BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034406
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2019
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Keywords:	INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE, SEPSIS, ASCORBIC ACID, THIAMINE

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Protocol and Statistical Analysis Plan: a prospective, multi-center, double-blind, randomized, placebo controlled, clinical trial

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Abstract

Introduction: Septic shock is a common and highly morbid condition. To date, there is no specific therapy proven to attenuate organ injury in septic shock. Recent studies have suggested a role for the combination of ascorbic acid, corticosteroids, and thiamine, although randomized data is lacking.

Methods and Analysis: The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial is a multi-center, double-blind, randomized, placebo-controlled clinical trial that aims to determine the impact of ascorbic acid, corticosteroids, and thiamine vs. placebo on organ injury and mortality in patients with septic shock. Patients are randomized to receive 1,500mg of ascorbic acid, 100mg of thiamine, and 50mg of hydrocortisone parenterally vs. matching placebo every 6 hours for 4 days. Clinical and laboratory data are collected at time of study enrollment, at 24-hours, 72-hours, and at 120-hours. The primary end-point for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours. Additional key secondary outcomes include the incidence of renal failure and 30-day mortality.

Ethics and Dissemination: The study was approved by the International Review Board (IRB) of each participating study site. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial Registration: The trial is registered on clinicaltrials.gov (NCT03389555). It was posted January 3rd, 2018.

Strengths and Limitations of this Study

- No specific therapy has been found to reliably attenuate organ injury in septic shock.
- This article describes a multicenter, randomized, blinded clinical trial of ascorbic acid, corticosteroids, and thiamine vs. placebo for the attenuation of organ injury in sepsis.
- The primary outcome for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours after enrollment.
- The primary outcome will be analyzed using a linear mixed effects model to assess changes in SOFA score over time.
- Limitation: 30-day mortality is a secondary outcome for this study, but the trial may be underpowered for this important patient-centered outcome.

Introduction:

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial was developed to assess the clinical efficacy and safety of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. The rationale for this trial has previously been published by the trial investigators[1]. We describe our protocol and proposed statistical analysis plan (SAP), which was designed by the trial chief investigators and statisticians. All analyses specified in this SAP have been defined prospectively. The complete study protocol can be found on clinicaltrials.gov[2].

Methods and Analysis:

Trial design

The ACTS trial is a multicenter, double-blind, randomized, placebo-controlled, parallel group, superiority trial of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. A total of 200 patients will be randomized to receive ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the intensive care unit (ICU). The primary hypothesis is that the administration of ascorbic acid, hydrocortisone, and thiamine will lead to a greater decrease in Sequential Organ Failure Assessment (SOFA) score from enrollment to 72 hours post-enrollment in patients with septic shock as compared to placebo. The trial is registered on clinicaltrials.gov (NCT03389555).

Patient population

Patients will be enrolled from 14 academic centers in the United States. Patients will be enrolled without respect to age, sex, or race. Patients will be enrolled within 24-hours of meeting all inclusion criteria.

Inclusion criteria

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

Exclusion criteria

1. Member of a protected population (pregnant, prisoner)
2. Known kidney stones within the past 1 year (except for asymptomatic, incidentally noted stones on imaging)
3. End stage renal disease (ESRD) requiring dialysis*
4. Known Glucose-6-Phosphate Dehydrogenase deficiency
5. Known Hemachromatosis
6. Comfort Measures Only status
7. Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)
8. Receiving supplemental thiamine in a dose greater than that contained in a multivitamin
9. Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug

10. Clinical indication for thiamine as determined by the clinical team providing this drug
11. Clinical indication for ascorbic acid as determined by the clinical team providing this drug
12. Known allergy to vitamin C, hydrocortisone, or thiamine

*This exclusion criterion was changed from Stage IIIb chronic kidney disease after 19 patients were enrolled

Randomization and blinding

Participants will be randomized in a 1:1 ratio to either the combination of ascorbic acid, hydrocortisone, and thiamine or placebo in blocks with random sizes of 2 or 4. The randomization will be stratified according to site. An independent statistician created the randomization list using a random number generator. With the exception of the research pharmacist (who is not involved in patient care, monitoring, or other study activities), the patient and all clinical and research staff will be blinded to study arm allocation.

Intervention

Trial participants will be randomized to ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the ICU.

Data Collection and Monitoring Plan

All data will be collected by local study staff and entered into an online case report form (CRF) using the REDCap Cloud (www.redcapcloud.com) SaaS-based Unified Data

Management system. Data will be monitored automatically through REDCap Cloud and manually by the data coordinating center.

Interim analyses

An independent Data Safety and Monitoring Board (DSMB) will review blinded (group A vs group B) data to examine patient characteristics, treatment compliance, outcomes and adverse events, on three occasions (after enrollment of 50, 100, and 150 patients). The trial will not be stopped based on evidence of intervention futility or efficacy. The trial can be stopped for excess mortality in the intervention group. If one group appears to have excess mortality, the DSMB will request unblinding and a detailed evaluation of the two groups and those who died will take place. A recommendation to discontinue the trial for safety would be made only after a thorough review of all available data to ensure that differences were not due to imbalances or extenuating circumstances between the two study groups.

Outcomes

Primary outcome

The primary outcome is the absolute change in the SOFA score from enrollment to 72 hours after enrollment. The SOFA score will be defined using a modification in which the SaO_2/FiO_2 ratio is substituted for the PaO_2/FiO_2 ratio as has been previously described[3]. This modified score (Table 1) will be used so that participants without an existing arterial catheter can be spared arterial puncture.

Key secondary outcomes

- All-cause mortality 30 days after initial study drug administration.

- Renal failure within 7 days, which is a composite outcome of all-cause death or KDIGO stage 3 acute renal failure (as defined in Table 2) within the first 7 days after enrollment. Patients who met KDIGO 3 acute renal failure criteria at the time of initial study drug administration would not be identified as having an adverse kidney event unless they expired within 7 days after enrollment. Patients who were alive, not in the ICU, and had not developed acute renal failure while in the ICU were assumed to not have renal failure for the purposes of this analysis.

Additional secondary outcomes

- 72-hour change in each individual component of the SOFA score
- Number of ICU-free days in the first 28 days following enrollment
- All-cause mortality to ICU discharge and hospital discharge
- Hospital disposition in patients who survived to hospital discharge
- Number of shock-free days over the first 7 days after enrollment
- Number of ventilator-free days over the first 7 days after enrollment
- Incidence of delirium as measured by the CAM-ICU[4] on study day 3

Further information on how secondary outcomes are defined can be found in Table 2.

Safety outcomes

Patients enrolled in the trial will be assessed daily during their hospitalization for any adverse event not anticipated as part of the overall disease process. Expected adverse events can be found in Table 3. The relatedness of the adverse event to study drug will also be assessed by the site principal investigator.

Sample size

The study sample will have 200 patients (100 per group), providing >99% power to detect a difference of 2 in the decrease of SOFA score over 72 hours (a decrease of 6 [standard deviation(SD): 4] in the treatment arm compared to a decrease of 4 [SD: 2] in the placebo arm) using a t-test of unequal variance and an alpha of 0.05. This was based on preliminary data from a pre-post study using the same intervention from Marik et al.[6], which found a change of 4 in the decrease of SOFA over 72 hours (a decrease of 4.8±2.4 in the treatment arm compared to a decrease of 0.8±2.7 in the placebo arm).

This sample size will allow for adequate power to detect a difference in 30-day mortality. We anticipate that the control group will have a mortality of 40%, based on previous data[6, 7, 8] and estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the treatment group. With these estimates, 182 participants will lead to 80% power.

Statistical analysis

Analysis principles

Analyses will be conducted on a modified intention-to-treat (ITT) basis: all participants receiving at least the first dose of the study medications will be analyzed according to the group to which they were assigned, regardless of treatment compliance after the first dose. This approach is unbiased while increasing precision in a blinded trial[9]. The analysis will be performed after the last enrolled patient has been followed to 30 days.

The analyses of primary and secondary outcomes will control for site to account for randomization stratification[10]. Pre-specified subgroup analyses will be conducted regardless

of whether a statistically significant treatment effect on the primary outcome is observed in the overall sample. Covariates included in each analysis are specified in the sections below and analyses will not be additionally adjusted for potential imbalances in the treatment groups.

No formal adjustments for multiplicity of testing will be applied, but the outcome will be ordered by degree of importance (i.e., primary versus secondary) and significant test results will be interpreted in light of the multiple comparisons made.

All tests will be two-sided and the nominal level of statistical significance (α) will be 5%. All confidence intervals will have 95% coverage. All statistics will be performed using STATA, version 15 (College Station, TX, StataCorp LP, USA).

Trial profile

The flow of patients through the trial will be shown using a Consolidated Standards of Reporting Trials diagram (CONSORT)[11]. This will include the number of screened patients who met study inclusion criteria, the number of patients who were included, and exclusion reasons for non-included patients.

Baseline characteristics

A description of the baseline characteristics will be presented by treatment group (Table 4). Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous

variables will be summarized using means ± SD or medians and first and third quartiles (IQR). Basic demographic data for all patients screened will be included.

Compliance with the administration of study drug

The following compliance with study drug variables will be summarized by treatment group:

- Cumulative dose of study drugs received (mg or mg equivalent)
- Overall compliance, defined as the number of doses given divided by the number of expected doses

These variables will be presented as mean ± SD or median (IQR).

Protocol deviations

Protocol deviations will be summarized by treatment group as the number and proportion of deviations by type. Any withdrawals of consent resulting in permanent discontinuation of study drug will also be summarized in this fashion. Timing of withdrawals will be reported.

Concomitant therapies

The number and proportion of patients receiving open-label thiamine, hydrocortisone, and ascorbic acid during the 4-day study period will be described. Time to first open label use of study drug will be summarized using mean ± SD or median (IQR).

Analysis of primary outcome

The primary hypothesis that the combination of ascorbic acid, hydrocortisone, and thiamine will attenuate organ dysfunction in septic shock will be tested by calculating the group

difference (intervention vs. placebo) in SOFA score change from baseline to 72 hours using a linear mixed effects model with an appropriate covariance structure. Fixed effects will include age, sex, the allocated treatment, study day (as a categorical variable defined as baseline, 24 hours, 48 hours, and 72 hours), and the interaction between treatment and study day. Study site will be included as a random effect. The placebo group is the reference variable for group, and baseline is the reference variable for time. Means and 95% confidence intervals of SOFA score over time will be presented, by treatment, using longitudinal plots.

A sensitivity analysis will be performed on the cohort of participants whose SOFA score at 72 hours is available (i.e., not missing due to early mortality, hospital discharged, etc) using linear regression. The outcome variable is SOFA score at 72 hours and the predictors are the allocated treatment, baseline SOFA score, and study site.

Analysis of key secondary outcomes

Renal failure: a logistic model controlling for site will be used to compare the incidence of renal failure between the intervention and placebo groups. Results will be reported as odds ratios and 95% confidence intervals.

A sensitivity analysis will be performed with the composite outcome defined as receipt of renal replacement therapy or death while meeting other elements of KDIGO 3 acute renal failure criteria during the index ICU stay using the method described above.

30-day mortality: Kaplan-Meier log-rank test and Cox proportional hazards model controlling for site will be used to compare the treatment groups in terms of survival. The outcome variable is 30-day mortality and the predictor is the allocated treatment. If the proportional hazards assumption is not met, a logistic regression controlling for site will be performed to obtain odds ratios with 95% confidence intervals.

Analysis of additional secondary outcomes

The following outcomes will be summarized using mean (SD) or median (IQR) and linear regression controlling for site will be performed to assess the differences between treatment groups.

- Absolute change in individual components of the SOFA score from enrollment to 72 hours
- Number of ICU-free days in the first 28 days following enrollment
- Length of hospital stay during index admission
- Number of days free of mechanical ventilation during the first 7 days after enrollment
- Number of days free of hemodynamic shock during the first 7 days after enrollment
- Overall health status at 90 days after randomization will be measured using the SF-36[5].

The following outcomes will be summarized using frequencies and percentages and logistic regression will be performed to assess the differences between treatment groups.

- Survival to ICU discharge and survival to hospital discharge
- Delirium, as measured by the CAM-ICU, on day 3 of the patient's ICU stay

Analysis of adverse events

Rates of serious expected and unexpected adverse events will be reported by group assignment. Proportions of patients with adverse events will be compared between the treatment groups using Fisher's exact test.

Analysis of subgroups

The analysis will include the following pre-defined subgroup analyses for the primary and key secondary outcomes:

- Grouped by high/low initial severity of illness. High and low levels will be defined by a baseline SOFA score above or below the study median.
- Grouped by high/low baseline serum lactate level. High and low levels will be defined by a cut-off at a serum lactate ≥3mmol/L. This level was chosen to reflect the population of patients enrolled in our prior pilot randomized trial of thiamine vs. placebo in septic shock.[7]
- Grouped by investigator prediction of survival at 30-days. The enrolling provider was asked at the time of enrollment whether they thought it was likely, unclear, or unlikely that the patient would be alive at 30-days.
- Grouped by timing of enrollment with respect to vasopressor start time. Timing will be defined by a cut-off of 12-hours. This level was chosen based on a review of the median time to enrollment from the data collected to date.

The trial is not powered to detect subgroup differences and these will be considered exploratory and hypothesis generating.

Blood samples will be collected as above for the measurement of baseline and subsequent levels of thiamine, ascorbic acid, and cortisol. Exploratory analyses based on this testing will not be presented in the primary trial manuscript, but will be described in follow-up manuscripts.

Missing data

If missing data for any key variable (i.e. those used in the primary outcome analysis) are > 15%, multiple imputation with chained equations will be performed.

