Thiamine as a Renal Protective Agent in Septic Shock

CLINICAL TRIAL PROTOCOL

Version 2.1
July 2nd, 2021
IND: 107, 135

Clinical Trials.Gov Identifier: NCT03550794

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Funded By:
National Institutes of Health
National Institute of General Medical Sciences

Revision history:
V1.0 June 15th, 2018
V2.0 December 1st, 2020 (change in PI, added site)
V2.1 July 2nd, 2021 (clarification of dosing procedures)

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SYNOPSIS

The “The “Thiamine for Renal Protection in Septic Shock (TRPSS)” study is a randomized, clinical trial that aims to determine the impact of Thiamine vs. Placebo on kidney injury in patients with septic shock. The trial will be conducted in accordance with all applicable national and international laws, regulations, and guidelines The trial and this protocol is developed in accordance with the International Conference on Harmonization (ICH) guidelines[1-3] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[4,5]. The principal investigator wrote the protocol with input from the steering committee. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

TRIAL OVERVIEW

Title	Thiamine for Renal Protection in Septic Shock (TRPSS)

Clinical Trials Number	NCT03550794
Sources of monetary or material support	National Institute of General Medical Sciences
Study Sites	Beth Israel Deaconess Medical Center, Long Island Jewish Medical Center, North Shore Medical Center
Condition studied	Septic Shock
Interventions	Thiamine 200mg IV twice daily for 3 days
Comparator	Placebo
Inclusion criteria	1) Adult ≥18 years of age 2) Suspected or Confirmed Infection (defined as collection of a blood/fluid culture and provision of an antimicrobial) 3) Receipt of a vasopressor agent (e.g. norepinephrine, phenylephrine, vasopressin) 4) Serum lactate ≥2mmol/L 5) Creatinine >1.0mg/dL
Exclusion criteria	1) Clinical indication for thiamine administration (alcoholism, known or highly suspected deficiency) or treatment with thiamine beyond the amount found in a standard multivitamin within the last 10 days 2) Renal replacement therapy within the past 30 days 3) Comfort measures only or anticipated withdrawal of support within 24 hours 4) Protected populations (pregnant women, prisoners) 5) Known thiamine allergy
Study type	Interventional Allocation: Randomized (1:1) Intervention model: Parallel group Masking: Double-blind
Target sample size	88 Participants (44/arm)
Primary outcome	Change in creatinine over the first 72-hours after enrollment
Key secondary outcomes	• Incidence of renal failure requiring renal replacement during index ICU stay • Length of ICU stay • Hospital mortality

STEERING COMMITTEE

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

1. BACKGROUND AND SIGNIFICANCE

1.1 Scope of the Problem

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

1.2 Existing Interventions

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

1.3 Renal failure is a common sequela of septic shock and is associated with poor outcomes. Renal failure has been estimated to occur in 23% of patients with severe sepsis and 51% of patients with septic shock.[36] Further, the development of renal failure during sepsis or septic shock portends a significantly worse outcome.[36] In one study of patients with septic shock, there was a step-wise increase in mortality with worsening AKI.[37] These data suggest that attenuating kidney injury in sepsis will improve outcomes.

1.4 Thiamine (vitamin B1) is an essential component of mitochondrial energy production and may reduce oxidative stress. Thiamine is a key component in aerobic metabolism, working as a cofactor for pyruvate dehydrogenase. When thiamine levels are insufficient, pyruvate is unable to enter the Krebs Cycle, and pyruvate is converted to lactate, rather than acetyl-coenzyme A.[24,25] Relative thiamine deficiency, therefore, causes a shift in metabolism to the anaerobic pathway, resulting in elevated serum lactate levels. Thiamine is also a critical component of the pentose phosphate pathway, which may reduce oxidative stress.[9,10] As the kidney maintains a high mitochondrial abundance relative to other organs,[8] it may be especially susceptible to perturbations in mitochondrial function.

