PROTOCOL TITLE:

Evaluating Vitamin C in Septic Shock: A Randomized Double Blind Control Trial

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VERSION HISTORY

Version #	Version Date	Summary of Changes	Consent Change?
1	11/08/2017	Initial Protocol	N/A
2	11/21/2017	Biobanking is convenience sample only.	Yes
3	02/16/2018	Add fluid collection during standard of care BAL or Tracheal Aspirate for assay. Add additional references to risk section.	No
4	03/20/2018	Update names for DSMB, infection disease testing	No
5	07/24/2018	Update UMMC MICU to UMMC ICU	No
6	05/30/2019	Update withdrawal conditions	No
7	07/18/2019	Clarification to inclusion criteria; add Essentia Health as external site location	Yes
8	08/06/2019	Clarification to inclusion criteria (units of procalcitonin)	No
9	3/17/2020	Add option of eConsenting	No

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ABBREVIATIONS/DEFINITIONS

- BAL: Bronchoalveolar lavage
- BDAC: Biostatical Design and Analysis Center
- DSMB: Data and Safety Monitoring Board
- ICU: intensive care unit
- LAR: legally authorized representative
- TA: Tracheal aspirate
- Vitamin C: also known as ascorbic acid

STUDY SUMMARY

Study Title	Evaluating Vitamin C in Septic Shock: A Randomized Double Blind Control Trial
Study Design	Phase 3, randomized double-blind
Primary Objective	Evaluate effect of Vitamin C supplementation on survival in patients presenting with septic shock
Secondary Objective(s)	Evaluate effect of Vitamin C supplementation on resolution of shock
Research Intervention(s)/ Investigational Agents	Vitamin C (ascorbic acid)
IND/IDE # (if applicable)	N/A: Exempt
Study Population	Patients admitted to ICU with septic shock
Sample Size (number of participants)	Approximately 140 Approximately 70 per group (study drug or placebo)
Study Duration for Individual Participants	Up to 4 days, plus a Day 28 chart review with no participant interaction

1.0 Objectives

1.1 Purpose:

This is a randomized, double-blind, placebo-controlled clinical trial to compare Vitamin C versus placebo for patients presenting to the ICU with a diagnosis of septic shock.

Specific Aim 1: Determine if patient survival is improved with the use of Vitamin C.

Hypothesis Aim 1: Compared to placebo, moderate-dose Vitamin C will improve survival.

Specific Aim 2: Determine whether Vitamin C improves secondary clinical outcomes including but not limited to: duration of vasopressor therapy, duration of ICU stay, lactate clearance, and organ failure.

Hypothesis Aim 2: Compared to placebo, moderate-dose Vitamin C will improve clinical outcomes.

Specific Aim 3: Identify individual and clinical characteristics associated with responses to Vitamin C.

Hypothesis Aim 3: Specific characteristics exist that can identify those with a greater chance for a therapeutic response.

2.0 Background

2.1 Significance of Research Question/Purpose:

Sepsis is defined as life threatening organ dysfunction caused by a dysregulated response to infection. Sepsis and septic shock, the latter defined as persistent hypotension refractory to volume resuscitation and requiring vasopressor therapy to maintain adequate blood pressure, are common reasons for admission to the intensive care unit[1]. It is estimated that approximately 1 million Americans are diagnosed every year[2]. Despite concerted efforts focused on early recognition and stabilization of septic patients, mortality rates of patients admitted with septic shock remain high at 25%-50%[1] and survival is still associated with significant comorbidity[3]. This is of particular importance when sepsis-associated organ failure is prolonged, as the extended recovery period keeps patients vulnerable to adverse effects associated with prolonged ICU stays (e.g., myopathy, delirium). All of this highlights the need for novel effective therapies.

The main tenets of therapy in sepsis have been focused on early recognition, hemodynamic stabilization (correction of low blood pressure) and antimicrobial therapies. This involves early aggressive fluid resuscitation and vasopressor therapy (medications such as epinephrine which increase blood pressure), as well as early empiric antibiotic therapy and effective source control, the latter of which consistently correlates with survival[1,3,4]. Over the last two decades, most efforts to improve outcomes in sepsis have focused on resuscitation at the systemic level (e.g. blood pressure and cardiac output goals). Unfortunately, although several 'targeted' systemic resuscitation studies have shown promise during early studies (e.g. early goal directed therapy protocol[5], large-scale confirmatory studies of these treatments have been disappointing[6-10]). As a result, renewed attention has shifted towards identification of sepsis-induced abnormalities at the cellular and microcirculation level, such as dysfunction of mitochondria (the parts of cells which generate energy), endothelium (the lining of blood vessels which plays a role in controlling blood supply to tissues) and cellular oxygen metabolism despite adequate tissue blood supply[11].

