – At select study sites with the requisite experience and infrastructure for timed specimen collection, processing, storage and shipping, we will carry out baseline and timed measurements of Vitamin C (ascorbate), thiamine and cortisol, in order to characterize the relationship between these substances to disease severity, progression of disease and response to treatment. We will also assess baseline levels and pharmacokinetics of varied biomarkers associated with sepsis progression and response to therapy, in order to define the clinical utility of these biomarkers in the context of the TP. Sepsis biomarkers to be assessed will include complete blood count with differential, serum lactate, procalcitonin, C-reactive protein, and F2 isoprostane (a reliable sensitive biomarker of oxidative stress).

See table below. Initial blood and urine samples will be obtained after informed consent but prior to first study drug or placebo administration. The second sample collection will occur 30 minutes after completion of the first dose of study drugs or placebos. Subsequent sample collections will occur daily while in the ICU up to calendar day 4. The time of the daily specimen collection may be determined by the site research team, but these collections should occur at approximately the same time each day and within 90 minutes prior to the scheduled administration of study drug.

Collection Timepoint	Calendar Day <sup>ψ</sup>	Timing Description
1	1	After randomization, BEFORE any study drug administration
2	1 or 2	30 minutes after 1 <sup>st</sup> administration of all 3 study drugs is complete
3	2	Immediately prior to administration of study drugs
4	3	Immediately prior to administration of study drugs
5	4	Immediately prior to administration of study drugs

<sup>ψ</sup>: *Calendar Day* does not correspond with the EDC study day data collection. In most cases, collection 1 and 2 will occur on the same calendar day, except in cases where first drug is administered at ~midnight. Collection 3 should always be performed on the calendar day after collection 1 to prevent collection of blood volume that exceeds 45 mL on any single calendar day.

Samples will be processed and stored initially on site and then shipped to a central biorepository at Johns Hopkins University School of Medicine. Specimens will be aliquoted for biomarker and pharmacokinetic studies related the VICTAS study. Samples will be analyzed both at Johns Hopkins University and collaborating laboratories. Additional aliquots will be stored for the purpose of future studies that may include exploratory or development-phase assays. All biospecimens collected will be de-identified and associated with the subject using the unique subject code. No genetics will be collected.

Explicit consent will be sought for collection and storage of biospecimens for use in this study and unrelated future studies. However, consent to contribute to the biorepository is not required for participation in other aspects of the VICTAS study.

## 11. Statistical Considerations

### 11.1. General Considerations

Unless otherwise specified, continuous variables will be summarized by randomized treatment group with the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentile displayed. Categorical data will be summarized by randomized treatment group as counts and percentages. All summaries and analyses will be performed using data pooled across centers.

### 11.2. Power and Sample Size

The trial has a flexible sample size that will be determined adaptively using a “Goldilocks” strategy with an initial enrollment target of up to 500 subjects. Patients will be randomized in a 1:1 ratio to receive either the Treatment Protocol (TP) or Control Protocol (CP), plus standard of care treatment (hereafter referred to in a combined manner as the “Study Intervention” or “Intervention”).

Our analytical approach maximizes the potential for the trial to detect benefit, if it exists, by powering the study to detect a moderate effect on the VVFD endpoint (described in further detail below), while also allowing the trial to stop early if a very large effect is observed on our secondary outcome of mortality. This approach is desirable because an isolated study suggests a very strong effect on mortality (reference 20), yet clinical and research experience (references 18 and 19) suggest such a strong mortality benefit is unlikely and that more modest, but clinically meaningful, effects will be observed. Since we cannot preclude the possible large mortality benefit, we will check for it at the earliest adaptations. If the very large effect on mortality is not observed, we will continue enrollment with frequent interims that may stop the trial for benefit on VVFD. We will perform early interim analyses of the mortality endpoint when N=200, 300, and 400 subjects are enrolled. The trial may stop accrual if sufficiently robust results are observed on mortality at these interim analyses. If accrual is stopped in this way at any point, enrolled patients complete the study protocol for all outcome assessments and the primary analysis will be conducted with the complete data (see section 6: Study Design for additional details)..