1.5 Thiamine may attenuate renal injury in patients with septic shock. In a *post-hoc* analysis of data collected during a randomized trial of thiamine vs. placebo,[3] patients who received thiamine were less likely to require renal replacement therapy (RRT) and had lower creatinine levels over time as compared to patients who received placebo.[4] That study, however, was limited by its *post-hoc* design, an imbalance in premorbid renal function between groups, and inconsistency with regards to the timing of biomarker measurement. In a non-randomized observation study of patients with severe sepsis or septic shock at a single center, those who received the combination of thiamine, vitamin C, and hydrocortisone were less likely to require RRT as compared to historical controls at the same site (3/31 [10%] vs. 11/30 [33%], p=0.02).[26] This study likewise provides some support for thiamine as a renal protective agent in sepsis, but is limited by its quasi-experimental design and the associated potential for bias.

2. TRIAL DESIGN

2.1 Overview

This will be an investigator-initiated, randomized, placebo-controlled, parallel group, double-blind, superiority trial of thiamine vs. placebo in participants with septic shock. A total of 88 adult participants will be enrolled. The primary outcome will be the change serum creatinine between enrollment and 72-hours. Key secondary outcomes include the incidence of renal failure during the index ICU stay and survival at 30 days.

2.2 Allocation

Participants will be randomized in a 1:1 ratio to either thiamine or placebo in blocks with random sizes of 2 or 4. The randomization will be stratified according to site.[38] An independent statistician will create the randomization list using a random number generator. The complete list will only be shared with an independent pharmacy consultant, who will not be involved in clinical care. The pharmacy consultant and the independent statistician will both store the randomization list.

2.3 Intervention

2.3.1 Thiamine

The study drug will consist of thiamine 200mg in 50ml of 0.9%NACL saline solution given parenterally every 12 hours for 3 days.

2.3.2 Placebo

The placebo will consist of matching volumes of normal saline (0.9% NaCl).

2.4 Blinding

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

Vitamin B1 is not known to have distinctive rapid effects or other characteristics which could lead to unblinding.

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

2.5 Regulatory Issues

An Investigational New Drug (IND) application was submitted to and approved by the Food and Drug Administration (FDA) for this study (IND # 107, 135).

The trial has been registered on ClinicalTrials.gov: NCT03550794

3. SETTING AND PARTICIPANT POPULATION

3.1 Setting

The trial will be conducted at Beth Israel Deaconess Medical Center. Additional sites might be recruited if needed.

Enrolling Sites

Enrolling Site	Site Investigator
Beth Israel Deaconess Medical Center	Ari Moskowitz MD; Michael Donnino MD
North Shore Medical Center	Jonathan Gong MD
Long Island Jewish Medical Center	Jonathan Gong MD

3.2 Inclusion criteria

Inclusion criteria:

1) Adult ≥18 years of age
2) Suspected or Confirmed Infection (defined as collection of a blood/fluid culture and provision of an antimicrobial)
3) Receipt of a vasopressor agent (e.g. norepinephrine, phenylephrine, vasopressin)
4) Serum lactate ≥2mmol/L
5) Creatinine >1.0mg/dL

3.3 Exclusion criteria

Exclusion criteria:

1) Clinical indication for thiamine administration (alcoholism, known or highly suspected deficiency) or treatment with thiamine beyond the amount found in a standard multivitamin within the last 10 days
2) Renal replacement therapy within the past 30 days
3) Comfort measures only or anticipated withdrawal of support within 24 hours
4) Protected populations (pregnant women, prisoners)
5) Known thiamine allergy

Justification of Inclusion and Exclusion Criteria: The inclusion criteria reflect the definition of septic shock put forth by the Society of Critical Care Medicine and European Society of Intensive Care Medicine Task Force.[16] We will include only patients with a creatinine of >1.0mg/dL to ensure we are evaluating a true 'at-risk' population for kidney injury. The trial end-points cannot be assessed in patients already receiving renal replacement therapy, and this population will therefore be excluded. We have chosen to include adult patients only due to differences in etiology and treatment of septic shock in children. Also, BIDMC does not have a pediatric unit. We will exclude patients who are presently receiving or who will likely receive supplemental thiamine for clinical purposes as we feel it would be unethical to randomize these patients to the placebo arm. We will also exclude patients with a known thiamine allergy.