Therapies aiming to correct oxygen metabolism, mitochondrial, and endothelial dysfunction have been dubbed "metabolic resuscitation"[12,13].

2.2 Preliminary Data:

Clinical studies of Vitamin C in critical illness date back 40 years[13]. More recent work in burn victims had demonstrated that Vitamin C supplementation was able to reduce fluid volume resuscitation to achieve hemodynamic (blood pressure) resuscitative goals[14]. Subsequent studies have demonstrated trends in decreased multiorgan failure support with broad antioxidant supplementation[15].

Further studies expand on the positive therapeutic potential of Vitamin C supplementation for sepsis. Fowler et al performed a Phase 1 randomized controlled trial of 24 patients admitted to the Intensive care unit with sepsis. Subjects received either low dose or high dose Vitamin C supplementation or placebo. Whilst the primary endpoint of safety and tolerability was met, most intriguing was the finding of a dose dependent improvement in SOFA score (surrogate for organ failure) as well improvement in inflammatory markers[16]. These findings were expanded upon by Zabet et al in 2016, who tested the effect of Vitamin C supplementation had upon vasopressor dose and duration of therapy. Twenty four patients admitted to a surgical ICU were randomized to receive placebo or Vitamin C supplementation. Not only did the cohort receiving Vitamin C experience significant reduction in dosing requirement and duration of therapy there was a significant reduction in mortality[17]. Most recently a before-and-after retrospective study of a combination of Vitamin C, thiamine and hydrocortisone supplementation in severe sepsis and septic shock patient also demonstrated a remarkable survival benefit in the supplemented patients compared to usual care[18].

Together, these preliminary results suggest that supplementation of Vitamin C may play an important role in the metabolic resuscitation of patients with septic shock. While intriguing, the limitations of the non-blinded before-and-after study combined with a history of false-positive results in adjuvant therapy trials in sepsis (e.g. activated protein C administration[19,20], atorvastatin administration[21]) temper these dramatic results, and further validation via prospective analysis is justified and necessary to clarify a possible novel therapeutic approach.

2.3 Existing Literature:

The pathophysiological abnormalities in sepsis and septic shock which are the targets of metabolic resuscitation include diminished vascular tone (improper relaxation of the muscles controlling blood vessel diameter), porous microvascular junctions caused by barrier dysfunction (leakiness of the cell layer surrounding blood vessels), and inappropriate leukocyte adhesion with activation of inflammation microvascular coagulation cascades (dysregulated immune system activation)[22]. While the pathophysiology of sepsis is multifaceted, metabolic derangements are common, including several antioxidant vitamin levels which invariably fall during sepsis[23]. These deficiencies include Vitamin C (Vitamin C), and thiamine with low levels of each correlating with progressive multiorgan failure and death[24-27]. Emerging clinical data (as outlined in section 2.2) as well as laboratory findings suggest that supplementation of Vitamin C during septic shock may play a key role in metabolic resuscitation by resolving microvascular dysfunction[28,29], augmenting vascular tone, and providing a cofactor for catecholamine (steroids such as adrenaline) synthesis[30].

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

First outcome endpoint for Specific Aim 1: all-cause mortality measured at ICU discharge.

Second outcome endpoint for Specific Aim 1: all-cause mortality measured at 28 days post Day 0.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Outcome endpoint for Specific Aim 2: Difference in clinical outcomes between both groups at ICU discharge. Specific secondary endpoints may include, depending on power and final enrollment:

a. Duration of vasopressor therapy post administration of Vitamin C (or placebo). Conclusion of vasopressor therapy will be defined as the time point when pressors are stopped, following which they are not restarted for 24 hours.
b. Duration of ICU stay post administration of Vitamin C (or placebo).
c. Time to lactate clearance post administration of Vitamin C (or placebo). Time of lactate clearance will be defined as the first time point at which measured lactate level drops below the normal level as defined by the measuring laboratory.
d. Rate of lactate and procalcitonin clearance over 24, 48 and 96 hours following Vitamin C (or placebo) administration (in patients for whom values are available). Defined as the change in lactate and procalcitonin level from the initial measurement to the measurement at the designated time point if available, or closest measurement within 4 hours of the designated time point.
e. Duration of mechanical ventilation post administration of Vitamin C (or placebo). Cessation of mechanical ventilation will be defined as the time of extubation following which re-intubation is not required for a full 24 hours.
f. Incidence of need for renal replacement therapy during the 96 hour drug administration period
g. Change in serum creatinine at 24, 48, 72, and 96 hours after Vitamin C (or placebo) administration compared to level at enrollment (in patients for whom values are available). The measurement closest in time to the designated time-point (within 12 hours) will be used. Patients who are dialysis-dependent at baseline or are currently receiving renal replacement therapy will be excluded from this endpoint.
h. Change to SOFA and/or APACHE scores from initiation of Vitamin C (or placebo) as measured at 24, 48, 72, and 96 hours.
i. Total intravenous fluid administered from presentation until various intervals (3 hours, 6 hours, and 24hours), until resolution of shock, and from Vitamin C (or placebo) administration until resolution of shock.
j. Effect of standard of care medications including corticosteroids as an sub-group analysis.