Using a conservative estimate of the potential mortality difference of 20%, compared to the 32% mortality difference observed by Marik, et al.<sup>20</sup>, the study has a power exceeding 90% in a one-sided test of proportions with  $\alpha = 0.001$ . As such, the study is highly powered and very likely to stop at one of the interim analyses if the 20% treatment effect is real. If a more moderate treatment effect applies, the trial is more likely to continue beyond 500 subjects and would achieve lower power for the mortality endpoint. If the data are indeterminate on mortality after enrolling 400 patients, the trial may continue to a larger sample size (up to 2000).

For the primary outcome measure (VVFD), we will use an adaptive strategy with assessments at 500, 1000, 1500, or 2000 subjects randomized to either the TP or CP. When the data are sufficiently strong on the primary endpoint (VVFD), the trial may select a smaller sample size, but when necessary (e.g. for a moderate effect), the trial may continue to a larger sample size.

The overall Type I error rate for the trial is controlled at 2.5%. The early interims at N=200, 300, 400 are designed to conservatively spend alpha so that 2.4% remains for the analysis at N=500 (or beyond).

Anticipated alpha expenditures at all interim analyses, determined through clinical trial simulation, are as follows:

<b>Interim Analysis</b>	<b>Alpha Spend</b>
<b>N = 200</b>	0.0002
<b>N = 300</b>	<0.0001
<b>N = 400</b>	0.0003
<b>N = 500</b>	0.010
<b>N = 1000</b>	0.0026
<b>N = 1500</b>	0.0033

The power estimates used for sample size selection if the trial progresses to N=500 and beyond were also determined through clinical trial simulation, and take into account both the primary outcome of VVFD and the secondary mortality outcome. Indeed, these two outcomes are inter-related, with our primary efficacy endpoint (VVFD) representing a combination of treatment effect on mortality (all deaths are recorded as zero VVFD) and effect on vasopressor and ventilator support dependence in survivors. Full details of these simulations, over a wide range of assumptions, may be found in a separate document entitled *VICTAS Trial Adaptive Design Report*.

### 11.3. Analysis Sets

#### 11.3.1. Intent-to-Treat (ITT) Analysis Set

All randomized subjects will be included in the ITT analysis set. The ITT population will be used for all primary, secondary, and other efficacy analyses. In these analyses, subjects will be classified according to the treatment randomized (not actual treatment received).

#### 11.3.2. Per Protocol (PP) Analysis Set

Patients in the PP analysis must meet all inclusion criteria and no exclusion criteria. All subjects who are included in the ITT analysis set, receive at least 4 doses of study drug/placebo, and did not have major protocol deviations will be included in the PP analysis set. Major protocol violations will be identified prior to the unblinding of the study at the final analysis. Note, patients who die, or are discharged from the ICU before 4 doses can be given will be included in the PP analysis.

#### 11.3.3. Safety Analysis Set

The safety analysis set includes all subjects who are randomized and received at least one administration of study drug. Subjects will be classified according to actual treatment received.

### 11.4. Final Data Analysis

The final data analysis will be performed after all enrolled subjects have completed follow up. If the trial stops for expected success on the mortality endpoint at N=200, 300, or 400, the final analysis will be based solely on mortality and will require  $p < 0.001$ . If the trial reaches N=500 or more without predicted success on mortality, indicating more moderate effects, the primary analysis will be based on the more sensitive VVFD endpoint using the remaining 2.4% alpha.

#### 11.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is vasopressor and ventilator-free days (VVFD) in the first 30 days after start of treatment. The endpoint will be recorded to the nearest day. Subjects who die will be scored zero days, even if there is a period during which the subject is alive and free of vasopressors and mechanical ventilation. Subjects who must return to ventilation and/or vasopressors will have their counters reset at zero days. If the trial reaches N=500 or more, the primary analysis is a Wilcoxon rank-sum test (also known as a Mann-Whitney U test), which will be performed using a one-sided alpha of 0.022. If the study is extended beyond N=500, then the final analysis on VVFD requires  $p < 0.022$ . This p-value threshold was selected through simulations in order to control type I error and account for the multiple analyses at N=500, 1000, 1500 and 2000.

The primary analysis will be performed on the ITT population. A sensitivity analysis will be performed on the PP analysis set.

