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Ascorbic Acid, Corticosteroids and Thiamine in Sepsis (ACTS) protocol and statistical analysis plan: a prospective, multicentre, double-blind, randomised, 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 randomised data are lacking.

Methods and analysis The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis trial is a multi-centre, double-blind, randomised, placebo-controlled clinical trial that aims to determine the impact of ascorbic acid, corticosteroids and thiamine versus placebo on organ injury and mortality in patients with septic shock. Patients are randomised to receive 1500 mg of ascorbic acid, 100 mg of thiamine and 50 mg of hydrocortisone parenterally versus matching placebo every 6 hours for 4 days. Clinical and laboratory data are collected at the time of study enrolment, at 24, 72 and 120 hours. The primary end-point for the trial is change in the Sequential Organ Failure Assessment score between enrolment 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 of each participating study site. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number The trial is registered on clinicaltrials.gov (NCT03389555). It was posted on 3 January 2018.

Strengths and limitations of this study

- This article describes a multicentre, randomised, blinded clinical trial of ascorbic acid, corticosteroids and thiamine versus placebo in septic shock.
- The described study will be among the earliest completed randomised 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 score between enrolment and 72 hours after enrolment 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-centred 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 recognised 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 multicentre, double-blind, randomised, placebo-controlled, parallel group, superiority trial of ascorbic acid, hydrocortisone and thiamine in patients with septic shock. A total of 200 patients will be randomised to receive ascorbic acid (1.5 g every 6 hours), hydrocortisone (50 mg every 6 hours) and thiamine (100 mg 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 SOFA score from enrolment to 72 hours post-enrolment in patients with septic shock as compared with placebo.

Patient population

Patients will be enrolled from 14 academic centres in the USA. 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 (eg, 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 requiring dialysis.*
4. Known glucose-6-phosphate dehydrogenase deficiency.
5. Known haemochromatosis.
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 (eg, 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.

Randomisation and blinding

Participants will be randomised 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 randomisation will be stratified according to site. An independent statistician created the randomisation list using a random number generator. Each site's randomisation list will be held by the local research pharmacy, which then will inform the research team of treatment allocation at the time of randomisation. 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 versus 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 randomised to ascorbic acid (1.5 g every 6 hours), hydrocortisone (50 mg every 6 hours) and thiamine (100 mg every 6 hours) or placebo for 4 days or until discharge from the ICU. The ascorbic acid and thiamine will be diluted in 100 mL 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 regard 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 enrolment 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 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 centre. In-person site visits by study monitors will

be conducted at each site early in study enrolment 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 randomisation 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 enrolment 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 enrolment to 72 hours after enrolment. 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 Kidney Disease Improving Global Outcomes (KDIGO) stage 3 acute renal failure (as defined in table 2) within the index ICU stay after enrolment. 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 hours change in each individual component of the SOFA score.
- Number of ICU-free days in the first 28 days following enrolment.
- 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 enrolment.
- Number of ventilator-free days over the first 7 days after enrolment.
- Incidence of delirium as measured by the Confusion Assessment Method (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 hospitalisation 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

Table 1 Modified Sequential organ Failure Assessment score

Points	SaO_2/FiO_2	Blood pressure	GCS	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets ($x10^9$/L)
0	>399	MAP≥70 mm Hg	15	<1.2	<1.2	≥150
1	316–399	MAP <70 mm Hg	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<500 mL/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<200 mL/day	<20

FiO_2, Fraction of inspired oxygen (%).; GCS, Glasgow Coma Scale; MAP, Mean arterial pressure; SaO_2, Oxygen saturation (%); UOP, 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 three based on creatinine or urine output: creatinine criteria: Increase in serum creatinine to more than 300% (>threefold) 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 (ie, respiratory, coagulation, liver, neurological, cardiovascular, renal).
Number of ICU-free days in the first 28 days	Number of days during the first 28 days following study enrolment 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 centre, 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 seven calendar days after enrolment, number of days in which the patient received <6 hours of any vasopressor agent.
Invasive ventilation-free days	Over the first seven calendar days after enrolment, number of days in which the patient received <6 hours invasive mechanical ventilation.
Delirium 72 hours of ICU stay (as measured via CAM-ICU)	Delirium on the third day (at approximately 72 hours) after the first study drug dose. Delirium is defined by the CAM-ICU or by the regular CAM if the patient is on the hospital ward.

CAM, Confusion Assessment Method; ICU, intensive care unit; SOFA, sequential organ failure assessment.