Outcome endpoint for Specific Aim 3: In general, clinical and biochemical characteristics associated with Vitamin C responsiveness will be examined. Specifics include:

a. Assessment of whether time from onset of septic shock to receipt of Vitamin C (or placebo) influences effectiveness of Vitamin C therapy.
b. Treatment effects as associated with or without initial presentation of inflammatory response

- Fever versus hypothermia
- Leukocytosis versus leukopenia
- Surgical versus medical source control

c. Biobanking of blood specimens for future assessment of:

- Vitamin C levels
- Cytokine and chemokine levels
- Danger associated molecular patterns (DAMPS)
- Markers of necroptosis (RIP1 and RIP3)
- Mitochondrial DNA and RNA for gene expressions
- Genetic features favorable to Vitamin C therapy

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

This is a multi-center, randomized, double-blind, placebo-controlled clinical trial to compare Vitamin C versus placebo for patients presenting to the ICU with a diagnosis of septic shock.

The investigational product is parenteral Vitamin C (also known as ascorbic acid); 1000 mg bolus IV followed by a continuous infusion at 250 mg/hr or matched placebo.

4.2 Drug/Device Handling:

Investigational Drug Services and the research pharmacist will handle all drug requirements including randomization, blinding, and dispensing. Study clinicians as listed on the Delegation of Authority Log will manage ordering and prescribing. Clinical care staff will administer study drug/placebo infusions to the participant.

Vitamin C is available parenterally in a single dose 50 mL vial (500mg/mL). One 50 mL vial will be drawn up into five x 10 mL syringes containing 5000 mg of Vitamin C. These syringes will be refrigerated, protected from light, and given 9 day beyond use dating per USP 797 as a low-risk compounding product. The 5000mg/10mL pre-drawn syringes will be utilized in the preparation of the continuous infusion.

<u>Total, Approximate Infusion Amounts</u>

- 6875mg in first 24 hours, including initial bolus
- 6000mg per day for all following 24 hour periods
    - 7000mg maximum allowable per 24 hour period
- 25 grams per study period

Total infusion daily amount would be approximately 6000mg. More or less than 6000mg is acceptable given prioritization for septic shock treatment, body habitus concerns, or other clinically relevant decision made by the study clinician with the treating clinician. No more than 7000mg daily would be allowed, as a maximum amount of infusion. There will be no minimum amount provided as the infusion could be stopped early.

1. Preparation of Active Drug
    a. The Vitamin C infusion will be prepared as a 10mg/mL continuous infusion by adding the 5000mg (10 mL) syringe of Vitamin C to a 500 ml Normal Saline infusion bag.
    b. The Vitamin C 5000mg/500mL infusion bag will last 20 hours when running at the study rate of 250 mg/hour (25 ml/hour). The 1st infusion bag will last less than 20 hours since the initial bolus is administered from the infusion bag.
    c. The infusion bag will be given a 24 hour expiration date. At room temperature and protected from light, Vitamin C is compatible in Normal Saline for 24 hours.
    d. The infusion will be protected from light with an amber bag. IV tubing will not be protected from light.
2. Preparation of Placebo
    a. The placebo infusion bag will be a 500 mL Normal Saline Infusion bag.
    b. The placebo infusion will be protected from light with a brown bag in the same manner as the active drug. IV tubing will not be protected from light.
3. Drug Administration
    a. The 1000mg bolus (100 ml) of active drug or placebo will be administered over 30 minutes from the active drug or placebo continuous infusion bag, respectively.
    b. After the initial bolus is complete, the continuous infusion will run at a rate of 250mg/hr (25 mL/hour).
    c. A dedicated line for the Ascorbic Acid or placebo infusions is not required. IV compatibility with other IV solutions should be checked per standard of practice.
    d. Infusion can be administered peripherally.
    e. Infusion will be stopped if the participant transitions to comfort care measures only

4.3 IND/IDE:

Not applicable, exempt. There is no intent to report to the FDA for a new indication, nor intent of this study is to support a significant change in the advertisement of Vitamin C. The administration of Vitamin C or placebo in septic shock population does not significantly increase risk or decrease acceptability of risk with its proposed route of administration and dosing.

5.0 Procedures Involved

5.1 Study Design:

This is a multi-site, randomized, double-blind, placebo-controlled trial comparing a regimen of moderate-dose (6000 mg per day) Vitamin C supplementation versus placebo for the treatment of patients presenting to the ICU with septic shock. Both groups will continue to receive all other standard of care measures for septic shock as clinically indicated. Groups will be enrolled and receive study drug/placebo for 4 days (96 hours) or until 24 hours post-last pressor dose, whichever is sooner.