For subjects with missing data on the primary endpoint, a “last status carried forward” approach will be used. If a subject was last seen on either vasopressors or mechanical ventilation, it is assumed that the subject remained so, and is imputed to a value of zero VVFD. If the subject was last seen off of vasopressors and mechanical ventilation and is not known to be dead, it is also assumed that the subject remained so in the remainder of the 30-day period.

VVFDs will be tabulated by arm and presented graphically by histograms and cumulative distribution functions.

#### 11.4.2. Key Secondary Endpoint

The mortality endpoint will be tested using a Chi-square test. If the trial stops accrual at N=200, 300, or 400, all subjects will be followed and the primary analysis will be based on mortality, with trial success defined as  $p < 0.001$ . If the trial reaches N=500 or more, a gatekeeping strategy will be used such that the mortality endpoint will only be tested if the primary endpoint meets success. In that case, the mortality endpoint will be tested with one-sided alpha of 0.024. The mortality test will be performed on the ITT population. A sensitivity analysis will be performed on the PP analysis set.

#### 11.4.3. Additional Efficacy Endpoints

The following endpoints will be analyzed as supportive evidence of treatment benefit. The tests will not be included in the gatekeeping strategy, so that type I error will not be adjusted for multiple testing:

##### Other outcomes

- Mortality at 180 days

- Length of ICU stay

- Length of hospital stay

- Physical, emotional and cognitive outcomes at 180 days

#### 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:

- $PP_{\text{mort}}$  (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.
- $PP_{\text{mort}}$  (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	<i>may be recommended by DSMB</i>
	Expected success (mortality)	$PP_{mort}(\text{current } N) > 0.90$
	Continue	$PP_{mort}(\text{current } N) < 0.90$
N $\geq$ 500	Futility	$PP_{VVFD}(\text{max } N) < 0.10$
	Expected success (both endpoints)	$PP_{VVFD}(\text{current } N) > 0.95 \text{ AND } PP_{mort}(\text{current } N) > 0.95$
	Expected success (VVFD only)	$PP_{VVFD}(\text{current } N) > 0.95 \text{ AND } PP_{mort}(\text{max } N) < 0.10$
	Continue	<i>otherwise</i>

## 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

treatment assignment for the subject. The subject is considered randomized and enrolled at the time the REDCap system generates the treatment assignment.

#### 12.4. Study Record Retention

In keeping with DCC (Vanderbilt University Medical Center) data retention regulations, study records will be retained at all sites for a minimum of 7 years following notification that all investigations have ended. Prior to archiving records, the site should contact the PI to ensure that all required time limits for regulatory compliance have been satisfied.

#### 12.5. Data Clarification Requests

Data for each participant should be entered by the site according to the timeline provided in the Monitoring Plan. The entered data will be checked and verified by the DCC for consistency with the provided source records. When a data point has been verified as accurate, the DCC will generate a green check beside that data entry field indicating that the data point has been verified. Any omissions, discrepancies, or inaccuracies among the data will be noted and the DCC team will issue a query. Site users will then be required to respond to the query. More information regarding query resolution can be found in the Monitoring Plan.

#### 12.6. Protocol Deviations

A protocol deviation is a departure from the approved protocol's procedures made with or without prior IRB approval. Such departures may be major or minor/administrative in nature (see below).

#### **Emergency Deviations require prompt reporting to the IRB after they occur**

*Emergency deviations* are those occurring in an **emergency situation**, such as when a departure from the protocol is required immediately to protect the life or physical well-being of a participant. In such cases there is no time to prospectively seek the approval of the IRB. The CCC and the IRB of record must be notified as soon as possible, but not later than 5 days after the *emergency* situation occurred. The PI must submit a report to the IRB of record in eIRB via a Further Study Action for Protocol Event Report. Deviations of this nature are always considered to be unanticipated problems involving risks to subjects or others.

#### **Major, non-emergent deviations require approval by the IRB before they occur**

*Major, non-emergent deviations* are planned deviations that are non-emergent and represent a major change in the approved protocol. These deviations are changes that the IRB must approve before the proposed change is implemented (via submission of a Further Study Action for Change in Research in eIRB). Examples include exceptions to eligibility criteria, exceptions to the form and manner of obtaining informed consent, and exceptions to the schedule of administration of an investigational product.