Trial progress

This manuscript describes the SAP for the ACTS trial. The SAP is published prior to unblinding of the study and provides transparency in decisions with respect to statistical analysis. The ACTS trial has now enrolled more than 75% of its intended with recruitment expected to continue through November 2019. As such, 30-day follow-up will be complete for all patients by the end of December 2019. At the time of this submission, treatment allocations remain blinded.

Ethics and Dissemination:

The study protocol was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation (protocol 2017P-000436). The Institutional Review Board at each participating site also approved the study protocol. The trial was registered on clinicaltrials.gov (NCT03389555) prior to the enrollment of the first patient. The Food and Drug Administration (FDA) approved an Investigational New Drug (IND) application (IND 136882). Study progress and safety will be monitored by an independent DSMB as described above.

Informed, written consent will be obtained prior to enrollment from all participants or their legally authorized representatives by trained investigators. Patients and their legally authorized representatives will be made aware that participation is strictly voluntary and that consent can be withdrawn at any time.

Results of this study will be presented at one or more major scientific conferences and will be published in a peer-reviewed scientific journal. Patient level data will be available to the ACTS trial investigator team and to other academic investigators upon request as adjudicated by the ACTS Steering Committee.

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Authors' contributions:

All authors made substantial contributions to the concept and design of the manuscript. Authors TY and AM equally contributed to the initial draft of the manuscript, after which all authors provided important intellectual content. All authors read and approved the final manuscript.

Funding:

The ACTS trial is supported by a grant from the Open Philanthropy Project. Dr. Moskowitz is supported by a grant from the National Institutes of Health (K23GM128005–01). Dr. Grossestreuer is supported by a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst |The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100).

Competing Interests:

The authors declare no competing interests.

Acknowledgements:

ACTS Clinical Trial Investigators (listed alphabetically)

Andersen, Lars W; Becker, Lance B; Berg, Katherine M; Chase, Maureen; Cocchi, Michael N; Donnino, Michael W; Doshi, Pratik; Gong, Jonathan; Grossestreuer, Anne V; Hershey, Mark; Hilewitz, Ayelet; Hou, Peter C; Huang, David T; Kim, Hyung K; Korotun, Maksim; McCannon, Jessica B; Marik, Paul E; Moskowitz, Ari; Sen, Ayan; Sherwin, Robert L; Otero, Ronny; Uduman, Junior

Tables

Table 1: Modified Sequential organ Failure Assessment Score

Points	SaO2*/FiO2§	Blood Pressure	GCS‖	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10^{3}µL)
0	>399	MAP# ≥ 70 mmHg	15	<1.2	<1.2	≥150
1	316-399	MAP < 70 mmHg	13–14	1.2–1.9	1.2 – 1.9	<150
2	236-315	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	151-235 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 5 µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP†<500ml/day	<50
4	<151(and receiving invasive or non-invasive mechanical ventilation)	dopamine > 15 µg/kg/min, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	≥12	≥5.0 UOP†<200ml/day	<20

*SaO2=Oxygen saturation (%); § = Fraction of inspired oxygen (%); ‖ = Glasgow Coma Scale; # = Mean arterial pressure; † = Urine Output

Table 2: Definitions of secondary outcomes

Variable	DESCRIPTION
KDIGO Stage 3 Renal Injury During Index ICU Stay	Acute renal failure any time during the index ICU stay. Defined as KDIGO stage 3 based on creatinine or urine output: Creatinine criteria: Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl) Urine output criteria: Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours or new renal replacement therapy
Number of ICU-Free Days in the first 28 Days	Number of days during the first 28 days following study enrollment when the patient was not in the ICU or dead (all days after hospital discharge are considered ICU free). Note: patient would be considered "in the ICU" if they were a patient there for ≥6 hours in the course of a day or if they expired prior to 28 days. For example, a patient who expired while still in the ICU on day 5 would have 0 ICU-free days. A patient who was discharged from the ICU on day 3 and readmitted on day 7 and discharged again on day 21 would have 10 ICU free days (days 4-6 and 22-28). A patient who was discharged from the ICU on day 3 and did not return to the ICU would have 25 ICU-free days.
Survived to ICU discharge	Survived to ICU discharge
Survived to Hospital discharge	Survived to hospital discharge
Hospital Disposition	Hospital disposition in survivors. Extended care facilities include home with service, rehabilitation center, nursing home, skilled nursing facility/extended care 6, hospice (home or inpatient), and transferred to another acute care facility
Shock free days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours of any vasopressor agent.
Invasive Ventilation Free Days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours invasive mechanical ventilation.
Delirium 72 Hour of ICU Stay (as measured via CAM-ICU)	Delirium on the 3rd day (at approximately 72 hours) after the first study drug dose. Delirium is defined by the Confusion Assessment Method (CAM)-ICU or by the regular CAM if the patient is on the hospital ward.
90-day quality of life outcome score	Scoring is based on SF-36. Lower score defines a less favorable health stage

Table 3: Definitions of adverse events and safety outcomes

The following definitions will be used:

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

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

Suspected unexpected serious adverse event (SUSAR): a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

LABEL	DESCRIPTION
Serious Adverse Events	Hyperglycemia: Blood glucose >300mg/dL or new insulin infusion occurring in the first 120-hours after enrollment Hypernatremia: Serum sodium (>150 mmol/L) occurring in the first 120-hours after enrollment New Infection: As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics. Serious allergic reaction: Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Renal calculus: Development of a renal calculus between enrollment and 30-day follow-up. Others/Unexpected: Any other serious adverse event possibly related to study drug or study participation
Related to Study?	Definitely related: no other potential cause of SAE is identified. Investigator certain or near certain the hyperglycemia is related to study drug Possibly related: other potential causes of SAE exist. There is at least a 50% chance the hyperglycemia is related to the study drug Unlikely related: a clear alternative reason for SAE exists. The investigators believe that there is a <50% change the SAE is related to study drug

Other serious adverse event severity grading	Grade I: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade II: Moderate; minimal, local or noninvasive intervention indicated Grade III: Severe or Medically Significant BUT not Immediately Life-threatening Grade IV: Life-threatening Consequences; urgent intervention indicated Grade V: Death Related to Adverse Event

Table 4: Baseline characteristics of patients stratified by treatment group

Characteristics	Overall (N =)	Ascorbic acid, Hydrocortisone, and Thiamine (N =)	Placebo (N =)
Demographics			
Age, yr			
Body mass index, kg/m^2			
Female, n (%)			
Race, n (%)			
African-American			
White			
Other			
Past medical history, n (%)			
None of the below			
Coronary artery disease			
Cancer			
Congestive heart failure			
Chronic obstructive pulmonary disease			
Dementia/Alzheimer's			
Diabetes			
Alcohol use disorder			
HIV/AIDS			
Liver disease			
Renal disease			
Stroke/Transient ischemic attack			
History of tobacco use			
Organ or Bone Marrow Transplant			
Chronic renal disease stage, n (%)			
Stage 2			
Stage 3a			
Septic Shock Characteristics			
Source of sepsis, n (%)			
Pneumonia			
Urinary Tract Infection			
Intra-Abdominal Infection			
Skin or Soft Tissue Infection			
Vascular Catheter-related Infection			
Central Nervous System Infection			
Endocarditis			
Infection of Unknown Source			
Other			
Vasopressors at Time of Study Drug, n (%)			
Norepinephrine			
Epinephrine			
Phenylephrine			
Vasopressin			

Dopamine			
Dobutamine			
Angiotensin			
Milrinone			
Midodrine			
Mechanical ventilation, n (%)			
Volume of IV fluids[a], ml			
Baseline vital signs			
Temperature, Celsius			
Heart rate, beats/minute			
Systolic blood pressure, mmHg			
Diastolic blood pressure, mmHg			
Respiratory rate, inspirations/minute			
Lactate, mmol/L			
WBC x10^9			
Creatinine, mg/dL			
ICU physician prediction[b]			
Predicted survival at 30 days[b], n (%)			
Very likely			
Uncertain			
Very unlikely			
SOFA score			
Baseline SOFA score			

a. Volume of IV fluids received in the 12-hours preceding enrollment
b. At time of enrollment, the physician enrolling the patient is asked to predict 30-day survival.

Ascorbic acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Clinical Trial: SPIRIT 2013 Checklist

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	See referenced full protocol
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See referenced full protocol
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	See referenced full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	See referenced full protocol
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See referenced full protocol
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	See referenced full protocol
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Information available upon request
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Information available upon request
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Information available upon request
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16

	31b	Authorship eligibility guidelines and any intended use of professional writers	See referenced full protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See referenced full protocol

BMJ Open

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Protocol and Statistical Analysis Plan: a prospective, multi-center, double-blind, randomized, placebo controlled, clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034406.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Nov-2019
Complete List of Authors:	Moskowitz, Ari ; Harvard University, Yankama, Tuyen ; Beth Israel Deaconess Medical Center, Andersen, Lars; Aarhus University Hospital Dermato-Venerological Department David T, Huang; University of Pittsburgh Donnino, Michael W.; Beth Israel Deaconess Medical Center Grossestreuer, Anne ; Beth Israel Deaconess Medical Center, Emergency Medicine Clinical Trial Investigators, ACTS
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Research methods, Nutrition and metabolism, Infectious diseases
Keywords:	INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE, SEPSIS, ASCORBIC ACID, THIAMINE

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Protocol and Statistical Analysis Plan: a prospective, multi-center, double-blind, randomized, placebo controlled, clinical trial

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Abstract

Introduction: Septic shock is a common and highly morbid condition. To date, there is no specific therapy proven to attenuate organ injury in septic shock. Recent studies have suggested a role for the combination of ascorbic acid, corticosteroids, and thiamine, although randomized data is lacking.

Methods and Analysis: The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial is a multi-center, double-blind, randomized, placebo-controlled clinical trial that aims to determine the impact of ascorbic acid, corticosteroids, and thiamine vs. placebo on organ injury and mortality in patients with septic shock. Patients are randomized to receive 1,500mg of ascorbic acid, 100mg of thiamine, and 50mg of hydrocortisone parenterally vs. matching placebo every 6 hours for 4 days. Clinical and laboratory data are collected at time of study enrollment, at 24-hours, 72-hours, and at 120-hours. The primary end-point for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours. Additional key secondary outcomes include the incidence of renal failure and 30-day mortality.

Ethics and Dissemination: The study was approved by the International Review Board (IRB) of each participating study site. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial Registration: The trial is registered on clinicaltrials.gov (NCT03389555). It was posted January 3rd, 2018.

Strengths and Limitations of this Study

- No specific therapy has been found to reliably attenuate organ injury in septic shock.
- In observational studies, the combination of ascorbic acid, corticosteroids, and thiamine has been shown to attenuate organ injury and improve mortality in septic shock.
- This article describes a multicenter, randomized, blinded clinical trial of ascorbic acid, corticosteroids, and thiamine vs. placebo in septic shock.
- The primary outcome for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours after enrollment, which will be analyzed using a linear mixed effects model to assess changes in SOFA score over time.
- 30-day mortality is a secondary outcome for this study, but the trial may be underpowered for this important patient-centered outcome.

Introduction:

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial was developed to assess the clinical efficacy and safety of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. The rationale for this trial has previously been published by the trial investigators[1]. In short, there is presently no directed therapy proven to attenuate organ injury in septic shock. Whereas the traditional paradigm of organ injury in sepsis has focused on impaired oxygen delivery, there is increasing evidence that non-oxygen delivery dependent mechanisms of organ injury may play an important role. In particular, mitochondrial dysfunction has been recognized as a likely contributor to organ injury in many sepsis victims.[2,3] Ascorbic acid, a potent antioxidant, and thiamine, a key co-factor in aerobic respiration, may have roles as mitochondrial resuscitators in septic shock. In observational studies and small clinical trials, both ascorbic acid and thiamine have shown promise as directed therapies for the attenuation of organ injury in sepsis.[4,5] More recently, a phase II clinical trial of high-dose ascorbic acid in sepsis victims with the acute respiratory distress syndrome found that the intervention was safe and may have improved mortality. Notably however, ascorbic acid did not attenuate organ injury as measured by the sequential organ failure assessment (SOFA) score, although this may have resulted from an imbalance in early mortality between groups, resulting in excess missing data from the sickest patients in the placebo arm.[6]

Herein we describe the protocol and proposed statistical analysis plan (SAP) for the ACTS trial, which was designed by the trial chief investigators and statisticians. All analyses specified in this SAP have been defined prospectively. The complete study protocol can be found on clinicaltrials.gov[7].

Methods and Analysis:

Trial design

The ACTS trial is a multicenter, double-blind, randomized, placebo-controlled, parallel group, superiority trial of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. A total of 200 patients will be randomized to receive ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the intensive care unit (ICU). The primary hypothesis is that the administration of ascorbic acid, hydrocortisone, and thiamine will lead to a greater decrease in Sequential Organ Failure Assessment (SOFA) score from enrollment to 72 hours post-enrollment in patients with septic shock as compared to placebo. The trial is registered on clinicaltrials.gov (NCT03389555).

Patient population

Patients will be enrolled from 14 academic centers in the United States. Patients will be enrolled without respect to age, sex, or race. Patients will be enrolled within 24-hours of meeting all inclusion criteria.