5.2 Study Procedures:

When a potentially eligible participant is identified, the PI or other clinical research team member will approach the individual with floor staff permission and coordination to explain the research.

After signing the consent and completing eligibility procedures, IDS will be notified. IDS will perform randomization and dispense appropriate study drug/placebo infusion materials.

Infusions must be started within 24 hours post-presentation of septic shock. Those participants who consent but cannot start an infusion within 24 hours will still follow all research procedures related to data collection except for banking of biospecimens.

Participants randomized to Vitamin C will receive IV parenteral Vitamin C; with a 1000 mg bolus to start and followed by a continuous infusion at 250 mg/hr for four days or off pressors for 24 hours, whichever is sooner. Placebo will be given as a matched infusion on the same schedule.

Chart review will take place at 24 hour time periods (Day 0, 1, 2, 3, and 4).

Blood draws for biobanking will occur at Day 0, 1, and 3 (0, 24 and 72 hours), 25 mL on day 0, and then 20 mL on days 1 and 3. Patients discharged from the hospital will not undergo blood draws following discharge. Those still in the hospital, any floor or unit, will have blood drawn if clinically possible. Blood draw will be based on a convenience sample only. Blood draw will only be done when study clinician is available and when time is available for processing and transporting. Not all participants will have all, or any, blood draw done for biobanking.

Excessive biospecimens will be collected during routine, standard of care procedures for use in refinement of an infectious disease laboratory analysis. Remaining sputum, tracheal aspirate, bronchoalveolar lavage specimens, blood, serum, urine or other bodily fluid will be obtained from standard of care procedures and shipped to an outside laboratory for assay refinement.

The biospecimens will be used to compare concurrently collected specimen culture growth with those findings from this specific assay. This assay is FDA-approved, and will only be used to refine the algorithm that defines something as pathological. It is not meant to diagnose or aid in any way treatment procedures. Results from this assay refinement test will not be shared with the patient, their provider, or placed in their medical record. Specimens will be collected on a convenience sample only.

5.3 Follow-Up:

28 days following Day 0 (time of first infusion), a chart review for final outcomes will be performed. Chart review will include both medical record data as well as CTSI's Clinical Data Repository to collect non-hospital mortality information and other clinical information that might not be available in the medical record.

	Screening[2] (-24 hours to +0 hours)	Day 0[3] (+0 hours)	Day 1 (+24 hours)	Day 2 (+48 hours)	Day 3 (+72 hours)	Day 4 (+96 hours)	Day 28
Septic Shock Identification[1]	X						
Consent	X						
Medical History	X						
Physical Exam	X						
Eligibility Review	X						
Study Drug or Placebo		X	X	X	X	X[4]	
Blood Banking Specimen[5]		X (25ml)	X (20ml)		X (20ml)		
Baseline Chart Review		X					
Daily Chart Review			X	X	X	X	
Follow-Up Chart Review							X

1: Identification is defined as: onset of shock if already in hospital OR presentation to hospital/emergency department
2: All screening procedures must be completed in 24 hour window between identification and infusion start
3: Infusion of study drug/placebo must happen within 24 hours of septic shock identification
4: Day 4 or 24 hours post last pressor dose, whichever comes first
5: Will occur at alltime points stated even if participant is off infusion but still in hospital. Only done when possible given clinician and time constraints.

6.0 Data and Specimen Banking

6.1 Storage and Access:

Blood will be obtained at three different time points (0, 24 hours, and 72 hours) and will be coupled with clinical care blood draws when possible. These samples will be stored in a -80°C freezer in lab space utilized by the PACCS division at the University of Minnesota for future analysis. Serum, RNA, and cell lysates will be separated and stored with study code only.

6.2 Data:

Specimens will be stored by study code. All study data will be associated with the specimen through the study code link.

6.3 Release/Sharing:

Data will be shared with other researchers who request it, under the following conditions:

- Requester provides protocol and IRB approval or Determination of Non-Human Subjects Research.
- Requester completes Data Use Agreement form as developed by the Health Information Privacy and Compliance Office at the University of Minnesota.
- Any data or specimen can be shared but all identifiers will be stripped. Requester will not be provided with link between identity and study code.

7.0 Sharing of Results with Participants

Not applicable. No results will be shared with participants.

8.0 Study Duration

Each participant will be on the study drug for up to four days. There is a final data collection time point at 28 days but no participant interaction is needed for this; it will be chart review only.

It is expected that it will take up to 1.5 years to enroll all study participants. It is expected that it will take up to 2 years to complete all study procedures and data analysis.