If a planned major, non-emergent deviation occurs without prior IRB approval, the event is non-compliance which must be reported promptly to the IRB via Further study Action for Protocol Event

Report in eIRB. A PI's failure to report promptly any major, non-emergent deviation for which the PI did not obtain prior approval is itself an incident of non-compliance. Incidents of non-compliance will be managed in accordance with the Organization Policy on Investigator Non-Compliance Policy No. 103.7.

### **Minor or administrative protocol deviations require reporting to the IRB at continuing review**

*Minor or administrative deviations* are those which do not “affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects.” If a protocol deviation occurs which meets this definition, the deviation should be reported to the JHM IRB at the time the continuing review application is submitted. Examples of minor or administrative deviations include: follow up visits occurring outside the protocol required time frame because of the participant's schedule, or blood samples being obtained at times close to but not precisely at the time points specified in the protocol.

#### 12.7. Security, Privacy, and Confidentiality

VUMC employs several layers of data protection to ensure data security. The first part of security is physical protection of the hardware systems, access to which is limited to authorized personnel. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal. Additionally, REDCap has a built-in audit trail that tracks all user activity and changes made to the data entry fields with a date-time stamp.

## **13. Human Subjects Safety**

#### 13.1. Ethical Conduct of the Study

The study will be conducted according to Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The VICTAS PIs, CCC, DCC, Medical Monitors, and Investigators must comply with all instructions, regulations, and agreements in this protocol.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

#### 13.2. Institutional Review Board

The Johns Hopkins Medicine IRB will act as the single IRB of record (SIRB) for the VICTAS protocol. JHM IRB will initiate reliance agreements with each participating site (and any affiliate, where necessary) through the SMART IRB mechanism. All sites will be responsible for conducting a local context review, to ensure that the protocol is appropriate and reasonable for their respective study populations, however the JHM SIRB approval will serve as the IRB approval of record for the entire study. JHM IRB will

provide a letter of support from JHM IRB to serve as SIRB, a templated letter of support for relying sites to complete, a draft protocol to be adapted for local context, FWA instructions for participating sites, as applicable, and, SMART IRB instructions for participating sites.

The protocol and consent form will be reviewed and approved by the SIRB at Johns Hopkins University, School of Medicine and each participating center will perform a local context review prior to study initiation. Serious adverse experiences regardless of causality will be reported to the SIRB in accordance with the standard operating procedures and policies of the SIRB, and the study team will keep the SIRB informed as to the progress of the study. Any documents that the SIRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the SIRB. The SIRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. No study materials or supplies will be shipped to any participating site until SIRB approval of that site has been secured. The IRB unconditional approval statement will be transmitted by the clinical coordinating center to each site investigator prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written SIRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the SIRB and written verification that the modification was submitted and subsequently approved should be obtained.

The SIRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the SIRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

### 13.3. Informed Consent

Informed consent will be obtained in accordance with US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The CCC will prepare the informed consent form (ICF), assent and HIPAA authorization and provide the documents to the study team for approval prior to submission to the SIRB. The consent form generated by the Investigator must be acceptable to the VICTAS PIs and PI of the DCCC, and be approved by the SIRB. The written consent document will comply with local regulations. The CCC will send an SIRB-approved copy of the Informed Consent Form to each site for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the ICF and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the

original will be maintained with the subject's records. As described in *9.2: Screening and Informed Consent*, subjects will be assessed regularly during trial participation for return of cognitive function and their ability to provide informed consent. If the subject regains capacity during their hospital stay, written consent will be obtained directly from the study participant. In the event that a subject who regains capacity does not wish to continue study participation, this will be documented and no further study activity will be conducted. This includes any contact for the long-term outcome assessments.

At the discretion of individual sites, patients whose primary language is not English may be enrolled. In such cases, a translated version of the ICF and HIPAA authorization will be provided to subjects or legal representatives in the primary language of the subject or legally authorized representative (LAR), as appropriate. All information, both oral and written, will be given in the primary language of the subject or LAR, both at the time of enrollment and at short term (in-hospital) follow-up. Long term outcomes can only be performed in English.