Inclusion criteria

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

Exclusion criteria

1. Member of a protected population (pregnant, prisoner)
2. Known kidney stones within the past 1 year (except for asymptomatic, incidentally noted stones on imaging)
3. End stage renal disease (ESRD) requiring dialysis*
4. Known Glucose-6-Phosphate Dehydrogenase deficiency
5. Known Hemachromatosis
6. Comfort Measures Only status
7. Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)
8. Receiving supplemental thiamine in a dose greater than that contained in a multivitamin
9. Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug
10. Clinical indication for thiamine as determined by the clinical team providing this drug
11. Clinical indication for ascorbic acid as determined by the clinical team providing this drug
12. Known allergy to vitamin C, hydrocortisone, or thiamine

*This exclusion criterion was changed from Stage IIIb chronic kidney disease after 19 patients were enrolled

Randomization and blinding

Participants will be randomized in a 1:1 ratio to either the combination of ascorbic acid, hydrocortisone, and thiamine or placebo in blocks with random sizes of 2 or 4. The

randomization will be stratified according to site. An independent statistician created the randomization list using a random number generator. Each site's randomization list will be held by the local research pharmacy, which then will inform the research team of treatment allocation at the time of randomization. With the exception of the research pharmacist (who is not involved in patient care, monitoring, or other study activities), the patient and all clinical and research staff will be blinded to study arm allocation.

As ascorbic acid possesses a yellow tinge, the bags containing ascorbic acid will be covered with light-protective bags. In testing, after dilution there was no distinguishing characteristics of the ascorbic acid vs. placebo in the intravenous line tubing. Ascorbic acid, hydrocortisone, and thiamine are not known to have distinctive rapid effects which could lead to unblinding.

Intervention

Trial participants will be randomized to ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the ICU. The ascorbic acid and thiamine will be diluted in 100ml of 0.9%NaCl crystalloid fluid and the hydrocortisone was given as a 'push' dose.

A placebo (as opposed to a hydrocortisone only control arm) was selected to allow for clinician discretion with regards to the use of corticosteroids in septic shock, thus avoiding potential deviations from 'usual care' associated with the comparison of two fixed treatment arms. We note that study enrollment began prior to publication of the ADRENAL and APPROCHS trials[8,9].

Data Collection and Monitoring Plan

All data will be collected by local study staff and entered into an online case report form (CRF) using the REDCap Cloud (www.redcapcloud.com) SaaS-based Unified Data Management system. Data will be monitored automatically through REDCap Cloud and manually by the data coordinating center. In-person site visits by study monitors will be conducted at each site early in study enrollment and again at study close-out for verification of primary data, regulatory processes, and pharmacy standards.

Patient and Public Involvement

No patients will be involved in the design, recruitment, or conduct of the study. We anticipate disseminating the results of the study through publication in a high-impact scientific journal. Patients or their representatives will assess the burden of the intervention at the time of randomization through the informed consent process.

Interim analyses

An independent Data Safety and Monitoring Board (DSMB) will review blinded (group A vs group B) data to examine patient characteristics, treatment compliance, outcomes and adverse events, on three occasions (after enrollment of 50, 100, and 150 patients). The trial will not be stopped based on evidence of intervention futility or efficacy. The trial can be stopped for excess mortality in the intervention group. If one group appears to have excess mortality, the DSMB will request unblinding and a detailed evaluation of the two groups and those who died will take place. A recommendation to discontinue the trial for safety would

be made only after a thorough review of all available data to ensure that differences were not due to imbalances or extenuating circumstances between the two study groups.

Outcomes

Primary outcome

The primary outcome is the absolute change in the SOFA score from enrollment to 72 hours after enrollment. The SOFA score will be defined using a modification in which the SaO_2/FiO_2 ratio is substituted for the PaO_2/FiO_2 ratio as has been previously described[10]. This modified score (Table 1) will be used so that participants without an existing arterial catheter can be spared arterial puncture.

Key secondary outcomes

- All-cause mortality 30 days after initial study drug administration.
- Renal failure within 7 days, which is a composite outcome of all-cause death or KDIGO stage 3 acute renal failure (as defined in Table 2) within the first 7 days after enrollment. Patients who met KDIGO 3 acute renal failure criteria at the time of initial study drug administration would not be identified as having an adverse kidney event unless they died within 7 days after enrollment. Patients who were alive, not in the ICU, and had not developed acute renal failure while in the ICU were assumed to not have renal failure for the purposes of this analysis.

Additional secondary outcomes

- 72-hour change in each individual component of the SOFA score
- Number of ICU-free days in the first 28 days following enrollment

- All-cause mortality to ICU discharge and hospital discharge
- Hospital disposition in patients who survived to hospital discharge
- Number of shock-free days over the first 7 days after enrollment
- Number of ventilator-free days over the first 7 days after enrollment
- Incidence of delirium as measured by the CAM-ICU[11] on study day 3

Further information on how secondary outcomes are defined can be found in Table 2.

Safety outcomes

Patients enrolled in the trial will be assessed daily during their hospitalization for any adverse event not anticipated as part of the overall disease process. Expected adverse events can be found in Table 3. The relatedness of the adverse event to study drug will also be assessed by the site principal investigator.

Sample size

The study sample will have 200 evaluable patients (100 per group), providing >99% power to detect a difference of 2 in the decrease of SOFA score over 72 hours (a decrease of 6 [standard deviation(SD): 4] in the treatment arm compared to a decrease of 4 [SD: 2] in the placebo arm) using a t-test of unequal variance and an alpha of 0.05. This was based on preliminary data from a pre-post study using the same intervention from Marik et al.[12], which found a change of 4 in the decrease of SOFA over 72 hours (a decrease of 4.8±2.4 in the treatment arm compared to a decrease of 0.8±2.7 in the placebo arm).

This sample size will allow for adequate power to detect a difference in 30-day mortality. We anticipate that the control group will have a mortality of 40%, based on previous data[5,

[12,13] and estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the treatment group. With these estimates, 182 participants will lead to 80% power.

Statistical analysis

Analysis principles

Analyses will be conducted on a modified intention-to-treat (ITT) basis: all participants receiving at least the first dose of the study medications will be analyzed according to the group to which they were assigned, regardless of treatment compliance after the first dose. This approach is unbiased while increasing precision in a blinded trial[14]. The analysis will be performed after the last enrolled patient has been followed to 30 days.

The analyses of primary and secondary outcomes will control for site to account for randomization stratification[15]. Pre-specified subgroup analyses will be conducted regardless of whether a statistically significant treatment effect on the primary outcome is observed in the overall sample. Covariates included in each analysis are specified in the sections below and analyses will not be additionally adjusted for potential imbalances in the treatment groups.

No formal adjustments for multiplicity of testing will be applied, but the outcome will be ordered by degree of importance (i.e., primary versus secondary) and significant test results will be interpreted in light of the multiple comparisons made.

All tests will be two-sided and the nominal level of statistical significance (α) will be 5%. All confidence intervals will have 95% coverage. All statistics will be performed using STATA, version 15 (College Station, TX, StataCorp LP, USA).

Trial profile

The flow of patients through the trial will be shown using a Consolidated Standards of Reporting Trials diagram (CONSORT)[16]. This will include the number of screened patients who met study inclusion criteria, the number of patients who were included, and exclusion reasons for non-included patients.

Baseline characteristics

A description of the baseline characteristics will be presented by treatment group (Table 4). Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarized using means ± SD or medians and first and third quartiles (IQR). Basic demographic data for all patients screened will be included.

Compliance with the administration of study drug

The following compliance with study drug variables will be summarized by treatment group:

- Cumulative dose of study drugs received (mg or mg equivalent)
- Overall compliance, defined as the number of doses given divided by the number of expected doses

These variables will be presented as mean ± SD or median (IQR).

Protocol deviations

Protocol deviations will be summarized by treatment group as the number and proportion of deviations by type. Any withdrawals of consent resulting in permanent discontinuation of study drug will also be summarized in this fashion. Timing of withdrawals will be reported.

Concomitant therapies

The number and proportion of patients receiving open-label thiamine, hydrocortisone, and ascorbic acid during the 4-day study period will be described. Time to first open label use of study drug will be summarized using mean ± SD or median (IQR).

Analysis of primary outcome

The primary hypothesis that the combination of ascorbic acid, hydrocortisone, and thiamine will attenuate organ dysfunction in septic shock will be tested by calculating the group difference (intervention vs. placebo) in SOFA score change from baseline to 72 hours using a linear mixed effects model with an appropriate covariance structure. Fixed effects will include age, sex, the allocated treatment, study day (as a categorical variable defined as baseline, 24 hours, 48 hours, and 72 hours), and the interaction between treatment and study day. Study site will be included as a random effect. The placebo group is the reference variable for group, and baseline is the reference variable for time. Means and 95% confidence intervals of SOFA score over time will be presented, by treatment, using longitudinal plots.

If a patient is missing an element of the SOFA score for reasons other than death or early hospital discharge (e.g. laboratory error), we will use the available value in closest temporal proximity. A sensitivity analysis will be performed on the cohort of participants whose SOFA score at 72 hours is available (i.e., not missing due to early mortality, hospital discharged, etc) using linear regression. An additional sensitivity analysis will be conducted with a SOFA score penalty for early death. Specifically, if a participant expires before 72-hours, a 20% increase from their last available SOFA score will be imputed.

Analysis of key secondary outcomes

Renal failure: a logistic model controlling for site will be used to compare the incidence of renal failure between the intervention and placebo groups. Results will be reported as odds ratios and 95% confidence intervals.

A sensitivity analysis will be performed with the composite outcome defined as receipt of renal replacement therapy or death while meeting other elements of KDIGO 3 acute renal failure criteria during the index ICU stay using the method described above.

30-day mortality: Kaplan-Meier log-rank test and Cox proportional hazards model controlling for site will be used to compare the treatment groups in terms of survival. The outcome variable is 30-day mortality and the predictor is the allocated treatment. If the proportional hazards assumption is not met, a logistic regression controlling for site will be performed to obtain odds ratios with 95% confidence intervals.

Analysis of additional secondary outcomes

The following outcomes will be summarized using mean (SD) or median (IQR) and linear regression controlling for site will be performed to assess the differences between treatment groups.

- Absolute change in individual components of the SOFA score from enrollment to 72 hours
- Number of ICU-free days in the first 28 days following enrollment
- Length of hospital stay during index admission
- Number of days free of mechanical ventilation during the first 7 days after enrollment
- Number of days free of hemodynamic shock during the first 7 days after enrollment

The following outcomes will be summarized using frequencies and percentages and logistic regression will be performed to assess the differences between treatment groups.

- Survival to ICU discharge and survival to hospital discharge
- Delirium, as measured by the CAM-ICU, on day 3 of the patient's ICU stay

Analysis of adverse events

Rates of serious expected and unexpected adverse events will be reported by group assignment. Proportions of patients with adverse events will be compared between the treatment groups using Fisher's exact test.

Analysis of subgroups

The analysis will include the following pre-defined subgroup analyses for the primary and key secondary outcomes:

- Grouped by high/low initial severity of illness. High and low levels will be defined by a baseline SOFA score above or below the study median.
- Grouped by high/low baseline serum lactate level. High and low levels will be defined by a cut-off at a serum lactate ≥3mmol/L. This level was chosen to reflect the population of patients enrolled in our prior pilot randomized trial of thiamine vs. placebo in septic shock.[5]
- Grouped by investigator prediction of survival at 30-days. The enrolling provider was asked at the time of enrollment whether they thought it was likely, unclear, or unlikely that the patient would be alive at 30-days.
- Grouped by timing of enrollment with respect to vasopressor start time. Timing will be defined by a cut-off of 12-hours. This level was chosen based on a review of the median time to enrollment from the data collected to date.

The trial is not powered to detect subgroup differences and these will be considered exploratory and hypothesis generating.

Blood samples will be collected for the measurement of baseline and subsequent levels of thiamine, ascorbic acid, and cortisol. Exploratory analyses based on this testing will not be presented in the primary trial manuscript, but will be described in follow-up manuscripts.

Missing data

If missing data for any key variable (i.e. those used in the primary outcome analysis) are > 15%, multiple imputation with chained equations will be performed.

Trial progress

This manuscript describes the SAP for the ACTS trial. The SAP is published prior to unblinding of the study and provides transparency in decisions with respect to statistical analysis. The ACTS trial has now enrolled more than 75% of its intended with recruitment expected to continue through October 2019. As such, 30-day follow-up will be complete for all patients by the end of November 2019. At the time of this submission, treatment allocations remain blinded.

Ethics and Dissemination:

The study protocol was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation (protocol 2017P-000436). The Institutional Review Board at each participating site also approved the study protocol. The trial was registered on clinicaltrials.gov (NCT03389555) prior to the enrollment of the first patient. The Food and Drug Administration (FDA) approved an Investigational New Drug (IND) application (IND 136882). Study progress and safety will be monitored by an independent DSMB as described above. Informed, written consent will be obtained prior to enrollment from all participants or their legally authorized representatives by trained investigators. A sample informed consent form is included in the supplementary materials. Patients and their legally authorized representatives will be made aware that participation is strictly voluntary and that consent can be withdrawn at any time.

Results of this study will be presented at one or more major scientific conferences and will be published in a peer-reviewed scientific journal. Patient level data will be available to the

ACTS trial investigator team and to other academic investigators upon request as adjudicated by the ACTS Steering Committee.

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Authors' contributions:

All authors made substantial contributions to the concept and design of the manuscript. Authors TY and AM equally contributed to the initial draft of the manuscript, after which all authors (AM, TY, LWA, DTH, MWD, AVG) provided important intellectual content. All authors read and approved the final manuscript.

Funding:

The ACTS trial is supported by a grant from the Open Philanthropy Project. Dr. Moskowitz is supported by a grant from the National Institutes of Health (K23GM128005–01). Dr. Grossestreuer is supported by a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst |The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100).

Competing Interests:

The authors declare no competing interests.