9.0 Study Population

9.1 Inclusion Criteria:

- Capability to provide written consent from participant or legally authorized representative (LAR) if the participant is unable or incapacitated due to severity of illness.
- Age ≥ 18 years
- Septic shock as pragmatically defined as:
    - Order for intravenous antimicrobials with either procalcitonin > 2 ng/mL within 24 hours of enrollment OR other clinical suspicion of infection or confirmed infection AND
        - Hypotension requiring vasopressor therapy, despite fluid resuscitation of at least 30 mL/kg ideal body weight AND
        - Lactate > 2 mmol/L 24 hr prior to enrollment AND

- Presence of sepsis defined as equal to or greater than 2 SIRS criteria and/or acute increase in qSOFA score of 2 points or more.
    - *SIRS criteria: 1) Temperature greater than 38° or less than 36° Celsius. 2) Heart rate greater than 90 beats per minute. 3) Respiratory rate greater than 20 breaths per minute OR arterial carbon dioxide tension less than 32 mmHg. 4) White blood cell count greater than 12,000 cell/µL, less than 4,000 cells/µL, OR band cells greater than 10% of the total white blood cell population.*
    - *qSOFA: 1 point each is assigned for: 1) systolic blood pressure below 100, 2) respiratory rate greater than 22, and 3) mental status not at baseline.*

9.2 Exclusion Criteria:

- Unable to start infusion within 24 hours of septic shock identification
- Currently pregnant or breastfeeding
- Patient to receive comfort measures only
- Cardiac Arrest
- Cardiovascular Surgery patients receiving prophylactic peri-operative antibiotics < 48 hours post-operation
- Participation in another study involving an investigational product within 30 days of the baseline visit
- Allergy to Vitamin C
- History of nephrolithiasis
- History of G6PD deficiency
- ESRD patients, transplant eligible on dialysis currently taking vitamin C supplementation
- Clinical course that treating clinician decides would preclude safe participation

9.3 Screening:

Potential participants will be identified by clinic staff at sites identified in Section 23.0. Once identified, the study team will review the medical record for basic eligibility and research opt-out status. Once the medical record has been reviewed, the investigator or coordinator and floor staff will approach the potential participant to explain the study.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☒ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☒ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.

☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

10.2 Adults lacking capacity to consent and/or adults with diminished capacity to consent:

Patients who are in septic shock often have brain dysfunction or encephalopathy. This dysfunction is part of the sepsis syndrome and medical care often involves the use of surrogates to make urgent medical decisions for them. The same surrogates will act as an LAR for this study so they will be well versed in what this means, consenting to something for the participant. Those experiencing brain dysfunction are often those who are experiencing more severe symptoms of septic shock and thus, are those who would be most benefited by the use of this treatment. There are no additional risks for enrolling participants who cannot consent for themselves.

10.3 Additional Safeguards: Not applicable.

No individuals (pregnant women, neonates, nor prisoners) required additional safeguards will be enrolled.

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented:

Approximately 140 (70 per group) will be enrolled for an expected 124 (62 per group) for the final analysis. As there is a rolling startup for the sites, it is expected that the largest number of participants will be from Fairview Southdale.

12.0 Local Recruitment Methods

12.1 Recruitment Process:

Potential participants will be recruited from the ICU by study investigator after identified by intensivist physician on the floor or made aware of septic patient elsewhere in the hospital. Recruitment will take place at any time when a study investigator or trained coordinator is available for a consenting discussion and eligibility review. The investigator or other study team member will review opt-out status and medical records for basic eligibility before approaching the candidate. Once basic eligibility has been established, the investigator or coordinator and floor staff as necessary will approach the candidate.

12.2 Source of Participants:

Potential participants will be sourced from all patients admitted to the adult ICU with diagnostic criteria for septic shock who have not opted out of research. It is expected that participants could present to the ICU from either the emergency department or another floor or unit in the hospital. Please see Section 23.0 for list of sites.

12.3 Identification of Potential Participants:

Potential participants will be identified by the intensivist physician and study clinicians as those already admitted to the hospital for septic shock or suspicion of septic shock. Medical records will be reviewed for research opt-out status.

12.4 Recruitment Materials:

Not applicable. No recruitment materials to be used.

12.5 Payment:

No compensation or other payment will be provided to participants.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances:

Participants can be withdrawn from the infusion or the study completely at any time by the study clinician or their personal clinician for:

1. A serious adverse event suspected to be related to the study drug.
2. Any suspicion that further involvement would jeopardize medical care.
3. Transitioning to comfort care measures only

Unblinding of treatment allocation will occur when such information would be critical to the ongoing care of the participant. Researchers will work with IDS and the research pharmacist on the unblinding procedures.

13.2 Withdrawal Procedures:

At the point of a participant-requested withdrawal, the infusion will be halted and no further direct interaction will occur. Data collection including Day 28 medical record review will still be conducted.

13.3 Termination Procedures:

Data will continue to be used and analyzed after withdrawal or termination.