Consent for Long Term Outcome Assessments: At time of enrollment, subjects will be asked to provide explicit consent to long-term outcomes assessment. If subjects are not capable of providing consent due to cognitive impairment, explicit consent to long-term outcomes assessment will be obtained from a qualified surrogate. Re-consenting of subjects who regain capacity during their hospital stay will be handled as described above. For subjects who do not regain capacity to provide consent prior to discharge from the hospital or regain capacity during hospitalization but are not able to be contacted by the local study team prior to hospital departure, the procedure for re-consenting and/or consenting to continued participation in the long term outcome portion of the study will be as detailed as below:

Capacity for consent will be reassessed by the Vanderbilt long-term outcomes study team at the time of the long-term follow-up. Patients will be judged to have regained capacity if they are able to speak on the phone and independently participate in conversation with the long-term outcome assessments study team member, as evidenced by reasonable responses to basic questions. For participants who have not regained capacity, LAR consent will remain valid and the Vanderbilt long-term outcomes team will proceed with the long-term outcome assessment.

For participants who have regained capacity, the long-term outcomes team will seek verbal consent from the participant for continued participation in ongoing research related to the VICTAS Trial. For participants who provide consent for ongoing participation, the long-term outcomes team will proceed with the long-term outcomes assessment. For participants who indicate they do not want to participate in ongoing research, this decision will be documented and the long-term outcomes assessment will not be performed. There will be no further contact between the study team and participant.

All procedures for re-consenting and/or consenting to continued participation in the long term outcome portion of the study will be conducted in accordance with any applicable local IRB requirements and state laws. *Information about site-specific requirements for re-consent, when consent is initially obtained via LAR, will be collected from each relying site via the local context questionnaire and submitted to the SIRB for consideration as part of the site on-boarding process.* We will also use our EDC database to record and keep track of site-specific requirements in order to ensure any plans for re-consent/consent for continued participation in the research are handled in accordance with site requirements. In the event that local state regulations or institutional policies require written re-consent once a participant regains capacity to consent or written consent for participation in ongoing research,

the Vanderbilt long-term outcomes study team will facilitate the written consent process. This will occur via fax, mailing of consent forms with self-addressed and stamped return envelopes or other mechanism determined to comply with applicable local/state law requirements.

The Vanderbilt Long-Term Outcomes team will work closely with local coordinators to obtain contact information enabling them to contact patients. Specifically, addresses, multiple telephone numbers, and extensive contact information (both for patients and for family members or friends who can assist us in locating patients) will be obtained and will be shared in the EDC database which will be accessible in “real time” to Vanderbilt coordinators. Using well established strategies and “best practices” such as we’ve described above (i.e. obtaining multiple points of contact, building relationships with patients early in the process, etc.), we anticipate successfully assessing at least 90% of all eligible patients. Follow-up models similar to those described here have been used across many multi-site outcome studies and IRB approval for such studies has always been obtained.

#### 13.4. Data Safety Monitoring Board (DSMB)

Data and safety monitoring will be carried out by a designed Data Safety and Monitoring Board (DSMB) to ensure and maintain the scientific integrity and ethical balance of human subjects’ research, and to protect subjects from avoidable harm. Data review by the DSMB throughout the trial will assure that the trial can continue without exposing participants to avoidable or unreasonable risks or harm.

The VICTAS Trial Data and Safety Monitoring Board (DSMB) will be composed of 5 individuals (2 emergency medicine clinicians, 2 critical care clinicians and 1 statistician) with specific content expertise in sepsis, multicenter clinical trials, and adaptive trial design and implementation. The DSMB will meet at least twice a year until study completion. The DSMB will report and advise the VICTAS Executive Committee. The DSMB is charged with ensuring that the trial is implemented as designed, that the prespecified design continues to be scientifically and ethically appropriate, and with reviewing ongoing safety data at the designated time points during the trial. The DSMB’s obligation is to the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial in accordance with federal guidelines.