Acknowledgements:

ACTS Clinical Trial Investigators (listed alphabetically)

Andersen, Lars W; Becker, Lance B; Berg, Katherine M; Chase, Maureen; Cocchi, Michael N; Donnino, Michael W; Doshi, Pratik; Gong, Jonathan; Grossestreuer, Anne V; Hershey, Mark; Hilewitz, Ayelet; Hou, Peter C; Huang, David T; Kim, Hyung K; Korotun, Maksim; McCannon, Jessica B; Marik, Paul E; Moskowitz, Ari; Sen, Ayan; Sherwin, Robert L; Otero, Ronny; Uduman, Junior

Tables

Table 1: Modified Sequential organ Failure Assessment Score

Points	SaO2*/FiO2§	Blood Pressure	GCS‖	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10^{3}µL)
0	>399	MAP# ≥ 70 mmHg	15	<1.2	<1.2	≥150
1	316-399	MAP < 70 mmHg	13–14	1.2–1.9	1.2 – 1.9	<150
2	236-315	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	151-235 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 5 µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP†<500ml/day	<50
4	<151(and receiving invasive or non-invasive mechanical ventilation)	dopamine > 15 µg/kg/min, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	≥12	≥5.0 UOP†<200ml/day	<20

*SaO2=Oxygen saturation (%); § = Fraction of inspired oxygen (%); ‖ = Glasgow Coma Scale; # = Mean arterial pressure; † = Urine Output

Table 2: Definitions of secondary outcomes

Variable	DESCRIPTION
KDIGO Stage 3 Renal Injury During Index ICU Stay	Acute renal failure any time during the index ICU stay. Defined as KDIGO stage 3 based on creatinine or urine output: Creatinine criteria: Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl) Urine output criteria: Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours or new renal replacement therapy
Number of ICU-Free Days in the first 28 Days	Number of days during the first 28 days following study enrollment when the patient was not in the ICU or dead (all days after hospital discharge are considered ICU free). Note: patient would be considered "in the ICU" if they were a patient there for ≥6 hours in the course of a day or if they died prior to 28 days. For example, a patient who died while still in the ICU on day 5 would have 0 ICU-free days. A patient who was discharged from the ICU on day 3 and readmitted on day 7 and discharged again on day 21 would have 10 ICU free days (days 4-6 and 22-28). A patient who was discharged from the ICU on day 3 and did not return to the ICU would have 25 ICU-free days.
Survived to ICU discharge	Survived to ICU discharge
Survived to Hospital discharge	Survived to hospital discharge
Hospital Disposition	Hospital disposition in survivors. Extended care facilities include home with service, rehabilitation center, nursing home, skilled nursing facility/extended care 6, hospice (home or inpatient), and transferred to another acute care facility
Shock free days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours of any vasopressor agent.
Invasive Ventilation Free Days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours invasive mechanical ventilation.
Delirium 72 Hour of ICU Stay (as measured via CAM-ICU)	Delirium on the 3rd day (at approximately 72 hours) after the first study drug dose. Delirium is defined by the Confusion Assessment Method (CAM)-ICU or by the regular CAM if the patient is on the hospital ward.

Table 3: Definitions of adverse events and safety outcomes

The following definitions will be used:

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

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

Suspected unexpected serious adverse event (SUSAR): a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

LABEL	DESCRIPTION
Serious Adverse Events	Hyperglycemia: Blood glucose >300mg/dL or new insulin infusion occurring in the first 120-hours after enrollment Hypernatremia: Serum sodium (>150 mmol/L) occurring in the first 120-hours after enrollment New Infection: As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics. Serious allergic reaction: Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Renal calculus: Development of a renal calculus between enrollment and 30-day follow-up. Others/Unexpected: Any other serious adverse event possibly related to study drug or study participation
Related to Study?	Definitely related: no other potential cause of SAE is identified. Investigator certain or near certain the hyperglycemia is related to study drug Possibly related: other potential causes of SAE exist. There is at least a 50% chance the hyperglycemia is related to the study drug Unlikely related: a clear alternative reason for SAE exists. The investigators believe that there is a <50% change the SAE is related to study drug

Other serious adverse event severity grading	Grade I: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade II: Moderate; minimal, local or noninvasive intervention indicated Grade III: Severe or Medically Significant BUT not Immediately Life-threatening Grade IV: Life-threatening Consequences; urgent intervention indicated Grade V: Death Related to Adverse Event

Table 4: Baseline characteristics of patients stratified by treatment group

Characteristics	Overall (N =)	Ascorbic acid, Hydrocortisone, and Thiamine (N =)	Placebo (N =)
Demographics			
Age, yr			
Body mass index, kg/m^2			
Female, n (%)			
Race, n (%)			
African-American			
White			
Other			
Past medical history, n (%)			
None of the below			
Coronary artery disease			
Cancer			
Congestive heart failure			
Chronic obstructive pulmonary disease			
Dementia/Alzheimer's			
Diabetes			
Alcohol use disorder			
HIV/AIDS			
Liver disease			
Renal disease			
Stroke/Transient ischemic attack			
History of tobacco use			
Organ or Bone Marrow Transplant			
Chronic renal disease stage, n (%)			
Stage 2			
Stage 3a			
Septic Shock Characteristics			
Source of sepsis, n (%)			
Pneumonia			
Urinary Tract Infection			
Intra-Abdominal Infection			
Skin or Soft Tissue Infection			
Vascular Catheter-related Infection			
Central Nervous System Infection			
Endocarditis			
Infection of Unknown Source			
Other			
Vasopressors at Time of Study Drug, n (%)			
Norepinephrine			
Epinephrine			
Phenylephrine			
Vasopressin			

Dopamine			
Dobutamine			
Angiotensin			
Milrinone			
Midodrine			
Mechanical ventilation, n (%)			
Volume of IV fluids[a], ml			
Baseline vital signs			
Temperature, Celsius			
Heart rate, beats/minute			
Systolic blood pressure, mmHg			
Diastolic blood pressure, mmHg			
Respiratory rate, inspirations/minute			
Lactate, mmol/L			
WBC x10^9			
Creatinine, mg/dL			
ICU physician prediction[b]			
Predicted survival at 30 days[b], n (%)			
Very likely			
Uncertain			
Very unlikely			
SOFA score			
Baseline SOFA score			

a. Volume of IV fluids received in the 12-hours preceding enrollment
b. At time of enrollment, the physician enrolling the patient is asked to predict 30-day survival.

FOR CCI USE ONLY
Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Consent Approval Date: 9/10/18

Protocol Number: 2017P-000436

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE COMMITTEE ON CLINICAL INVESTIGATIONS
09/09/2019
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Vitamin C, Steroids, and Thiamine in Sepsis and Septic Shock
PRINCIPAL INVESTIGATOR: Michael Donnino, MD (BIDMC) **SITE PRINCIPAL INVESTIGATOR: PETER HOU MD (BWH)**
PROTOCOL NUMBER: 2017P-000436

INTRODUCTION:

- This is a research study;
- Your participation is voluntary;
- A research study includes only people who choose to take part;
- You may or may not benefit from participating in the study. However, your participation may help others in the future as a result of knowledge gained from the research;
- You may leave the study at any time;
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at Beth Israel Deaconess Medical Center (BIDMC) or Brigham and Women's Hospital (BWH).

Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records. Please keep your copy for your records. It has information, including important names and telephone numbers, for future reference.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC [Beth Israel Deaconess Medical Center], BWH [Brigham and Women's Hospital] AND INVESTIGATORS

This study is being conducted by Dr. Michael Donnino and Dr. Peter Hou. This study is funded by the Good Ventures Foundation (Open Philanthropy Project). The funding agency in this study, Good Ventures Foundation (Open Philanthropy Project), is paying Beth Israel Deaconess Medical Center to perform this research. Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Dr. Donnino, and Dr. Hou have no additional interests in this research project.

WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you are signing this consent at BIDMC and have any questions, concerns or complaints about this

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research or experience any problems, you should contact Dr. Donnino at [617] 754-2341. You can also call the ED Research Team at [617] 754-2882 with questions about this research study.

If you are signing this consent at Brigham and Women's Hospital, please contact Peter Hou, MD at (617) 732-6062, Monday – Friday 9 am-5 pm or he can be reached 24/7 via the hospital page operator by dialing (617) 732-5500 and ask to have him paged.

PURPOSE

We are conducting this study to see the effects of Vitamin C, Hydrocortisone and Thiamine administered together on organ injury in people with severe infections. We want to determine if these drugs administered together will be helpful for people with severe infections.

Vitamin C and Vitamin B1 (also called Thiamine) are vitamins which are essential for the function of the cells in your body. Without adequate Vitamin C and Thiamine, certain aspects of energy production would not take place properly. Hydrocortisone is a corticosteroid (a naturally occurring compound in your body) that is commonly used for the treatment of patients with low blood pressure caused by severe infections.

Recent studies have shown that patients with serious infections often have low levels of Thiamine and Vitamin C in their body. In addition, there is some evidence that giving Thiamine to animals with septic shock improves energy production, even in those who are not deficient. Further there is evidence that Vitamin C administered together with Hydrocortisone and Thiamine may improve survival in patients with severe infection.

STUDY PARTICIPANTS

You have been asked to be in the study because you have a serious infection, called Sepsis. Sepsis is a severe infection that causes low blood pressure and critical illness. This is a very serious condition that even with treatment can lead to organ dysfunction and even death.

Approximately 60 people will take part in this study at Beth Israel Deaconess Medical Center and 20 will participate at Brigham and Women's Hospital. A total of 200 people will take part in this study at all study sites.

DESCRIPTION OF STUDY DETAILS

If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen:

1. Screening Procedures: Screening procedures are tests and procedures that will be done to determine if you are eligible to take part in the research study. For this research study, the

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screening procedure will be a review of your medical record to see if you qualify for the study.

If you are a female aged <45 years, we will ensure that you have had a negative blood or urine pregnancy test performed as part of your care. This will generally be done as part of usual care.

2. Randomization Procedures: You will be randomly assigned (like the flip of a coin) to receive either Vitamin C, Hydrocortisone, and Thiamine or a Placebo. You have a 1 in 2 chance of receiving either the drugs or the placebo. You will not be able to choose the study group to which you will be assigned.

   If one treatment arm is found to be less effective then the other while you are taking part in the study, you will be informed and further treatment will be discussed.

   Depending upon the group to which you are assigned, you may receive a placebo instead of the study drugs. A placebo is an inactive substance that looks like the study drug, but a placebo contains no active medication. Placebos are used to help determine if the results of the study are truly from the study drug. The placebo used in this study will be an intravenous (IV) infusion of 0.9% Sodium Chloride. This is a solution of sodium chloride in water (salt water). You will not know whether you will be receiving the study drug or the placebo. However, this information can be learned in case of an emergency.

3. Research Procedures: Your chart will be reviewed to assure that you are appropriate for inclusion in the study. If you qualify to take part in this research study and you choose to participate you will undergo these research procedures:

   - A blood draw right after you sign the consent to examine chemicals in your blood which tell us something about how it is responding to an infection. We will draw no more than 30 milliliters/2 tablespoons of blood (depending on how much blood is available from clinical blood draws).

   - You will be assigned to one of the following groups:
     - **Vitamin C, Hydrocortisone, and Thiamine group**: If you are assigned to the Vitamin C, Hydrocortisone, and Thiamine group you will receive 4 daily doses of 1.5 grams of Vitamin C, 100 milligrams of Thiamine and 50 milligrams of Hydrocortisone. Vitamin C and Thiamine will be administered intravenously (i.e: into your veins) every 6 hours for a total of 4 days or until discharge from the ICU. Similarly, Hydrocortisone will be administered intravenously for up to 4 days or until you are discharged from the ICU (whatever happens first).

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- **Placebo group**: If you are assigned to the placebo group you will receive 4 daily doses of 0.9% Sodium Chloride for up to 4 days or until discharge from the ICU (whatever happens first).

- Blood samples will be drawn at enrollment (0 hours), 24 hours, 72 hours, and 120 hours for a maximum total of 240 milliliters (no more than16 tablespoons total). Portions of your blood collected for research will be used to:
  - Clinical laboratory tests, analysis of cells (how your organs are working), serum, and plasma (parts of your blood). Some of these exams, tests may be done as part of regular care; if so, they may not need to be repeated; this decision will be up to your study doctor.

  - Freeze and store any leftover blood for possible analysis in the future of proteins in your blood called biomarkers that increase and decrease when your body is under stress. This extra blood will be stored at BIDMC and may be kept for up to 10 years. Access to these samples will be limited to the investigator and collaborators. If at any point you choose to withdraw your consent, you may contact Dr. Donnino (BIDMC) or Dr. Hou (BWH) and these samples will be disposed of and will not be used for future research. Genetic testing will not be performed.

- Urine will be collected at enrollment (0 hours), 24 hours, and 72 hours for a maximum total of 30 milliliters. We will study the characteristics of your urine to better understand how your kidneys are functioning. Additional urine will be frozen and stored for possible analysis in the future of proteins in your urine called biomarkers that increase and decrease when your body is under stress. This urine may be stored for up to 10 years and access to these samples will be limited to the investigator and collaborators. If at any point you choose to withdraw your consent, you may contact Dr. Donnino (BIDMC) or Dr. Hou (BWH) and these samples will be disposed of and will not be used for future research. Genetic testing will not be performed.

- Assessment of organ support, which includes, for example, medications to maintain blood pressure, will be performed everyday while you are in the hospital.

- We will also perform a more thorough review of your chart to see how you are doing while you are in the hospital. Information regarding your progress and treatments will be reviewed by the research team. We will collect and record vital signs, laboratory results, treatments you may have received and any other tests done as part of your care. If you were not in this study, we would not be reviewing your medical record.

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- If you have been discharged from the hospital, you will receive a telephone call at 30-days after enrollment and 90-days after enrollment to see how you are doing after your hospitalization. If we are unable to reach you after two attempts, you may receive a follow-up letter.