14.0 Risks to Participants

14.1 Foreseeable Risks:

Vitamin C risks: Vitamin C has a good safety profile as evidenced in the background section of this proposal. Participants will be educated about potential adverse effects as part of the consent process, including inquiries about daily use of multi-vitamins, nutritional supplements or powders, or anything else that might contain vitamin C. Investigators will include known comorbidities that could affect vitamin C risk including kidney stones, diabetes, and cancer in their review of general eligibility. These would not make somebody automatically ineligible but would factor into a general clinical decision on whether or not it would be safe to enroll them.

There are no known major risks at the dose used in this study, approximately 6,000 milligrams per day to a total culminated dose of 25 grams. A tolerable upper limit of 2,000 milligrams per day oral administration was published in 2000[31]**.** At ingestions higher than 3,000 milligrams per day the most common adverse effect is diarrhea, but can include nausea, vomiting, heartburn, stomach cramps, and headaches. Clinical studies using dosing greater than 100,000 milligrams per day intravenously[14,] administered as quickly as 1g/min[32] have been well tolerated, with no indication of harm following administration[14]. Hyperoxaluria and oxalate nephropathy have been reported in an individual status post renal transplant who previously had taken daily vitamin c supplementation whilst on dialysis[33]., though additional studies suggest that ascorbic acid does not contribute to renal oxalate stone formation[34,35].

Blood draw risks and IV: The risks associated with the blood draw include minimal discomfort, and/or bruising. In very rare cases, a small blood clot can form at the site of the needle insertion. The risks of the intravenous line are similar to a blood draw but because it is kept in the vein for a longer period of time, the risk of bruising and discomfort are slightly higher. All participants will have an peripheral or central intravenous line catheter placed for standard of care medications and will have clinical blood drawn on at least a daily basis. Any research blood draw or IV placed for the infusion will be coupled with clinical care when possible.

General participation risks: There is always the risk for a breach of confidentiality during the course of any research study.

14.2 Reproduction Risks:

Not applicable. Because Vitamin C in doses exceeding RDA recommendations is classified as category C in pregnancy (insufficient evidence to determine safety), pregnant and breast-feeding women will be excluded.

14.3 Risks to Others:

Not applicable. No risk to others.

15.0 Potential Benefits to Participants

15.1 Potential Benefits:

No direct guaranteed benefit to individual participants.

16.0 Data Management

16.1 Data Analysis Plan:

Patient baseline characteristics will be summarized and presented using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Treatment groups will be compared using two-sample t test for continuous variables and Chi-square test for categorical variables.

Analysis plan for Aim 1: Mortality rates between treatment groups will be compared using Chi-square test. Logistic regression model will be used to model the probability of death. Model will include treatment group and covariates determined by the investigators to impact mortality and/or those that are significantly different between groups at baseline.

Analysis plan for Aim 2: Clinical outcomes at ICU discharge will be compared between groups using two-sample t test for continuous variables and Chi-square test for categorical variables. Multivariate linear and logistic regression analysis will be performed for continuous outcomes and dichotomous outcomes respectively to adjust for covariates.

Analysis plan for Aim 3: Correlation analysis will be conducted to examine the association between clinical characteristics and Vitamin C responsiveness.

Intention-to-treat analysis will be used. Analysis will be performed using Statistical Analysis Software (version 9.3, SAS Institute Inc., Cary, NC).

16.2 Power Analysis:

The trial will enroll enough participants to demonstrate a 20% mortality difference in between treatment groups. Based on this information, 124 patients, 62 patients in each arm, would be needed to have an 80% power to detect a 20 % decrease in hospital mortality between the two groups with a two-tailed alpha error of 0.05. To account for potential dropout of participants, planned enrollment will be 70 per arm, 140 total.

16.3 Data Integrity:

REDCap™ data will be periodically reviewed by the regulatory specialist and project manager or coordinator; to occur at the request of the PI and before final analysis occurs. Standard data quality checks will be run using REDCap™'s integrated programs.

17.0 Confidentiality

17.1 Data Security:

All standard confidentiality procedures will be observed for this study and all research staff will be trained on protocol and GCP standards before they will be allowed contact with participants or data. Any paper data, source or CRF or logs, will be kept in locked research offices. All University of Minnesota data protection policies will be reviewed and followed.

Electronic data will be entered into a REDCap™ database, which uses a MySQL database via secure web interface with data checks used during data entry to ensure data quality. REDCap™ includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be hosted on the secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap™ and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap™ will be restricted to the members of the study team by username and password.

Access to data exports will be limited with no member of staff given the ability to download full data sets; all exports will be limited to the "remove all tagged identifier fields" option when setting user rights. Additionally, all dates will be marked for date-shifting during the export process.

REDCap™ data files will be exported to shared drives housed under HIPAA-compliant AHC-IS servers on the MedDerm (\\med.ahc.umn.edu\med)(N:) shared drive.