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

Acting independently of the Marcus Foundation, without interest in influencing the outcome of the study, DSMB member responsibilities include:

- protecting the safety of the study participants from avoidable harm;
- reviewing the charter, the research protocol and plans for data and safety monitoring and the informed consent template;
- evaluating the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites and study, and other factors that can affect study safety and outcome;
- reviewing interim analyses for safety issues and making recommendations in accordance with pre-specified safety stopping rules agreed upon by the Executive Committee and the DSMB;
- making recommendations to the Executive committee chairs concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;

- considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- making recommendations to assist in the resolution of problems reported by the Co- and Principal Investigators or identified by the DSMB;
- ensuring the study is conducted as designed, including the implementation of the adaptive algorithm; and
- ensuring the confidentiality and blinding of study data and interim results.

DSMB meetings may be held by webinar or in person. The planned interim DSMB meetings will include both open and closed sessions. Discussions held in all sessions are confidential. During an open session, the VICTAS PI, Executive Committee Chairs, or other designees may be present. During open sessions, only information aggregated across treatment arms that does not threaten the integrity of the study blind will be discussed, such as general information regarding patient enrollment, compliance with the protocol, and external information that may affect the conduct of the study will be discussed.

Only DSMB members (both voting and ex officio non-voting), the study unblinded statistician, and the unblinded representatives from Berry Consultants (the adaptive design group) may attend closed sessions, unless a majority vote of the DSMB identifies other personnel whose presence is explicitly required to assist the DSMB during a closed session. All matters and information—including data presented by treatment group and information impacting the safety, ethics, and scientific validity and integrity of the study may be discussed during closed sessions. All formal recommendations considered by the DSMB will be first discussed during closed sessions.

The Executive Committee will decide whether to accept or decline the DSMB recommendation to continue, modify, or terminate the study. Recommendations and the rationale for recommendations will be provided in writing, to the extent necessary to support decision-making by the Executive Committee, with care not to unnecessarily unblind treatment assignments, following any formal DSMB meeting.

### 13.5. Risks to Subjects and Adequacy of Protection Against Risks

Known risks of high dose intravenous vitamin C include oxalate nephropathy that can progress to renal failure and hemolysis in patients with G6PD-deficiency. In an effort to fully avoid these events, patient with primary hyperoxaluria, previous or current oxalate nephropathy, and those with G6PD-deficiency will be excluded from the study.

Based on the reported potential risks of vitamin C, thiamine, and/or hydrocortisone as discussed above (section 3.5), important risks were identified that could be associated with administration of one or all three drugs and have been labeled as “potentially associated adverse events” (PAAE). PAAEs are listed below and will be recorded as detailed in Section 10.6 (Adverse Event Reporting):

Nephrolithiasis
Hemolysis
Hypersensitivity Reactions
Injection Site Reactions

Note: Individual cases of events that occur commonly based on the natural history of severe sepsis (e.g. acute kidney injury) and/or the treatments commonly administered as part of routine sepsis care such as steroids (e.g. adrenal insufficiency) will not be reported as PAAEs, but rather reviewed in aggregate at regular quarterly intervals by the DCC and DSMB to identify any potential effects related to the study intervention, with procedures for stopping in accordance with the DSMB charter.

Point of Care Glucometry – As discussed in section 3.5, there is a risk that some point of care glucometers could give falsely elevated readings when serum vitamin C concentrations are high. Therefore, participating sites will be required to use only point of care devices (Nova StatStrip), or central or critical care laboratory devices that have been validated for use during high dose intravenous vitamin C.

Further, participating sites using a StatStrip device for glucose monitoring will confirm serum glucose measurements using a central or critical care laboratory device before initiating insulin therapy, and for (or up to) 24 hours after study drug is completed (for patients who are not already on insulin therapy). Following initiation of insulin therapy, regular correlation of StatStrip and central or critical care glucose measurements will be performed daily with routine labs (this applies as well to patients who were already on insulin therapy, prior to study drug initiation). Consistent with standard of care, if the clinical team or site investigator believes a StatStrip measurement is erroneous or suspects symptomatic hypoglycemia, a confirmatory serum sample should be measured by a central or critical care laboratory.