4. Monitoring/Follow-Up Procedures. Procedures performed to evaluate the effectiveness and safety of the research procedures are called "monitoring" or "follow-up" procedures. For this research study, the monitoring/follow-up procedures include:
   - At each of the blood draws (0 hours, 24 hours, 72 hours, 120 hours) we will follow along in your chart and record lab results from your routine care. When you are discharged, we will record information about your length of stay and signs of organ failure during your hospital stay.

   - If you have been discharged from the hospital, you will receive a telephone call at 30-days after enrollment and 90-days after enrollment to see how you are doing after your hospitalization. If we are unable to reach you after two attempts, you may receive a follow-up letter.

For BWH site: Blood samples and data, with your name and identifying information removed by study staff will be sent to BIDMC analysis center. The BIDMC analysis center will not receive any protected health information.

RISKS AND DISCOMFORTS

As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

Blood Draw Risk:

The risks associated with venipuncture (for blood draws) include momentary pain during needle insertion and bruising at the site of needle insertion. Infection, excess bleeding, clotting, and fainting also are possible, though unlikely. However, it is very likely that you will have an intravenous line from which we may draw, and so the blood draw will be painless. There is a very small risk that air or microorganisms may be introduced in your blood stream, but many steps will be taken to keep this risk at an absolute minimum.

Thiamine Risk:

The only known side effect from Thiamine is the potential for an allergic reaction. Allergic reactions (anaphylaxis) from Thiamine, in general, are very rare. The chance of a serious allergic reaction from Thiamine is approximately 1 in 250,000. There may be a risk of feeling burning at the site of the administration of the study drug.

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Vitamin C Risk:
In high doses Vitamin C can increase the excretion of oxalate (a chemical substance) in your urine, which, in some cases, raises the risk of kidney stone formation. To prevent this from happening, individuals with a history of kidney stones within the past year will not participate in the study. There is also a chance you will feel dizzy and a rare chance of diarrhea and bloating. Allergic reactions (anaphylaxis) in general, are very rare.

Hydrocortisone Risk:
Multiple studies with the same dosages of steroids in severe infections over a short time course (similar to this study) have been performed and Hydrocortisone is a standard part of care for many patients with severe infections. Hydrocortisone may increase your risk of additional infections, higher blood sugars, higher levels of sodium, bleeding of the digestive tract and muscle weakness (although these effects have not been clearly seen in patients receiving Hydrocortisone for sepsis). In pregnancy, Hydrocortisone may increase the risk of cleft palate and there are concerns about the effects of Hydrocortisone on fetal growth and the adrenal gland function. If you are pregnant, you should not participate in this study.

LOSS OF CONFIDENTIALITY
There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information.

CONFIDENTIALITY

Information learned from your participation in this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, accreditation agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the Beth Israel Deaconess Medical Center and Brigham and Women's Hospital with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

MEDICAL RECORD

A copy of this consent form and information collected during this research may become part of your medical record, if the information is relevant to the care you receive at Beth Israel Deaconess Medical Center. Medical records are considered permanent records; therefore, information cannot be deleted from the record. Medical records are available to health care professionals at Beth Israel

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Deaconess Medical Center and may be reviewed by staff when carrying out their responsibilities, as well as by external parties such as health care insurers and others in certain circumstances. If you are not currently a patient at Beth Israel Deaconess Medical Center and do not have a medical record at Beth Israel Deaconess Medical Center, one may be created for you for your participation in this research. You may also be required to register as a patient of Beth Israel Deaconess Medical Center in order to participate in this research.

POSSIBLE BENEFITS

It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research.

OTHER AVAILABLE OPTIONS

Taking part in this study is voluntary. If you choose not to participate in this study, you will continue to receive clinical care from your ICU team as you have been.

It is important to note that it is possible to get Thiamine even if you do not take part in the study. Thiamine and Vitamin C have not been approved by the FDA for treatment of your condition; however, many doctors in the community commonly prescribe these drugs to treat vitamin deficiencies. Please be aware that not all doctors may agree to prescribe this drug for you, and that not all health insurance companies will pay for the drug when it is prescribed by your treating physician for sepsis (although will be provided free of charge to you if given as part of this study).

It is important to note that it is possible to get Hydrocortisone even if you do not take part in this study. Hydrocortisone has been approved by the FDA for treatment of your condition and is already used in certain clinical scenarios in patients with septic shock.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY

Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at Beth Israel Deaconess

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Medical Center or Brigham and Women's Hospital.

INVESTIGATORS RIGHT TO STOP THE STUDY

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center, Brigham and Women's Hospital or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU

COSTS COVERED BY STUDY

You will not be charged for the study drugs (Steroids, Vitamin C, Thiamine, Sodium Chloride) or blood tests that are part of this research study. However, you and your insurance company will be charged for other tests, procedures or medications of this study that are considered standard treatment for your medical condition.

CO-PAYMENT/DEDUCTIBLE STATEMENT

You will be responsible for any co-payments or deductibles that are standard for your insurance coverage.

PAYMENTS TO YOU:

There is no payment to you for participating in this study.

COST OF RESEARCH RELATED INJURY:

If you are injured as a direct result of your participation in this study you should contact the Investigator at the number provided under the section "Whom to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. You or your insurance company will be billed for medical care and/or hospitalization related to this injury. You will be responsible for all co-payments and deductibles required under your insurance. BIDMC will consider reimbursement of injury related expenses not covered by your insurance on a case-by-case basis. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

OTHER IMPORTANT INFORMATION

A description of this clinical trial will be available on www.ClinicalTrials.gov as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH

Beth Israel Deaconess Medical Center

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09/09/2019
APPROVAL EXPIRATION DATE

INFORMATION

As part of this study, we will be collecting, using and sharing with others information about you. Please review this section carefully as it contains information about the federal privacy rules and the use and disclosure of your information.

PROTECTED HEALTH INFORMATION [PHI]

By signing this informed consent document, you are allowing the investigators and other authorized personnel to use [internally at BIDMC, BIDMC] and disclose [to people and organizations outside the BIDMC and BWH workforce identified in this consent] health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information and the results of any laboratory tests as well as any new information generated as part of this study. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC AND BWH WHO WILL SHARE AND USE YOUR PROTECTED HEALTH INFORMATION

Your Protected Health Information may be shared with and used by investigators working on this study, including the supporting research team (such as research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, and administrative assistants), and may also be shared and used by other health care providers at BIDMC and BWH who have treated you in the past and have information relevant to the research, or who provide services to you in connection with the research. Your Protected Health Information may also be shared with the members and staff of the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center or the Partners Human Research Committee at Brigham and Women's Hospital, which are responsible for reviewing studies for the protection of the research subjects.

PEOPLE/GROUPS OUTSIDE OF BIDMC AND BWH WITH WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE SHARED

We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this study:

- Other researchers and medical centers that are part of this study.
- People from organizations that provide independent accreditation and oversight of hospitals and research.
- Statisticians and other data monitors not affiliated with BIDMC or Partners.
- The members and staff of any other IRBs (beyond the BIDMC Committee on Clinical Investigations) that oversee the research
- Centralized data collectors
- Your health insurance company

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: VITAMIN C, STEROIDS, AND THIAMINE IN SEPSIS AND SEPTIC SHOCK
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL DONNINO, MD (BIDMC) AND PETER HOU, MD (BWH)
PROTOCOL #: 2017P-000436

- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Hospital and Clinical Research Accrediting Agencies
- Data and Safety Monitoring boards that oversee this study

Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to others and use your information without being subject to penalties under those laws.

WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION

The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document. There are many other reasons beyond the research for which BIDMC and BWH may use or disclose your Protected Health Information. Not all of these reasons require your express written authorization. For example, we will use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities. The various ways in which BIDMC and BWH may use and disclose your protected health information without your authorization are explained in a document called the Notice of Privacy Practices. If you have not received a copy of BIDMC's and BWH's Notice of Privacy Practices, please ask us for one and review it before signing this form. In addition to signing this document, you may also be asked to sign a BIDMC and BWH General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION

Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to:

BIDMC: Dr. Michael Donnino at 330 Brookline Ave., Boston, MA 02215.
BWH: Dr. Peter Hou at Neville House 312C, 75 Francis Street, Boston, MA 02115

Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

Beth Israel Deaconess Medical Center

SUBJECT'S NAME:
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BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
09/09/2019
APPROVAL EXPIRATION DATE

REFUSAL TO SIGN

Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI

If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS

BIDMC: You may contact the Human Subjects Protection Office at [617] 975-8500 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

BWH: If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at [857] 282-1900. You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

ICF REVISION DATES:

10/23/17, 2/2/18, 02/16/18, 06/14/18, 08/07/18, 08/10/18

Beth Israel Deaconess Medical Center

SUBJECT'S NAME:
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THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO) at BIDMC.

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center/Brigham and Women's Hospital has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

Signature of Subject or Legally Authorized Representative (Parent if the subject is a minor) — Date

_____

Relationship of Legally Authorized Representative to Subject

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/Co-Investigator's NAME

A signing co-investigator must be listed on the study's approved Research Staffing Form at the time of consent.

Beth Israel Deaconess Medical Center

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: VITAMIN C, STEROIDS, AND THIAMINE IN SEPSIS AND SEPTIC SHOCK
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09/09/2019
APPROVAL EXPIRATION DATE

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand that I am currently participating in a research study. Permission for my participation in this study was obtained initially through from my legally authorized representative (surrogate). I have now recovered to the point where I feel that I can provide direct consent for continued participation in this research study.

I understand that if I decide not to continue in this study, it will not affect my relationship with my doctor or with Beth Israel Deaconess Medical Center and will not result in any penalty or loss of benefits to which I am otherwise entitled.

The study has been described to me and all of my questions have been answered. I have been told what to expect if I take part in this study, including risks and possible benefits.

Any additional questions or concerns about any aspect of this study will be answered by the researchers. Questions I might have about my rights as a research participant will be answered by the Human Subjects Protection Office (HSPO) at [617]667-0469

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Participant's Name (Print)	Date

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____
SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____
PRINT INVESTIGATOR'S/Co-Investigator's NAME

Beth Israel Deaconess Medical Center

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PROTOCOL #: 2017P-000436

THE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document.

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____

Ascorbic acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Clinical Trial: SPIRIT 2013 Checklist

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	See referenced full protocol
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See referenced full protocol
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	See referenced full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	See referenced full protocol
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See referenced full protocol
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	See referenced full protocol
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Information available upon request
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Information available upon request
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Information available upon request
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16

	31b	Authorship eligibility guidelines and any intended use of professional writers	See referenced full protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See referenced full protocol

BMJ Open

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Protocol and Statistical Analysis Plan: a prospective, multi-center, double-blind, randomized, placebo controlled, clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034406.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2019
Complete List of Authors:	Moskowitz, Ari ; Harvard University, Yankama, Tuyen ; Beth Israel Deaconess Medical Center, Andersen, Lars; Aarhus University Hospital Dermato-Venerological Department David T, Huang; University of Pittsburgh Donnino, Michael W.; Beth Israel Deaconess Medical Center Grossestreuer, Anne ; Beth Israel Deaconess Medical Center, Emergency Medicine Clinical Trial Investigators, ACTS
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Research methods, Nutrition and metabolism, Infectious diseases
Keywords:	INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE, SEPSIS, ASCORBIC ACID, THIAMINE

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Protocol and Statistical Analysis Plan: a prospective, multi-center, double-blind, randomized, placebo controlled, clinical trial

Authors: Ari Moskowitz MD[1,2*], Tuyen T. Yankama MPH[1*], Lars W. Andersen, MD, MPH, PhD, DMSc[1,3], David T Huang, MD, MPH[4,5], Michael W. Donnino MD[1,6], Anne V. Grossestreuer PhD[1], for the ACTS Clinical Trial Investigators

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Abstract

Introduction: Septic shock is a common and highly morbid condition. To date, there is no specific therapy proven to attenuate organ injury in septic shock. Recent studies have suggested a role for the combination of ascorbic acid, corticosteroids, and thiamine, although randomized data is lacking.

Methods and Analysis: The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial is a multi-center, double-blind, randomized, placebo-controlled clinical trial that aims to determine the impact of ascorbic acid, corticosteroids, and thiamine vs. placebo on organ injury and mortality in patients with septic shock. Patients are randomized to receive 1,500mg of ascorbic acid, 100mg of thiamine, and 50mg of hydrocortisone parenterally vs. matching placebo every 6 hours for 4 days. Clinical and laboratory data are collected at time of study enrollment, at 24-hours, 72-hours, and at 120-hours. The primary end-point for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours. Additional key secondary outcomes include the incidence of renal failure and 30-day mortality.

Ethics and Dissemination: The study was approved by the International Review Board (IRB) of each participating study site. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial Registration: The trial is registered on clinicaltrials.gov (NCT03389555). It was posted January 3rd, 2018.

Strengths and Limitations of this Study

- This article describes a multicenter, randomized, blinded clinical trial of ascorbic acid, corticosteroids, and thiamine vs. placebo in septic shock.
- The described study will be among the earliest completed randomized trials testing the promising combination of ascorbic acid, corticosteroids, and thiamine in septic shock, and thus will fill an important knowledge gap.
- The primary outcome for the trial is change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours after enrollment, which will provide important information regarding the effect of ascorbic acid, corticosteroids, and thiamine on the trajectory of organ injury in septic shock.
- 30-day mortality is a secondary outcome for this study, but the trial may be underpowered for this important patient-centered outcome.