4. TRIAL PROCEDURES

4.1 Participant Identification

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

4.2 Consent procedures

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

After it is determined that they meet all inclusion criteria and no exclusion criteria, the participant (or legally authorized representative [LAR] if the participant is not able to provide consent) will be approached for written informed consent by a physician co-investigator from the team. The

investigator will provide the participant/representative information regarding the background and significance of the study, eligibility criteria, and a description of the protocol. To ensure we are correctly identifying the potential participant's LAR, we communicate with members of the clinical team. The consent process may need to be modified based on site-specific IRB recommendations.

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

4.3 Randomization

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

4.4 Drug preparation and administration

The thiamine will be mixed in 50ml of normal saline and administered intravenously over 45-60 minutes. The placebo will be given using techniques and volumes matching those of the study medication.

All study medications will be continued for 3-days or until the participant expires.

4.4.1 Contingencies and Participant Withdrawal

- In the unlikely event that a participant is discharged alive from the hospital prior to 3 days after enrollment, all study medications will be stopped.The participant will remain in the study and will be followed for outcomes.
- If a patient is tranfserred to the hospital ward from the intensive care unit, the study drug will continue while the patient is in the hospital until 3 days.
- If the clinical team decides to give the participant vitamin B1 for clinical purposes, the study drug will be continued (including thiamine) as long as the total maximum dose of vitamin B1 is ≤1,500mg/day. 1,500mg day is a standard dose for Wernicke's encephalopathy at many institutions and has not been associated with any increased harm.
- If a participant withdraws from the study, further administration of study meds will be stopped. Data collected prior to withdrawal will be maintained and the patient will be followed for outcomes, but additional data will not be collected.

4.5 Specimen collection procedures

4.5.1 Timing and volume of blood draw

All participants will have a blood samples collected at four time-points. Blood will be obtained by venipuncture, or from an existing venous or arterial catheter.

Specimen Collection Time Points

1. T1=0 hrs (just before study drug administration)
2. T2=24 hrs (+/- 4 hrs)
3. T3=48 hrs (+/- 4 hrs)

4. T4=72hrs (+/- 4hrs)

4.5.2 Specimen samples
At the T1, T2, T3, and T4 time points, blood will be sent for complete serum creatinine and a venous/arterial blood gas to measure lactate. These tests will be performed by the clinical laboratory at each site. As many of these laboratory tests are commonly obtained for clinical purposes, these tests do not need to be repeated if a result is available from the clinical care of the participant within 4 hours of the time point.

In addition to traditional clinical markers, 20ml of blood will be obtained for future biomarker analysis (including inflammatory biomarkers, markers of endothelial function, and markers of mitochondrial function), and thiamine levels.

4.6 General Sepsis Management
Investigators should follow local sepsis management guidelines. No specific sepsis bundle is required by this study, however the early administration of antibiotics, maintenance of a mean arterial pressure ≥65mmHg with a combination of volume resuscitation and vasopressors, and early source control are recommended—as detailed in the Suriving Sepsis Guidelines.[39] Elements of sepsis care should be reported on the online case report form (CRF).

5. OUTCOMES
5.1 Definitions
5.1.1 Primary Outcome
The primary outcome will be creatinine change over the first 72-hours after enrollment with a focus on the 72-hour creatinine measurement.