Any other identifiable electronic data, including logs, will be stored on Box. Access to the study files on Box will be limited to those members of the study team.

Spreadsheets of data in aggregate form (summary statistics only, no individual data) will be electronically kept and may be electronically transmitted between study investigators only.

Documentation of research involvement will be recorded in the participant's medical record. Consents will not be placed in medical record.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

While there will be no planned full, interim data analysis, the PI will periodically review data for completeness and to ensure that all procedures are being followed as detailed in the protocol. The assigned Regulatory Specialist or CTSI monitor will also perform periodic quality assurance monitoring at any point requested by the PI or otherwise mandated by local policy.

18.2 Data Safety Monitoring.

Participants enrolled in this study will be monitored for adverse outcomes including adverse drug reactions, hospitalizations, and death. In addition, participants will be given contact information for the study team and will be counseled to report any adverse effects for duration of therapy. The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events. All adverse and serious adverse events will be discussed with the PI within 48 hours for standard assessments (causality, expectedness, severity, and seriousness). IRB and other regulatory reporting requirements will be reviewed by study staff and followed with assistance of the Regulatory Specialist assigned to the study.

A Data Safety and Monitoring Board (DSMB) will be formed as a part of this study. Two physicians, with adequate clinical knowledge of the subject matter and research experience, along with one statistician will make up the DSMB. No member will have any affiliation with the study or data other than their responsibilities on the DSMB. Members will sign a Statement of Confidentiality.

<u>DSMB members:</u>

- Craig Weinert, MD MPH: Associate Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine
- Greg Beilman, MD: Professor, Department of Surgery
- Ashley Peterson, PhD: Assistant Professor, Division of Biostatistics, School of Public Health

<u>Safety Data Collection:</u>
All adverse events will be collected with particular attention paid towards those listed as most frequent risks of Vitamin C, including nausea, vomiting, headaches, stomach cramps, and headaches. Adverse events will be collected on case report forms as completed within REDCap™. Three different types of events will be differentiated: those expected and/or related to study drug, those expected and/or related to any other research procedure, and those expected

and/or related to underlying septic shock condition. All safety data will be collected from the time of consent to the final 28 day chart review visit. All events will be followed until either resolution or 30 days-post last study visit, whichever comes first.

Mortality Data Review:
All mortality data will be collected when site becomes aware of death. This could happen while participant is still in hospital or during the 28-day final chart review or at any other time point. All deaths will be reviewed by PI and Regulatory Specialist for IRB prompt reporting guidelines.

Information Provided to DSMB
Reports to DSMB will be prepared in coordination with an independent statistician from BDAC. Data provided includes:

- Cumulative
  - Safety data (including adverse events)
  - Primary outcome data for Specific Aim 1 (mortality data)
  - Primary outcome data for Specific Aim 2 (clinical endpoints)
- Since last DSMB meeting
  - Relevant IRB submissions, including Reportable New Information and Modifications
  - Monitoring reports

DSMB Meeting Schedule

- 6 Months Post First Randomization
  - All data will be sent to DSMB.
  - Case report forms and paper documents, including consents, will be reviewed by Regulatory Specialist or CTSI monitor. Monitoring reports will be made available to DSMB.
- Annually Post First Randomization
  - All data will be sent to DSMB.
  - Case report forms and paper documents, including consents, will be reviewed by Regulatory Specialist or CTSI monitor. Monitoring reports will be made available to DSMB.

DSMB Meeting Components
The DSMB members will be provided with data reports before the meeting date, with sufficient time to allow for review. Reports and all necessary information will be electronically provided to DSMB members through email. DSMB members will meet either in-person or telephonically/electronically as necessary to allow for clinical schedule restraints. The Regulatory Specialist will attend all DSMB meetings to compile minutes. This individual will also prepare all DSMB Summaries.

DSMB IRB Reporting
All DSMB Summaries will be submitted to the IRB per local guidelines.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

Participants will sign a consent form and a HIPAA Authorization which will detail what data and under what circumstances will be shared with research staff and non-research staff. Study procedures will be explained in full detail in the consent so that participants can make informed decisions before they enroll. The consent will also detail under which conditions any information may be shared with those outside of the internal research staff.

19.2 Access to Participants:

Participants will sign a consent and HIPAA authorization.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the subject or their insurance company.

20.2 Contract Language:

Not applicable.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

In-person consent will be obtained by the delegated research staff within the participant's private hospital room. It is expected that this will be the PI or a Co-I (all ICU clinicians) the vast majority of the time. This study will employ a nurse-coordinator who could assist with consenting. Any waiting period will only be for necessary clinical procedures; priority for clinical treatments will always take priority over research.