Introduction:

The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial was developed to assess the clinical efficacy and safety of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. The rationale for this trial has previously been published by the trial investigators[1]. In short, there is presently no directed therapy proven to attenuate organ injury in septic shock. Whereas the traditional paradigm of organ injury in sepsis has focused on impaired oxygen delivery, there is increasing evidence that non-oxygen delivery dependent mechanisms of organ injury may play an important role. In particular, mitochondrial dysfunction has been recognized as a likely contributor to organ injury in many sepsis victims.[2,3] Ascorbic acid, a potent antioxidant, and thiamine, a key co-factor in aerobic respiration, may have roles as mitochondrial resuscitators in septic shock. In observational studies and small clinical trials, both ascorbic acid and thiamine have shown promise as directed therapies for the attenuation of organ injury in sepsis.[4,5] More recently, a phase II clinical trial of high-dose ascorbic acid in sepsis victims with the acute respiratory distress syndrome found that the intervention was safe and may have improved mortality. Notably however, ascorbic acid did not attenuate organ injury as measured by the sequential organ failure assessment (SOFA) score, although this may have resulted from an imbalance in early mortality between groups, resulting in excess missing data from the sickest patients in the placebo arm.[6]

Herein we describe the protocol and proposed statistical analysis plan (SAP) for the ACTS trial, which was designed by the trial chief investigators and statisticians. All analyses specified in this SAP have been defined prospectively. The complete study protocol can be found on clinicaltrials.gov[7].

Methods and Analysis:

Trial design

The ACTS trial is a multicenter, double-blind, randomized, placebo-controlled, parallel group, superiority trial of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock. A total of 200 patients will be randomized to receive ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the intensive care unit (ICU). The primary hypothesis is that the administration of ascorbic acid, hydrocortisone, and thiamine will lead to a greater decrease in Sequential Organ Failure Assessment (SOFA) score from enrollment to 72 hours post-enrollment in patients with septic shock as compared to placebo. The trial is registered on clinicaltrials.gov (NCT03389555).

Patient population

Patients will be enrolled from 14 academic centers in the United States. Patients will be enrolled without respect to age, sex, or race. Patients will be enrolled within 24-hours of meeting all inclusion criteria.

Inclusion criteria

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

Exclusion criteria

1. Member of a protected population (pregnant, prisoner)
2. Known kidney stones within the past 1 year (except for asymptomatic, incidentally noted stones on imaging)
3. End stage renal disease (ESRD) requiring dialysis*
4. Known Glucose-6-Phosphate Dehydrogenase deficiency
5. Known Hemachromatosis
6. Comfort Measures Only status
7. Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)
8. Receiving supplemental thiamine in a dose greater than that contained in a multivitamin
9. Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug
10. Clinical indication for thiamine as determined by the clinical team providing this drug
11. Clinical indication for ascorbic acid as determined by the clinical team providing this drug
12. Known allergy to vitamin C, hydrocortisone, or thiamine

*This exclusion criterion was changed from Stage IIIb chronic kidney disease after 19 patients were enrolled

Randomization and blinding

Participants will be randomized in a 1:1 ratio to either the combination of ascorbic acid, hydrocortisone, and thiamine or placebo in blocks with random sizes of 2 or 4. The

randomization will be stratified according to site. An independent statistician created the randomization list using a random number generator. Each site's randomization list will be held by the local research pharmacy, which then will inform the research team of treatment allocation at the time of randomization. With the exception of the research pharmacist (who is not involved in patient care, monitoring, or other study activities), the patient and all clinical and research staff will be blinded to study arm allocation.

As ascorbic acid possesses a yellow tinge, the bags containing ascorbic acid will be covered with light-protective bags. In testing, after dilution there was no distinguishing characteristics of the ascorbic acid vs. placebo in the intravenous line tubing. Ascorbic acid, hydrocortisone, and thiamine are not known to have distinctive rapid effects which could lead to unblinding.

Intervention

Trial participants will be randomized to ascorbic acid (1.5g every 6 hours), hydrocortisone (50mg every 6 hours), and thiamine (100mg every 6 hours) or placebo for 4 days or until discharge from the ICU. The ascorbic acid and thiamine will be diluted in 100ml of 0.9%NaCl crystalloid fluid and the hydrocortisone was given as a 'push' dose.

A placebo (as opposed to a hydrocortisone only control arm) was selected to allow for clinician discretion with regards to the use of corticosteroids in septic shock, thus avoiding potential deviations from 'usual care' associated with the comparison of two fixed treatment arms. We note that study enrollment began prior to publication of the ADRENAL and APPROCHS trials[8,9].

Data Collection and Monitoring Plan

All data will be collected by local study staff and entered into an online case report form (CRF) using the REDCap Cloud (www.redcapcloud.com) SaaS-based Unified Data Management system. Data will be monitored automatically through REDCap Cloud and manually by the data coordinating center. In-person site visits by study monitors will be conducted at each site early in study enrollment and again at study close-out for verification of primary data, regulatory processes, and pharmacy standards.

Patient and Public Involvement

No patients will be involved in the design, recruitment, or conduct of the study. We anticipate disseminating the results of the study through publication in a high-impact scientific journal. Patients or their representatives will assess the burden of the intervention at the time of randomization through the informed consent process.

Interim analyses

An independent Data Safety and Monitoring Board (DSMB) will review blinded (group A vs group B) data to examine patient characteristics, treatment compliance, outcomes and adverse events, on three occasions (after enrollment of 50, 100, and 150 patients). The trial will not be stopped based on evidence of intervention futility or efficacy. The trial can be stopped for excess mortality in the intervention group. If one group appears to have excess mortality, the DSMB will request unblinding and a detailed evaluation of the two groups and those who died will take place. A recommendation to discontinue the trial for safety would

be made only after a thorough review of all available data to ensure that differences were not due to imbalances or extenuating circumstances between the two study groups.

Outcomes

Primary outcome

The primary outcome is the absolute change in the SOFA score from enrollment to 72 hours after enrollment. The SOFA score will be defined using a modification in which the SaO_2/FiO_2 ratio is substituted for the PaO_2/FiO_2 ratio as has been previously described[10]. This modified score (Table 1) will be used so that participants without an existing arterial catheter can be spared arterial puncture.

Key secondary outcomes

- All-cause mortality over the first 30 days after initial study drug administration.
- Renal failure during the index ICU, which is a composite outcome of all-cause death or KDIGO stage 3 acute renal failure (as defined in Table 2) within the index ICU stay after enrollment. Patients who met KDIGO 3 acute renal failure criteria at the time of initial study drug administration would not be identified as having an adverse kidney event unless they died during the index ICU stay. Patients who were alive, not in the ICU, and had not developed acute renal failure while in the ICU were assumed to not have renal failure for the purposes of this analysis.

Additional secondary outcomes

- 72-hour change in each individual component of the SOFA score
- Number of ICU-free days in the first 28 days following enrollment

- All-cause mortality to ICU discharge and hospital discharge
- Hospital disposition in patients who survived to hospital discharge
- Number of shock-free days over the first 7 days after enrollment
- Number of ventilator-free days over the first 7 days after enrollment
- Incidence of delirium as measured by the CAM-ICU[11] on study day 3

Further information on how secondary outcomes are defined can be found in Table 2.

Safety outcomes

Patients enrolled in the trial will be assessed daily during their hospitalization for any adverse event not anticipated as part of the overall disease process. Expected adverse events can be found in Table 3. The relatedness of the adverse event to study drug will also be assessed by the site principal investigator.

Sample size

The study sample will have 200 evaluable patients (100 per group), providing >99% power to detect a difference of 2 in the decrease of SOFA score over 72 hours (a decrease of 6 [standard deviation(SD): 4] in the treatment arm compared to a decrease of 4 [SD: 2] in the placebo arm, 33.3% relative change) using a t-test of unequal variance and an alpha of 0.05. This was based on preliminary data from a pre-post study using the same intervention from Marik et al.[12], which found a change of 4 in the decrease of SOFA over 72 hours (a decrease of 4.8±2.4 in the treatment arm compared to a decrease of 0.8±2.7 in the placebo arm, 81.3% relative change). The greater expected absolute change in SOFA score in the treatment arm of the present trial is based on an expectation that patients enrolled will

have higher illness severity (and thus higher SOFA scores) at baseline given that patients are only included if receiving a vasopressor.

This sample size will allow for adequate power to detect a difference in 30-day mortality. We anticipate that the control group will have a mortality of 40%, based on previous data[5, 12,13] and estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the treatment group. With these estimates, 182 participants will lead to 80% power.

Evaluable patients include those who receive at least one dose of study drug. If a patient is randomized but does not ultimately receive study drug, they will be included in the patient flow diagram with the reason for withholding study drug provided.

Statistical analysis

Analysis principles

Analyses will be conducted on a modified intention-to-treat (ITT) basis: all participants receiving at least the first dose of the study medications will be analyzed according to the group to which they were assigned, regardless of treatment compliance after the first dose. This approach is unbiased while increasing precision in a blinded trial[14]. The analysis will be performed after the last enrolled patient has been followed to 30 days.

The analyses of primary and secondary outcomes will control for site to account for randomization stratification[15]. Pre-specified subgroup analyses will be conducted regardless of whether a statistically significant treatment effect on the primary outcome is observed in the overall sample. Covariates included in each analysis are specified in the sections below

and analyses will not be additionally adjusted for potential imbalances in the treatment groups.

No formal adjustments for multiplicity of testing will be applied, but the outcome will be ordered by degree of importance (i.e., primary versus secondary) and significant test results will be interpreted in light of the multiple comparisons made.

All tests will be two-sided and the nominal level of statistical significance (α) will be 5%. All confidence intervals will have 95% coverage. All statistics will be performed using STATA, version 15 (College Station, TX, StataCorp LP, USA).

Trial profile

The flow of patients through the trial will be shown using a Consolidated Standards of Reporting Trials diagram (CONSORT)[16]. This will include the number of screened patients who met study inclusion criteria, the number of patients who were included, and exclusion reasons for non-included patients.

Baseline characteristics

A description of the baseline characteristics will be presented by treatment group (Table 4). Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarized using means ± SD or medians and first and third quartiles (IQR). Basic demographic data for all patients screened will be included.

Compliance with the administration of study drug

The following compliance with study drug variables will be summarized by treatment group:

- Cumulative dose of study drugs received (mg or mg equivalent)
- Overall compliance, defined as the number of doses given divided by the number of expected doses

These variables will be presented as mean ± SD or median (IQR).

Protocol deviations

Protocol deviations will be summarized by treatment group as the number and proportion of deviations by type. Any withdrawals of consent resulting in permanent discontinuation of study drug will also be summarized in this fashion. Timing of withdrawals will be reported.

Concomitant therapies

The number and proportion of patients receiving open-label thiamine, hydrocortisone, and ascorbic acid during the 4-day study period will be described. Time to first open label use of study drug will be summarized using mean ± SD or median (IQR).

Analysis of primary outcome

The primary hypothesis that the combination of ascorbic acid, hydrocortisone, and thiamine will attenuate organ dysfunction in septic shock will be tested by calculating the group difference (intervention vs. placebo) in SOFA score change from baseline to 72 hours using a linear mixed effects model with an appropriate covariance structure. Fixed effects will include age, sex, the allocated treatment, study day (as a categorical variable defined as

baseline, 24 hours, 48 hours, and 72 hours), and the interaction between treatment and study day. Study site will be included as a random effect. The placebo group is the reference variable for group, and baseline is the reference variable for time. Means and 95% confidence intervals of SOFA score over time will be presented, by treatment, using longitudinal plots.

If a patient is missing an element of the SOFA score for reasons other than death or early hospital discharge (e.g. laboratory error), we will use the available value in closest temporal proximity. A sensitivity analysis will be performed on the cohort of participants whose SOFA score at 72 hours is available (i.e., not missing due to early mortality, hospital discharged, etc) using linear regression. An additional sensitivity analysis will be conducted with a SOFA score penalty for early death. Specifically, if a participant expires before 72-hours, a 20% increase from their last available SOFA score will be imputed. The increase of 20% was selected by a consensus of the trial steering committee and statisticians. Differential missingness in SOFA score could introduce bias, therefore rates of death and non-death related missingness will be reported by group.

Analysis of key secondary outcomes

Renal failure: a logistic model controlling for site will be used to compare the incidence of renal failure between the intervention and placebo groups. Results will be reported as odds ratios and 95% confidence intervals.

A sensitivity analysis will be performed with the composite outcome defined as receipt of renal replacement therapy or death while meeting other elements of KDIGO 3 acute renal failure criteria during the index ICU stay using the method described above.

30-day mortality: Kaplan-Meier log-rank test and Cox proportional hazards model controlling for site will be used to compare the treatment groups in terms of survival. The outcome variable is 30-day mortality and the predictor is the allocated treatment. If the proportional hazards assumption is not met, a logistic regression controlling for site will be performed to obtain odds ratios with 95% confidence intervals.

Analysis of additional secondary outcomes

The following outcomes will be summarized using mean (SD) or median (IQR) and linear regression controlling for site will be performed to assess the differences between treatment groups.

- Change in individual components of the SOFA score from enrollment to 72 hours
- Number of ICU-free days in the first 28 days following enrollment
- Number of days free of mechanical ventilation during the first 7 days after enrollment
- Number of days free of hemodynamic shock during the first 7 days after enrollment

The following outcomes will be summarized using frequencies and percentages and logistic regression will be performed to assess the differences between treatment groups.

- Survival to ICU discharge and survival to hospital discharge
- Delirium, as measured by the CAM-ICU, on day 3 of the patient's ICU stay

Analysis of adverse events

Rates of serious expected and unexpected adverse events will be reported by group assignment. Proportions of patients with adverse events will be compared between the treatment groups using Fisher's exact test.