5.1.2 Key Secondary Outcomes
- Incidence of Acute Renal Failure
- Length of ICU stay
- In-hospital Mortality
- Other biomarkers of renal injury (Serum cystatin C, NGAL, and KIM-1)
- Peripheral blood mononuclear cell mitochondrial oxygen consumption

5.2 Safety
5.4.1 Definitions
The following definitions will be used[40]:

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

Serious adverse event: any untoward medical occurrence that at any dose requires 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: a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

5.4.2 Specific adverse event data collection
To assess specific and potentially serious adverse events that may be related to the study medication, we will collect data on the following:

Serious Adverse Event	Definition
Serious allergic reaction	Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Allergic reaction should be related (or suspected to be related) to the study medicaiton

5.4.3 Adverse Event Reporting

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

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

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

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

The planned sample size is based on the proposed primary outcome. In this longitudinal repeated measures study design, we have 4 time points, and are interested in measuring the effect of the intervention (thiamine) on the mean level of creatinine at the last time point (72-hours). We hypothesized that at 72-hours, the estimated mean difference (placebo-thiamine) would have similar magnitude as the pilot study's [4] observed mean difference (about 0.51). We used a linear mixed-effects model to estimate the parameters of the variance-covariance structure of the repeated measures data and used these estimates in obtaining the effect estimate of the mean difference at each of the 4 time points, with emphasis on 72-hours. We simulated the data using the estimated variance-covariance components from the pilot data which 0.19 for within-subject variance, and 1.3 for between-subject variance, and the estimated mean differences for the 4 time points from the pilot data. These data were put through a linear mixed effects model where linear contrasts were used for estimation at each time point. We then computed the non-centrality parameter and the corresponding F-statistic value. Together with the numerator and denominator degrees of freedom, the estimate of power at each time point was derived. Through different iterations of sample size, at N=80 (40 patients in each arm), we obtained a power of 0.80 at 72-hours. This method of power analysis for linear mixed-effects model was published in 2000.[41] To account for drop-out and to

ensure adequate power at the end of the trial, we will plan to enroll a total of 88 patients (44 per arm).

6.2 Statistical analysis plan

6.2.1 General considerations

The statistical analyses and reporting will adhere to the CONSORT guidelines.[42,43] All tests will be two-sided, a p-value < 0.05 will be considered significant, and all confidence intervals will have 95% coverage. All analyses will be conducted on a modified intention-to-treat basis only including participants receiving at least the first dose of the study medications. In a double-blind trial, this approach is unbiased while increasing precision.[44] The two groups will be compared in relation to baseline characteristics using descriptive statistics.

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

6.2.2 Creatinine at 72-hours

Assuming no unbalanced potentially confounding variables (as would be expected in this randomized trial), we will compare repeated measures of creatinine levels at each time point (0h, 24h, 48h, 72h) between arms using repeated measures analysis. A compound symmetry covariance structure will be used. If a patient receives renal replacement therapy or dies before any time point, creatinine levels will be imputed by carrying forward the last known value before the event. Study site will be controlled for as a fixed-effect in the regression model.

6.2.3 Lactate at 72-hours

Assuming no unbalanced potentially confounding variables (as would be expected in this randomized trial), we will compare repeated measures of lactate levels at each time point (0h, 24h, 48h, 72h) between arms using repeated measures analysis. A compound symmetry covariance structure will be used. If a patient receives renal replacement therapy or dies before any time point, lactate levels will be imputed by carrying forward the last known value before the event.

6.2.4 Receipt of Renal Replacement Therapy

Fisher’s exact tests will be used to compare the incidence of renal failure requiring renal replacement therapy during the index ICU stay. This outcome will be truncated at 60 days if the patient remains alive and in the ICU at that time.

6.2.5 In-hospital mortality

In-hospital mortality will be analyzed using survival analysis. Results will be presented with Kaplan-Meier curves and the groups compared using the log-rank test.[45] Hazard ratios with 95% confidence intervals will be obtained using Cox’s proportional hazards models.[46] The proportional hazards assumption will be verified by visual inspection of the Kaplan-Meier curves and statistically by including a product term (i.e. “interaction”) between the treatment group variable and the natural logarithm of time in the model.[47] If the proportional hazards assumption is not met, only the Kaplan-Meier curves and the p-value from the log-rank test will be presented. The patient will be considered to have survived their hospitalization if they remais alive and in the hospital at 60 days.

6.2.6 Length of ICU stay

Length of ICU stay will be compared between groups using Wilcoxon Rank Sum tests. As in the above analyses, this will be truncated at 60 days.