Consent may also be done using an electronic informed consent document (eICD). This will occur either in-person or by remote in conjunction with telemedicine. The eICD will be presented as a REDCap survey on a device provided by the research study or on a participant/LAR's personal device. The investigator will conduct the consent process with the participant/LAR via the telemedicine system by way of face-to-face video or via telephone if the LAR is unable to be physically present at the telemedicine site. The consenting investigator will review the consent document in the same manner as a paper consent document. The *UMN Medical School Department of Emergency Medicine Standard Operating Procedures - Electronic Informed Consent (eConsent)* will be followed.

All those consenting will be trained on the MacArthur Competence Assessment tool.

21.2 Waiver or Alteration of Consent Process:

Not applicable. No waiver or alteration of consent.

21.3 Non-English Speaking Participants:

Not applicable. Non-English speaking patients will not be enrolled.

21.4 Participants Who Are Not Yet Adults:

Not applicable. No individual under the age of 18 will be enrolled.

21.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

For those patients with known capacity issues who are already using a clinical surrogate or LAR to consent to clinical procedures, these individuals will automatically be consented using the LAR, including those who are currently sedated. For those patients with questionable capacity, the MacArthur Competence Assessment Tool will be used to assess their ability to consent. Study clinicians will work with floor staff to assess current clinical presentation to ensure that the recruitment and consenting procedures do not take place during any period of greater than normal (for septic shock) impairment. This could include, but is not limited to, periods of greater stress due to medical treatments or intake procedures. As part of the clinical staff caring for the patient, the study clinicians will have the greatest ability to understand current and up-to-date patient temperament, cognitive abilities, and treatments.

21.6 Adults Unable to Consent:

- Permission:

  In order of priority for acting as an LAR, the established healthcare power of attorney, spouse, parent, adult children, and then adult sibling will be included in the consent process to obtain permission for the research study. In the case that this disagrees with the current surrogate providing permission for clinical care, the clinical care surrogate will be used.

- Assent:
  Informal, verbal assent will be attempted on those participants who might have some cognitive ability to understand what is being asked of them. This will be a clinical decision made between the study investigator and floor staff and will only be a verbal discussion of what is already included in the consent. No script or written document will be used during the assent process.

22.0 Setting

22.1 Research Sites:

Identification, recruitment, screening, and research visits will all take place within hospital ICUs. All research procedures will take place in the participant's private hospital room.

23.0 Multi-Site Research

This is a multi-site study that will have a phased rollout at Fairview Hospitals and HealthEast Hospitals.

1. Fairview Southdale ICU: this will be the pilot site and the study will be started at this location first. The PI is the director of the ICU at this location.
2. Fairview UMMC ICU (includes MICU and SICU) and Ridges ICU: these sites will be secondary sites and will be initiated after Southdale.
3. HealthEast St. Joseph's Hospital ICU: this site will be last and require additional IRB approval from the local human ethics board. This site will only be initiated if additional recruitment is necessary. If and when the site is initiated and receives IRB approval, those documents would be submitted to the UMN IRB, if necessary.

4. Essentia Health: this site will require additional IRB approval from the local IRB. This site will be initiated once local-IRB is secured.

23.1 Study-Wide Number of Participants:

140 participants.

23.2 Study-Wide Recruitment Methods:

Each local site will rely on internal study clinicians and floor staff to identify candidates for the study.

23.3 Study-Wide Recruitment Materials:

Not applicable. No recruitment materials.

23.4 Communication Among Sites:

The study will employ a lead Regulatory Specialist who will coordinate all communication and regulatory efforts. Box will be utilized to manage study-wide documents so that team members can easily obtain the most current version of all documents. The Regulatory Specialist will manage IRB reporting at all sites and will work with the PI to ensure all non-compliance, adverse events, and other reportable events are reviewed and reported in accordance with local policies. There will be three IRBs involved, UMN, HealthEast, and Essentia Health.

All study data will be entered into REDCap™ with each site being assigned a specific group so that staff at one site cannot see participant data from another site.

23.5 Communication to Sites:

The PI, the Project Manager, and the Regulatory Specialist will work together to release site-wide communications. As the study begins enrollment at each new site, it is expected to have semi-often meetings (telephone or in-person) to ensure an efficient and appropriate start-up.

24.0 Resources Available

24.1 Resources Available:

This study will include a PI, several co-investigators, project manager, coordinator, and a regulatory specialist. Bedside nursing will be used to assist PI with clinical assessments as necessary and as available. In the case of any medical or psychological event, clinical staff will be immediately available for assessment or treatment.

All staff will be trained on research procedures before being allowed access to participants or data. All training will be documented within the regulatory binder and reviewed by the PI and project manager.

As this study will involve staff at several sites, the Project Manager and the Regulatory Specialist will coordinate training efforts as required by each site.

This study will take place at Fairview Southdale, UMMC, Ridges, HealthEast St. Joseph's and Essentia Health in Duluth.

25.0 References

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