Analysis of subgroups

The analysis will include the following pre-defined subgroup analyses for the primary and key secondary outcomes:

- Grouped by high/low initial severity of illness. High and low levels will be defined by a baseline SOFA score above or below the study median.
- Grouped by high/low baseline serum lactate level. High and low levels will be defined by a cut-off at a serum lactate ≥3mmol/L. This level was chosen to reflect the population of patients enrolled in our prior pilot randomized trial of thiamine vs. placebo in septic shock.[5]
- Grouped by investigator prediction of survival at 30-days. The enrolling provider was asked at the time of enrollment whether they thought it was likely, unclear, or unlikely that the patient would be alive at 30-days.
- Grouped by timing of enrollment with respect to vasopressor start time. Timing will be defined by a cut-off of 12-hours. This level was chosen based on a review of the median time to enrollment from the data collected to date.

The trial is not powered to detect subgroup differences and these will be considered exploratory and hypothesis generating.

Blood samples will be collected for the measurement of baseline and subsequent levels of thiamine, ascorbic acid, and cortisol. Exploratory analyses based on this testing will not be presented in the primary trial manuscript, but will be described in follow-up manuscripts.

Missing data

If missing data for any key variable (i.e. those used in the primary outcome analysis) are > 15%, multiple imputation with chained equations will be performed.

Trial progress

This manuscript describes the SAP for the ACTS trial. The SAP is published prior to unblinding of the study and provides transparency in decisions with respect to statistical analysis. The ACTS trial has now enrolled more than 75% of its intended with recruitment expected to continue through October 2019. As such, 30-day follow-up will be complete for all patients by the end of November 2019. At the time of this submission, treatment allocations remain blinded.

Ethics and Dissemination:

The study protocol was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation (protocol 2017P-000436). The Institutional Review Board at each participating site also approved the study protocol. The trial was registered on clinicaltrials.gov (NCT03389555) prior to the enrollment of the first patient. The Food and Drug Administration (FDA) approved an Investigational New Drug (IND) application (IND 136882). Study progress and safety will be monitored by an independent DSMB as described above. Informed, written consent will be obtained prior to enrollment from all participants or their

legally authorized representatives by trained investigators. A sample informed consent form is included in the supplementary materials. Patients and their legally authorized representatives will be made aware that participation is strictly voluntary and that consent can be withdrawn at any time.

Results of this study will be presented at one or more major scientific conferences and will be published in a peer-reviewed scientific journal. Patient level data will be available to the ACTS trial investigator team and to other academic investigators upon request as adjudicated by the ACTS Steering Committee.

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Authors' contributions:

All authors made substantial contributions to the concept and design of the manuscript. Authors TY and AM equally contributed to the initial draft of the manuscript, after which all authors (AM, TY, LWA, DTH, MWD, AVG) provided important intellectual content. All authors read and approved the final manuscript.

Funding:

The ACTS trial is supported by a grant from the Open Philanthropy Project. Dr. Moskowitz is supported by a grant from the National Institutes of Health (K23GM128005–01). Dr. Grossestreuer is supported by a KL2/Catalyst Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst |The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR001100).

Competing Interests:

The authors declare no competing interests.

Acknowledgements:

ACTS Clinical Trial Investigators (listed alphabetically)

Andersen, Lars W; Becker, Lance B; Berg, Katherine M; Chase, Maureen; Cocchi, Michael N; Donnino, Michael W; Doshi, Pratik; Gong, Jonathan; Grossestreuer, Anne V; Hershey, Mark; Hilewitz, Ayelet; Hou, Peter C; Huang, David T; Kim, Hyung K; Korotun, Maksim; McCannon, Jessica B; Marik, Paul E; Moskowitz, Ari; Sen, Ayan; Sherwin, Robert L; Otero, Ronny; Uduman, Junior

Tables

Table 1: Modified Sequential organ Failure Assessment Score

Points	SaO2*/FiO2§	Blood Pressure	GCS‖	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10^{3}µL)
0	>399	MAP# ≥ 70 mmHg	15	<1.2	<1.2	≥150
1	316-399	MAP < 70 mmHg	13–14	1.2–1.9	1.2 – 1.9	<150
2	236-315	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	151-235 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 5 µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP†<500ml/day	<50
4	<151(and receiving invasive or non-invasive mechanical ventilation)	dopamine > 15 µg/kg/min, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	≥12	≥5.0 UOP†<200ml/day	<20

*SaO2=Oxygen saturation (%); § = Fraction of inspired oxygen (%); ‖ = Glasgow Coma Scale; # = Mean arterial pressure; † = Urine Output

Table 2: Definitions of secondary outcomes

Variable	DESCRIPTION
30-day mortality	All-cause mortality over the first 30 days after initial study drug administration.
KDIGO Stage 3 Renal Injury During Index ICU Stay	Acute renal failure any time during the index ICU stay. Defined as KDIGO stage 3 based on creatinine or urine output: Creatinine criteria: Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl) Urine output criteria: Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours or new renal replacement therapy
Change in individual SOFA score metrics	Change in organ specific SOFA scores (i.e. respiratory, coagulation, liver, neurologic, cardiovascular, renal)
Number of ICU-Free Days in the first 28 Days	Number of days during the first 28 days following study enrollment when the patient was not in the ICU or dead (all days after hospital discharge are considered ICU free). Note: patient would be considered "in the ICU" if they were a patient there for ≥6 hours in the course of a day or if they died prior to 28 days. For example, a patient who died while still in the ICU on day 5 would have 0 ICU-free days. A patient who was discharged from the ICU on day 3 and readmitted on day 7 and discharged again on day 21 would have 10 ICU free days (days 4-6 and 22-28). A patient who was discharged from the ICU on day 3 and did not return to the ICU would have 25 ICU-free days.
Survived to ICU discharge	Survived to ICU discharge
Survived to Hospital discharge	Survived to hospital discharge
Hospital Disposition	Hospital disposition in survivors. Extended care facilities include home with service, rehabilitation center, nursing home, skilled nursing facility/extended care 6, hospice (home or inpatient), and transferred to another acute care facility

Shock free days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours of any vasopressor agent.
Invasive Ventilation Free Days	Over the first 7 calendar days after enrollment, number of days in which the patient received <6 hours invasive mechanical ventilation.
Delirium 72 Hour of ICU Stay (as measured via CAM-ICU)	Delirium on the 3rd day (at approximately 72 hours) after the first study drug dose. Delirium is defined by the Confusion Assessment Method (CAM)-ICU or by the regular CAM if the patient is on the hospital ward.

Table 3: Definitions of adverse events and safety outcomes

The following definitions will be used:

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

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

Suspected unexpected serious adverse event (SUSAR): a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

LABEL	DESCRIPTION
Serious Adverse Events	Hyperglycemia: Blood glucose >300mg/dL or new insulin infusion occurring in the first 120-hours after enrollment Hypernatremia: Serum sodium (>150 mmol/L) occurring in the first 120-hours after enrollment New Infection: As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics. Serious allergic reaction: Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Renal calculus: Development of a renal calculus between enrollment and 30-day follow-up. Others/Unexpected: Any other serious adverse event possibly related to study drug or study participation
Related to Study?	Definitely related: no other potential cause of SAE is identified. Investigator certain or near certain the hyperglycemia is related to study drug Possibly related: other potential causes of SAE exist. There is at least a 50% chance the hyperglycemia is related to the study drug Unlikely related: a clear alternative reason for SAE exists. The investigators believe that there is a <50% change the SAE is related to study drug

Other serious adverse event severity grading	Grade I: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade II: Moderate; minimal, local or noninvasive intervention indicated Grade III: Severe or Medically Significant BUT not Immediately Life-threatening Grade IV: Life-threatening Consequences; urgent intervention indicated Grade V: Death Related to Adverse Event

Table 4: Baseline characteristics of patients stratified by treatment group

Characteristics	Overall (N =)	Ascorbic acid, Hydrocortisone, and Thiamine (N =)	Placebo (N =)
Demographics			
Age, yr			
Body mass index, kg/m^2			
Female, n (%)			
Race, n (%)			
African-American			
White			
Other			
Past medical history, n (%)			
None of the below			
Coronary artery disease			
Cancer			
Congestive heart failure			
Chronic obstructive pulmonary disease			
Dementia/Alzheimer's			
Diabetes			
Alcohol use disorder			
HIV/AIDS			
Liver disease			
Renal disease			
Stroke/Transient ischemic attack			
History of tobacco use			
Organ or Bone Marrow Transplant			
Chronic renal disease stage, n (%)			
Stage 2			
Stage 3a			
Septic Shock Characteristics			
Source of sepsis, n (%)			
Pneumonia			
Urinary Tract Infection			
Intra-Abdominal Infection			
Skin or Soft Tissue Infection			
Vascular Catheter-related Infection			
Central Nervous System Infection			
Endocarditis			
Infection of Unknown Source			
Other			
Vasopressors at Time of Study Drug, n (%)			
Norepinephrine			
Epinephrine			
Phenylephrine			
Vasopressin			

Dopamine			
Dobutamine			
Angiotensin			
Milrinone			
Midodrine			
Mechanical ventilation, n (%)			
Volume of IV fluids[a], ml			
Baseline vital signs			
Temperature, Celsius			
Heart rate, beats/minute			
Systolic blood pressure, mmHg			
Diastolic blood pressure, mmHg			
Respiratory rate, inspirations/minute			
Lactate, mmol/L			
WBC $x10^9$			
Creatinine, mg/dL			
ICU physician prediction[b]			
Predicted survival at 30 days[b], n (%)			
Very likely			
Uncertain			
Very unlikely			
SOFA score			
Baseline SOFA score			

a. Volume of IV fluids received in the 12-hours preceding enrollment
b. At time of enrollment, the physician enrolling the patient is asked to predict 30-day survival.

Beth Israel Deaconess Medical Center

FOR CCI USE ONLY
Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Consent Approval Date: 9/10/18

Protocol Number: 2017P-000436

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE COMMITTEE ON CLINICAL INVESTIGATIONS
09/09/2019
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Vitamin C, Steroids, and Thiamine in Sepsis and Septic Shock
PRINCIPAL INVESTIGATOR: Michael Donnino, MD (BIDMC) **SITE PRINCIPAL INVESTIGATOR: PETER HOU MD (BWH)**
PROTOCOL NUMBER: 2017P-000436

INTRODUCTION:

- This is a research study;
- Your participation is voluntary;
- A research study includes only people who choose to take part;
- You may or may not benefit from participating in the study. However, your participation may help others in the future as a result of knowledge gained from the research;
- You may leave the study at any time;
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at Beth Israel Deaconess Medical Center (BIDMC) or Brigham and Women's Hospital (BWH).

Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records. Please keep your copy for your records. It has information, including important names and telephone numbers, for future reference.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC [Beth Israel Deaconess Medical Center], BWH [Brigham and Women's Hospital] AND INVESTIGATORS

This study is being conducted by Dr. Michael Donnino and Dr. Peter Hou. This study is funded by the Good Ventures Foundation (Open Philanthropy Project). The funding agency in this study, Good Ventures Foundation (Open Philanthropy Project), is paying Beth Israel Deaconess Medical Center to perform this research. Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Dr. Donnino, and Dr. Hou have no additional interests in this research project.

WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you are signing this consent at BIDMC and have any questions, concerns or complaints about this

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: VITAMIN C, STEROIDS, AND THIAMINE IN SEPSIS AND SEPTIC SHOCK
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL DONNINO, MD (BIDMC) AND PETER HOU, MD (BWH)
PROTOCOL #: 2017P-000436

research or experience any problems, you should contact Dr. Donnino at [617] 754-2341. You can also call the ED Research Team at [617] 754-2882 with questions about this research study.

If you are signing this consent at Brigham and Women's Hospital, please contact Peter Hou, MD at (617) 732-6062, Monday – Friday 9 am-5 pm or he can be reached 24/7 via the hospital page operator by dialing (617) 732-5500 and ask to have him paged.

PURPOSE

We are conducting this study to see the effects of Vitamin C, Hydrocortisone and Thiamine administered together on organ injury in people with severe infections. We want to determine if these drugs administered together will be helpful for people with severe infections.

Vitamin C and Vitamin B1 (also called Thiamine) are vitamins which are essential for the function of the cells in your body. Without adequate Vitamin C and Thiamine, certain aspects of energy production would not take place properly. Hydrocortisone is a corticosteroid (a naturally occurring compound in your body) that is commonly used for the treatment of patients with low blood pressure caused by severe infections.

Recent studies have shown that patients with serious infections often have low levels of Thiamine and Vitamin C in their body. In addition, there is some evidence that giving Thiamine to animals with septic shock improves energy production, even in those who are not deficient. Further there is evidence that Vitamin C administered together with Hydrocortisone and Thiamine may improve survival in patients with severe infection.

STUDY PARTICIPANTS

You have been asked to be in the study because you have a serious infection, called Sepsis. Sepsis is a severe infection that causes low blood pressure and critical illness. This is a very serious condition that even with treatment can lead to organ dysfunction and even death.

Approximately 60 people will take part in this study at Beth Israel Deaconess Medical Center and 20 will participate at Brigham and Women's Hospital. A total of 200 people will take part in this study at all study sites.

DESCRIPTION OF STUDY DETAILS

If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen:

1. Screening Procedures: Screening procedures are tests and procedures that will be done to determine if you are eligible to take part in the research study. For this research study, the

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PROTOCOL #: 2017P-000436

screening procedure will be a review of your medical record to see if you qualify for the study.

If you are a female aged <45 years, we will ensure that you have had a negative blood or urine pregnancy test performed as part of your care. This will generally be done as part of usual care.

2. Randomization Procedures: You will be randomly assigned (like the flip of a coin) to receive either Vitamin C, Hydrocortisone, and Thiamine or a Placebo. You have a 1 in 2 chance of receiving either the drugs or the placebo. You will not be able to choose the study group to which you will be assigned.