6.2.7 Cellular Oxygen Consumption
Basal and maximum cellular oxygen consumption by peripheral blood mononuclear cells will be compared using a t-test

6.2.7 Other biomarkers of renal injury
Other renal injury biomarkers (cystatin C, NGAL, and KIM-1) will be measured at enrollment and 24-hours and compared using repeated measures analysis to account for within subject correlation. Days alive and free of renal failure, frequency and duration of renal replacement therapy, and hospital mortality will be compared using t-tests and chi-square tests where appropriate. Basal and maximum cellular oxygen consumption will be compared using a t-test. Analyses will be conducted on a modified intention-to-treat basis, including only those subjects who receive a dose of study drug.

6.2.8 Subanalyses
A pre-planned subanalysis of the primary outcome will be performed in the group with baseline thiamine deficiency. Thiamine deficiency will be defined as a plasma vitamin B1 level ≤ 7 nmol/L as has been previously described.[48] The trial is not powered to detect subgroup differences, hence this analysis will be considered exploratory and hypothesis-generating.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data collection process
Data collection will be the responsibility of the principal investigator. Creatinine and lactate levels will be obtained from blood draws at 0hr, 24hr, 48hr, and 72hr. Most other variables (i.e. demographics, sepsis characteristics and laboratory results) will be obtained prospectively from the electronic medical record up until the time the patient dies or is discharged from the hospital. Data will be entered directly into the online database software (see below).

7.2 Variables
Will be provided on the online CRF.

7.3 Data quality and validity
Several measures are taken to assure data quality. They are as follows:

1) Database access is restricted to team members specifically trained in data entry for this study. In addition, team members will only have access specific to their roles and only data abstractors will have the capacity to enter/change data entries.

2) The REDCap Cloud database is specifically designed to maintain data integrity by preventing unintentional changes or lost data. Servers back up all data on a nightly basis with redundant systems. The REDCap data management system is fully HIPAA-compliant and includes a complete audit-trail for data entry validation. For additional details, see below.

3) Our group has a full-time database manager who will oversee the database and maintain quality. They will perform weekly data checks evaluating for any missing data or other concerns. Weekly reports will be generated on all missing data elements and feedback provided directly to the data abstractors on any issues that are identified. The weekly reports will allow for accounting of all data in real-time and allow for direct feedback to data abstractors such that future recurrences of missing data entry will be minimized. Of note, all missing data will be coded indicating the reason for being missing.

7.4 Data storage and security

The database application we will use is REDCap Cloud (https://www.redcapcloud.com/). REDCap Cloud is a professional database that provides a user-friendly interface with capacity for easy statistical interface and is endorsed by the National Institutes of Health. The principal investigator and other members of the Center for Resuscitation Science are experienced with REDCap. The REDCap Cloud data management system is secure, fully compliant with all regulatory guidelines, and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, participant confidentiality will be safeguarded. All members of the research team will be required to complete standardized training in REDCap cloud, which will be documented within the software.

The consent form and other trial documents for each participant will initially be stored in a secure, locked place. Following completion of the trial, documents will be maintained for a period of at least 2-years per FDA regulations (or longer depending on local IRB guidelines).

8. ETHICAL CONSIDERATIONS

8.1 Risks and Benefits

8.1.1 Potential benefits

Potential Benefits to Individual Subject: Assuming our hypothesis is correct and our results are comparable to those previously published, individual patients enrolled in our study and randomized to the treatment arm will benefit from the attenuated risk of kidney injury. All patients participating in this study, including those in the placebo arm, may see a future benefit from knowledge gained since many patients who survive an initial episode of sepsis will have a future admission for sepsis.

Potential Benefits to Society: Septic shock remains a highly morbid clinical condition for which there is no specific therapy. Assuming our hypothesis is confirmed, our study will provide strong support for the widespread adoption of Thiamine therapy for patients with septic shock. This, in turn, will significantly improve patient outcomes and potentially reduce the global burden of death due to septic shock.