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 (SD: 4) in the treatment arm compared with 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*,[4] 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 with 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[4 5 12] 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 randomised 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 basis: all participants receiving at least the first dose of the study medications will be analysed 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.[13]

Table 3 Definitions of adverse events and safety outcomes

Label	Description
Serious Adverse Events (SAE)	Hyperglycaemia: Blood glucose >300 mg/dL or new insulin infusion occurring in the first 120 hours after enrolment. Hypernatraemia: Serum sodium (>150 mmol/L) occurring in the first 120 hours after enrolment. 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 enrolment and 30-day follow-up. Others/unexpected: Any other SAE 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 hyperglycaemia is related to study drug. Possibly related: Other potential causes of SAE exist. There is at least a 50% chance the hyperglycaemia 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 SAE 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.

The following definitions will be used:.
Adverse event: any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
SAE: any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, 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: a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

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 randomisation stratification.[14] Prespecified 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 (ie, primary vs 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 CIs will have 95% coverage. All statistics will be performed using STATA V.15.

Trial profile

The flow of patients through the trial will be shown using a Consolidated Standards of Reporting Trials diagram.[15] 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 summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised 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 summarised 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 summarised by treatment group as the number and proportion of deviations by type. Any withdrawals of consent resulting in permanent

Table 4 Baseline characteristics of patients stratified by treatment group

Characteristics	Overall (N =)	Ascorbic acid, hydrocortisone and thiamine (N =)	Placebo (N =)
Demographics			
Age, years			
Body mass index, kg/m^2			
Female, n (%)			
Race, n (%)			
African-American			
White			
Other			
Medical history, n (%)			
None of the below			
Coronary artery disease			
Cancer			
Congestive heart failure			
Chronic obstructive pulmonary disease			
Dementia/Alzheimer's disease			
Diabetes			
Alcohol use disorder			
HIV/AIDS			
Liver disease			
Renal disease			
Stroke/transient ischaemic 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			

Continued

Table 4 Continued

Characteristics	Overall (N =)	Ascorbic acid, hydrocortisone and thiamine (N =)	Placebo (N =)
Angiotensin			
Milrinone			
Midodrine			
Mechanical ventilation, n (%)			
Volume of IV fluids*, mL			
Baseline vital signs			
Temperature, °C			
Heart rate, beats/min			
Systolic blood pressure, mm Hg			
Diastolic blood pressure, mm Hg			
Respiratory rate, inspirations/min			
Lactate, mmol/L			
WCC, $x10^9$/L			
Creatinine, mg/dL			
ICU physician prediction†			
Predicted survival at 30 days†, n (%)			
Very likely			
Uncertain			
Very unlikely			
SOFA score			
Baseline SOFA score			

*Volume of IV fluids received in the 12 hours preceding enrolment.
†At time of enrolment, the physician enrolling the patient is asked to predict 30-day survival.
ICU, intensive care unit.; SOFA, sequential organ failure assessment; WCC, white cell count.

discontinuation of study drug will also be summarised 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 summarised 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, 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% CIs 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 (eg, 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 (ie, 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 ORs and 95% CIs.

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 ORs with 95% CIs.

Analysis of additional secondary outcomes

The following outcomes will be summarised 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 enrolment to 72 hours
- Number of ICU-free days in the first 28 days following enrolment.
- Number of days free of mechanical ventilation during the first 7 days after enrolment.
- Number of days free of haemodynamic shock during the first 7 days after enrolment

The following outcomes will be summarised 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 ≥3 mmol/L. This level was chosen to reflect the population of patients enrolled in our prior pilot randomised trial of thiamine versus placebo in septic shock.[5]
- Grouped by investigator prediction of survival at 30 days. The enrolling provider was asked at the time of enrolment whether they thought it was likely, unclear or unlikely that the patient would be alive at 30 days.
- Grouped by timing of enrolment 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 enrolment 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 (ie, 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

Study progress and safety will be monitored by an independent DSMB as described above. Informed, written consent will be obtained prior to enrolment from all participants or their legally authorised representatives by trained investigators. A sample informed consent form is included in the online supplementary materials. Patients and their legally authorised 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 on request as adjudicated by the ACTS Steering Committee.

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Contributors 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.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation (protocol 2017 P-000436). The institutional review board at each participating site also approved the study protocol. The Food and Drug Administration (FDA) approved an Investigational New Drug (IND) application (IND 136882).

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