   If one treatment arm is found to be less effective then the other while you are taking part in the study, you will be informed and further treatment will be discussed.

   Depending upon the group to which you are assigned, you may receive a placebo instead of the study drugs. A placebo is an inactive substance that looks like the study drug, but a placebo contains no active medication. Placebos are used to help determine if the results of the study are truly from the study drug. The placebo used in this study will be an intravenous (IV) infusion of 0.9% Sodium Chloride. This is a solution of sodium chloride in water (salt water). You will not know whether you will be receiving the study drug or the placebo. However, this information can be learned in case of an emergency.

3. Research Procedures: Your chart will be reviewed to assure that you are appropriate for inclusion in the study. If you qualify to take part in this research study and you choose to participate you will undergo these research procedures:

   - A blood draw right after you sign the consent to examine chemicals in your blood which tell us something about how it is responding to an infection. We will draw no more than 30 milliliters/2 tablespoons of blood (depending on how much blood is available from clinical blood draws).

   - You will be assigned to one of the following groups:
     - **Vitamin C, Hydrocortisone, and Thiamine group**: If you are assigned to the Vitamin C, Hydrocortisone, and Thiamine group you will receive 4 daily doses of 1.5 grams of Vitamin C, 100 milligrams of Thiamine and 50 milligrams of Hydrocortisone. Vitamin C and Thiamine will be administered intravenously (i.e: into your veins) every 6 hours for a total of 4 days or until discharge from the ICU. Similarly, Hydrocortisone will be administered intravenously for up to 4 days or until you are discharged from the ICU (whatever happens first).

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PROTOCOL #: 2017P-000436

- **Placebo group**: If you are assigned to the placebo group you will receive 4 daily doses of 0.9% Sodium Chloride for up to 4 days or until discharge from the ICU (whatever happens first).

- Blood samples will be drawn at enrollment (0 hours), 24 hours, 72 hours, and 120 hours for a maximum total of 240 milliliters (no more than16 tablespoons total). Portions of your blood collected for research will be used to:
  - Clinical laboratory tests, analysis of cells (how your organs are working), serum, and plasma (parts of your blood). Some of these exams, tests may be done as part of regular care; if so, they may not need to be repeated; this decision will be up to your study doctor.

  - Freeze and store any leftover blood for possible analysis in the future of proteins in your blood called biomarkers that increase and decrease when your body is under stress. This extra blood will be stored at BIDMC and may be kept for up to 10 years. Access to these samples will be limited to the investigator and collaborators. If at any point you choose to withdraw your consent, you may contact Dr. Donnino (BIDMC) or Dr. Hou (BWH) and these samples will be disposed of and will not be used for future research. Genetic testing will not be performed.

- Urine will be collected at enrollment (0 hours), 24 hours, and 72 hours for a maximum total of 30 milliliters. We will study the characteristics of your urine to better understand how your kidneys are functioning. Additional urine will be frozen and stored for possible analysis in the future of proteins in your urine called biomarkers that increase and decrease when your body is under stress. This urine may be stored for up to 10 years and access to these samples will be limited to the investigator and collaborators. If at any point you choose to withdraw your consent, you may contact Dr. Donnino (BIDMC) or Dr. Hou (BWH) and these samples will be disposed of and will not be used for future research. Genetic testing will not be performed.

- Assessment of organ support, which includes, for example, medications to maintain blood pressure, will be performed everyday while you are in the hospital.

- We will also perform a more thorough review of your chart to see how you are doing while you are in the hospital. Information regarding your progress and treatments will be reviewed by the research team. We will collect and record vital signs, laboratory results, treatments you may have received and any other tests done as part of your care. If you were not in this study, we would not be reviewing your medical record.

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- If you have been discharged from the hospital, you will receive a telephone call at 30-days after enrollment and 90-days after enrollment to see how you are doing after your hospitalization. If we are unable to reach you after two attempts, you may receive a follow-up letter.

4. Monitoring/Follow-Up Procedures. Procedures performed to evaluate the effectiveness and safety of the research procedures are called "monitoring" or "follow-up" procedures. For this research study, the monitoring/follow-up procedures include:
   - At each of the blood draws (0 hours, 24 hours, 72 hours, 120 hours) we will follow along in your chart and record lab results from your routine care. When you are discharged, we will record information about your length of stay and signs of organ failure during your hospital stay.

   - If you have been discharged from the hospital, you will receive a telephone call at 30-days after enrollment and 90-days after enrollment to see how you are doing after your hospitalization. If we are unable to reach you after two attempts, you may receive a follow-up letter.

For BWH site: Blood samples and data, with your name and identifying information removed by study staff will be sent to BIDMC analysis center. The BIDMC analysis center will not receive any protected health information.

RISKS AND DISCOMFORTS

As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

Blood Draw Risk:

The risks associated with venipuncture (for blood draws) include momentary pain during needle insertion and bruising at the site of needle insertion. Infection, excess bleeding, clotting, and fainting also are possible, though unlikely. However, it is very likely that you will have an intravenous line from which we may draw, and so the blood draw will be painless. There is a very small risk that air or microorganisms may be introduced in your blood stream, but many steps will be taken to keep this risk at an absolute minimum.

Thiamine Risk:

The only known side effect from Thiamine is the potential for an allergic reaction. Allergic reactions (anaphylaxis) from Thiamine, in general, are very rare. The chance of a serious allergic reaction from Thiamine is approximately 1 in 250,000. There may be a risk of feeling burning at the site of the administration of the study drug.

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Vitamin C Risk:
In high doses Vitamin C can increase the excretion of oxalate (a chemical substance) in your urine, which, in some cases, raises the risk of kidney stone formation. To prevent this from happening, individuals with a history of kidney stones within the past year will not participate in the study. There is also a chance you will feel dizzy and a rare chance of diarrhea and bloating. Allergic reactions (anaphylaxis) in general, are very rare.

Hydrocortisone Risk:
Multiple studies with the same dosages of steroids in severe infections over a short time course (similar to this study) have been performed and Hydrocortisone is a standard part of care for many patients with severe infections. Hydrocortisone may increase your risk of additional infections, higher blood sugars, higher levels of sodium, bleeding of the digestive tract and muscle weakness (although these effects have not been clearly seen in patients receiving Hydrocortisone for sepsis). In pregnancy, Hydrocortisone may increase the risk of cleft palate and there are concerns about the effects of Hydrocortisone on fetal growth and the adrenal gland function. If you are pregnant, you should not participate in this study.

LOSS OF CONFIDENTIALITY
There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information.

CONFIDENTIALITY

Information learned from your participation in this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, accreditation agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the Beth Israel Deaconess Medical Center and Brigham and Women's Hospital with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

MEDICAL RECORD

A copy of this consent form and information collected during this research may become part of your medical record, if the information is relevant to the care you receive at Beth Israel Deaconess Medical Center. Medical records are considered permanent records; therefore, information cannot be deleted from the record. Medical records are available to health care professionals at Beth Israel

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Deaconess Medical Center and may be reviewed by staff when carrying out their responsibilities, as well as by external parties such as health care insurers and others in certain circumstances. If you are not currently a patient at Beth Israel Deaconess Medical Center and do not have a medical record at Beth Israel Deaconess Medical Center, one may be created for you for your participation in this research. You may also be required to register as a patient of Beth Israel Deaconess Medical Center in order to participate in this research.

POSSIBLE BENEFITS

It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research.

OTHER AVAILABLE OPTIONS

Taking part in this study is voluntary. If you choose not to participate in this study, you will continue to receive clinical care from your ICU team as you have been.

It is important to note that it is possible to get Thiamine even if you do not take part in the study. Thiamine and Vitamin C have not been approved by the FDA for treatment of your condition; however, many doctors in the community commonly prescribe these drugs to treat vitamin deficiencies. Please be aware that not all doctors may agree to prescribe this drug for you, and that not all health insurance companies will pay for the drug when it is prescribed by your treating physician for sepsis (although will be provided free of charge to you if given as part of this study).

It is important to note that it is possible to get Hydrocortisone even if you do not take part in this study. Hydrocortisone has been approved by the FDA for treatment of your condition and is already used in certain clinical scenarios in patients with septic shock.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY

Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at Beth Israel Deaconess

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Medical Center or Brigham and Women's Hospital.

INVESTIGATORS RIGHT TO STOP THE STUDY

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center, Brigham and Women's Hospital or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU

COSTS COVERED BY STUDY

You will not be charged for the study drugs (Steroids, Vitamin C, Thiamine, Sodium Chloride) or blood tests that are part of this research study. However, you and your insurance company will be charged for other tests, procedures or medications of this study that are considered standard treatment for your medical condition.

CO-PAYMENT/DEDUCTIBLE STATEMENT

You will be responsible for any co-payments or deductibles that are standard for your insurance coverage.

PAYMENTS TO YOU:

There is no payment to you for participating in this study.

COST OF RESEARCH RELATED INJURY:

If you are injured as a direct result of your participation in this study you should contact the Investigator at the number provided under the section "Whom to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. You or your insurance company will be billed for medical care and/or hospitalization related to this injury. You will be responsible for all co-payments and deductibles required under your insurance. BIDMC will consider reimbursement of injury related expenses not covered by your insurance on a case-by-case basis. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

OTHER IMPORTANT INFORMATION

A description of this clinical trial will be available on www.ClinicalTrials.gov as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH

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INFORMATION

As part of this study, we will be collecting, using and sharing with others information about you. Please review this section carefully as it contains information about the federal privacy rules and the use and disclosure of your information.

PROTECTED HEALTH INFORMATION [PHI]

By signing this informed consent document, you are allowing the investigators and other authorized personnel to use [internally at BIDMC, BIDMC] and disclose [to people and organizations outside the BIDMC and BWH workforce identified in this consent] health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information and the results of any laboratory tests as well as any new information generated as part of this study. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC AND BWH WHO WILL SHARE AND USE YOUR PROTECTED HEALTH INFORMATION

Your Protected Health Information may be shared with and used by investigators working on this study, including the supporting research team (such as research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, and administrative assistants), and may also be shared and used by other health care providers at BIDMC and BWH who have treated you in the past and have information relevant to the research, or who provide services to you in connection with the research. Your Protected Health Information may also be shared with the members and staff of the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center or the Partners Human Research Committee at Brigham and Women's Hospital, which are responsible for reviewing studies for the protection of the research subjects.

PEOPLE/GROUPS OUTSIDE OF BIDMC AND BWH WITH WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE SHARED

We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this study:

- Other researchers and medical centers that are part of this study.
- People from organizations that provide independent accreditation and oversight of hospitals and research.
- Statisticians and other data monitors not affiliated with BIDMC or Partners.
- The members and staff of any other IRBs (beyond the BIDMC Committee on Clinical Investigations) that oversee the research
- Centralized data collectors
- Your health insurance company

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- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Hospital and Clinical Research Accrediting Agencies
- Data and Safety Monitoring boards that oversee this study

Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to others and use your information without being subject to penalties under those laws.

WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION

The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document. There are many other reasons beyond the research for which BIDMC and BWH may use or disclose your Protected Health Information. Not all of these reasons require your express written authorization. For example, we will use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities. The various ways in which BIDMC and BWH may use and disclose your protected health information without your authorization are explained in a document called the Notice of Privacy Practices. If you have not received a copy of BIDMC's and BWH's Notice of Privacy Practices, please ask us for one and review it before signing this form. In addition to signing this document, you may also be asked to sign a BIDMC and BWH General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION

Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to:

BIDMC: Dr. Michael Donnino at 330 Brookline Ave., Boston, MA 02215.
BWH: Dr. Peter Hou at Neville House 312C, 75 Francis Street, Boston, MA 02115

Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

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REFUSAL TO SIGN

Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI

If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS

BIDMC: You may contact the Human Subjects Protection Office at [617] 975-8500 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

BWH: If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at [857] 282-1900. You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

ICF REVISION DATES:

10/23/17, 2/2/18, 02/16/18, 06/14/18, 08/07/18, 08/10/18

Beth Israel Deaconess Medical Center

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BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
09/09/2019
APPROVAL EXPIRATION DATE

THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO) at BIDMC.

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center/Brigham and Women's Hospital has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

Signature of Subject or Legally Authorized Representative (Parent if the subject is a minor) Date

_____

Relationship of Legally Authorized Representative to Subject

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/Co-Investigator's NAME

A signing co-investigator must be listed on the study's approved Research Staffing Form at the time of consent.

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CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand that I am currently participating in a research study. Permission for my participation in this study was obtained initially through from my legally authorized representative (surrogate). I have now recovered to the point where I feel that I can provide direct consent for continued participation in this research study.

I understand that if I decide not to continue in this study, it will not affect my relationship with my doctor or with Beth Israel Deaconess Medical Center and will not result in any penalty or loss of benefits to which I am otherwise entitled.

The study has been described to me and all of my questions have been answered. I have been told what to expect if I take part in this study, including risks and possible benefits.

Any additional questions or concerns about any aspect of this study will be answered by the researchers. Questions I might have about my rights as a research participant will be answered by the Human Subjects Protection Office (HSPO) at [617]667-0469

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Participant's Name (Print)	Date

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____
SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____
PRINT INVESTIGATOR'S/Co-Investigator's NAME

Beth Israel Deaconess Medical Center

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THE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document.

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Ascorbic acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Clinical Trial: SPIRIT 2013 Checklist

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	See referenced full protocol
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See referenced full protocol
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	See referenced full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	See referenced full protocol
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See referenced full protocol
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	See referenced full protocol
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Information available upon request
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Information available upon request
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Information available upon request
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16

	31b	Authorship eligibility guidelines and any intended use of professional writers	See referenced full protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See referenced full protocol