8.1.2 Potential harms

Study Drug

Vitamin B1 – Vitamin B1 (thiamine) has an excellent safety profile. The only reported potentially serious side effect is an extremely rare anaphylactic reaction (1:250,000 cases) and this might not even be of issue with the current manufactured version of thiamine in the United States. The risk of an anaphylactic reaction was assessed with a vitamin complex dispensed in Europe and it is not known if thiamine was the actual offending agent. However, the 0.0004% theoretical chance of an adverse reaction seen in the European study is incredibly low. In a series of 989 patients in the United States who received intravenous thiamine, none had an anaphylactic reaction and the only reported side effects were minor consisting of transient local irritation, or in one case pruritus (0.093%).50 At BIDMC (approximately 600 inpatient beds), thiamine is provided liberally for patients with nutritional deficiency – for example, BIDMC has administered intravenous thiamine in over 8,000 separate patient encounters from 2002 until present. Despite this heavy usage, no adverse reactions have been reported.

Blood Collection

Most participants will have existing venous or arterial catheters in place and we will be able to collect blood from these ports, essentially eliminating the risks associated with blood collection. In the rare

case that a participant does not have an indwelling line, the risk of venipuncture is extremely low, and will not exceed the risk of clinical blood draws the participant will already be receiving.

Loss of Confidentiality
The risk of a privacy and confidentiality breach for all screened and enrolled patients will be minimized at multiple levels. After enrollment, trained research assistants will abstract all of the required data prospectively under the supervision of a research nurse, fellow, or senior investigator. All data will initially be recorded on a paper case report form, which will be stored in a locked file cabinet in a locked room while not in use. Two research assistants will independently enter the data into the secure online database (REDCap). In compliance with HIPPA privacy and security regulations, REDCap contains multiple levels of security including data safety (e.g., restricted access to fields), user safety (e.g. password authentication access), application security (e.g., role-based access to features, access audit trails), and hosting service security (e.g., firewall, secure sockets layer). Taken together, these features ensure access control, audit control, data integrity, user authentication, and transmission security. Data from the present trail will be set up in REDCap to ensure exported datasets are de-identified as defined in the HIPAA privacy regulation [45 C.F.R. §164.514 (b)(2)]. A 21 CFR Part 11 compliance document is available upon request from the software's creators. All study investigators have taken the CITI program exam and are well versed in patient confidentiality.

9. MONITORING

9.1 Institutional Review Board (IRB)
The study is approved by the IRB at BIDMC (#2018P000204).

9.2 Data Safety and Monitoring Board (DSMB)
A DSMB comprised of three physicianswith critical care experience in the management of septic pations will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. An independent biostatistician/epidemiologist will prepare all DSMB reports. The DSMB members will be chosen such to avoid any financial or intellectual conflicts of interest. The DSMB will review deidentified data after every 30 participants are enrolled to assess for safety; unless there are group differences necessitating unblinding (as determined by the DSMB), the DSMB will be blinded to treatment groups. The trial will continue while the DSMB review data. After each review, the DSMB will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. Criteria for recommending termination will be at the discretion of the DSMB and there will be no formal statistical criteria for termination due to efficacy or safety.

10 CLINICAL MONITORING PLAN
The detailed clinical monitoring plan has been developed and is available upon request. Subjects will be monitored throughout their hospital stay and will be immediately treated if any adverse events occur. All research procedures and monitoring will be conducted by experienced personnel, and almost all patients will be in the ICU given their potential comatose and critically ill state. Admittance to the ICU will permit closer observation and more detailed monitoring by clinicians familiar with the care and resuscitation of septic shock patients.

11. FUNDING
Funding for the present trial is provided by the National Institutes of Health, specifically the National Institure of General Medical Sciences.The funding agency will have no role in the design and

conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

12. DATA SHARING

Six months after the publication of the last results, all de-identified individual participant data will be made available for data sharing.[50] Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification of the data. All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent ethics review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Interested parties will be able to request the data by contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors.[49]

References

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