Subject Confidentiality – All data (case report forms, recordings, laboratory specimens, imaging, and other records) kept at the site will be physically and electronically secured to maintain subject confidentiality. Paper records with subject data will be stored in locked office or cabinet. Computer records will always be password protected, and encrypted when possible. The study database is maintained behind a secure firewall, access is password protected and it uses SSL encryption for all data entry and access.

### 13.6. Potential Benefit of the Research to Subjects and Others

There is equipoise regarding whether the TP will lower mortality and affect other important outcomes among patients with sepsis. Although preliminary published evidence suggests such a benefit, it is not guaranteed that specific benefit will be gained from participation in this study.

### 13.7. Importance of the Knowledge to be Gained

There are no specific medical therapies available that have been shown to improve the outcomes of patients with sepsis. The purpose of the current study is to determine (or confirm) the efficacy of the TP in the management of patients with circulatory and/or respiratory dysfunction resulting from sepsis. Therefore, the conduct of this trial may substantially expand and improve the available therapeutic options for the treatment of sepsis.

### 13.8. Data and Safety Monitoring Plan

The study will be monitored at regular intervals by the DCC and/or DSMB as specific in the DSMB Charter. Monitoring will be conducted in accordance with GCP guidelines. Investigators must allow monitors or other relevant health authorities to inspect facilities and records relevant to the study.

## 14. Regulatory Compliance

### 14.1. Investigator responsibilities

Each Site Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the SIRB, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation) at their site.
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the study team and CCC any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection by the DSMB.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the study team and clinical coordinating center, all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include protocol amendments).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

### 14.2. Publications and data sharing

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the VICTAS PIs and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

### 14.3. Protocol amendments

Any amendment to the protocol will be written by the CCC and PI team. Protocol amendments cannot be implemented without prior written approval from the SIRB except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the SIRB is notified within five working days. The study may be modified or discontinued at any time by the SIRB, OHRP, or other government agencies as

part of their duties to ensure that research subjects are protected. Subjects will be notified in accordance with SIRB requirements.

## 15. Contact Information

### VICTAS LEADERSHIP PERSONNEL

VICTAS National HOTLINE 1-800-372-9160		
TEAM MEMBER	ROLE	CONTACT
<b>Jon Sevransky, MD, MHS, FCCM</b> Principal Investigator	Medical and scientific questions Executive, Operations, and Steering Committees	404-778-0599 <a href="mailto:jsevran@emory.edu">jsevran@emory.edu</a>
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<b>Alex Hall, MS, RN</b> Clinical Trial Operations	Medical and scientific questions Executive, Operations, and Steering Committees Protocol Committee, Drug Delivery Committee Chair	404-778-1585 <a href="mailto:alex.hall@emory.edu">alex.hall@emory.edu</a>

## 16.Document History

Document Version	Date of Issue	Summary of Change
Draft Protocol	08/14/2017	First draft
Approved Protocol, v1.0	02/05/2018	IRB approved version
Approved Protocol, v1.1	03/25/2018	See summary of changes file
Approved Protocol, v1.2	07/10/2018	See summary of changes file
Approved Protocol, v1.3	09/21/2018	See summary of changes file
Approved Protocol, v1.4	11/30/2018	See summary of changes file

## 17. Appendices

### 17.1. APPENDIX A: Corticosteroid Conversion Table

<b>Corticosteroid Conversion Table</b>		
<b>Glucocorticoid</b>	<b>Equivalent Dose (mg)</b>	<b>Half-Life (hr)</b>
<b>Short-Acting</b>		
Cortisone	25	8-12
Hydrocortisone	20	8-12
<b>Intermediate-Acting</b>		
Methylprednisolone	4	12-36
Prednisolone	5	12-36
Prednisone	5	12-36
Triamcinolone	4	12-36
<b>Long-Acting</b>		
Betamethasone	0.75	36-72
Dexamethasone	0.75	36-72

\* *Fludrocortisone is not used for glucocorticoid effects.*

\*\* *Equivalent doses for oral and/or intravenous administration only. Intramuscular or intraarticular administration does not apply.*

*Bernard P. Schimmer; John W. Funder, Chapter 42: ACTH, Adrenal Steroids, and Pharmacology of the Adrenal Cortex, from Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e, 2011, Eds: Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann*

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