Author’s response to reviews

Title: The Vitamin C, Thiamine, and Steroids in patients with Sepsis (VICTAS) Protocol: A prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial

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Author’s response to reviews:

We would like to thank the reviewers for their thoughtful review of our manuscript and deeply appreciate their comments and suggestions.

Reviewer 1: No comments.

Reviewer 2:

C1. The inclusion and exclusion criteria section, what about a patient with fever or hypothermia?

R1. Thank you. We agree that fever and hypothermia are both potential indicators of infection. However, because abnormalities in temperature are absent in many patients with sepsis, we chose not to require abnormalities of body temperature in the inclusion or exclusion criteria.

C2. Data Collection and Data Analysis section, the primary outcomes were observed during the 30 days following randomization, but why "contacted by phone" at 180 days? Why observing "the mortality, physical, emotional and cognitive outcomes" at 180 days? Why not 30 days, 3 months, or 1 year? Please clarify.

R2: We agree that adding time points to the follow up would improve the granularity of the data we collect and might be informative. However, the budget for the trial requires us to be parsimonious in which data we collect and when. As you note, the primary outcome is ventilator and vasopressor free days (VVFDs) at day 30 following randomization. Similarly, follow-up on the key secondary outcome (mortality), and other exploratory outcomes, is limited to the 30 days following randomization.

As you have also stated, mortality as well as physical, emotional, and cognitive outcomes will be assessed at the 180 day follow up. We believe there are two important issues to address here; (1) the timing of follow up, and (2) who does the follow up.

(1) With regard to the timing of assessments (e.g. why not 30 days, 3 months, or 1 year), we acknowledge that any follow-up time point has “pros and cons”. However, for the physical, emotional, and cognitive outcomes, in general, 6 months is often judged to be the ideal time for follow-up because by 6 months, the transient effects of delirium and the cognitive fog that immediately follows ICU discharge are typically gone. As such, physical, emotional, and cognitive functioning observed at 6 months probably reflects, to a meaningful degree, a stable new baseline. For efficiency, we chose to assess mortality at the same time we assessed the long term neurocognitive outcomes. It may all be worth
mentioning that for sepsis, Prescott et al. (BMJ 2016; 353:i2375) have suggested that as many as one in five patients who survive sepsis, has a late death (out to 2 years) not explained by their health status prior to sepsis.

(2) The 180 day follow up is conducted by phone because we believe these assessments should be conducted by trained personnel with expertise in neurocognitive assessments as is the case with investigators at the "Critical Illness, Brain Dysfunction, and Survivorship Center" at the Vanderbilt University Medical Center. Training investigators at each contributing site to perform their own assessments would be expensive, very time intensive, and would not be feasible in the context of this short study. The Vanderbilt group is very well established, and not only has expertise in neurocognitive assessments, but has extensive expertise in conducting these assessments over-the-phone. Importantly, it is likely that in-person assessments would not be feasible as they require visiting patients in their homes, which are frequently a long distance from respective enrollment sites. As is detailed in the manuscript (page 15, paragraph 2, last sentence), by having one expert team do these long-term assessments, we ensure the consistency and quality of the assessments.

C3. As a multi-center clinical trial, how did you get the ethical support? Obtain ethical approval from each center, or other way?

R3. These are excellent questions. The approach to ethical approval for the trial overall was through a central IRB mechanism. In June of 2016, the National Institutes of Health released a policy mandating that NIH funded multi-center trials conducted in the United States use a single IRB structure. Though our study is not funded by the NIH, we chose to follow their policy in hopes of capitalizing on the efficiencies tied to its intended purpose. The purpose of this policy is as follows:

“The National Institutes of Health (NIH) is issuing this policy on the use of a single Institutional Review Board (IRB) for multi-site research to establish the expectation that a single IRB (sIRB) of record will be used in the ethical review of non-exempt human subjects research protocols funded by the NIH that are carried out at more than one site in the United States. The goal of this policy is to enhance and streamline the IRB review process in the context of multi-site research so that research can proceed as effectively and expeditiously as possible. Eliminating duplicative IRB review is expected to reduce unnecessary administrative burdens and systemic inefficiencies without diminishing human subjects’ protections. The shift in workload away from conducting redundant reviews is also expected to allow IRBs to concentrate more time and attention on the review of single site protocols, thereby enhancing research oversight.”

The details of the policy can be found here: https://grants.nih.gov/grants/guide/notice-files/not-od-16-094.html. In short, the central IRB reviews, and if appropriate, approves the research protocol and consent forms. Other sites seeking to participate in the trial must formally “agree to rely” on the central IRB and are referred to as “relying sites”. We have added a statement in the manuscript (page 8, line 2) to emphasize this reliance agreement.
The relying sites conduct a local context review of the protocol and consent forms to identify any site-specific issues/concerns or local regulatory issues that need to be addressed in the consent and/or protocol. Any necessary changes are then submitted from the relying site back to the central IRB for review. Protocol changes require approval of the central IRB as well as approval from the VICTAS Executive Committee. To date, most local context issues in this trial have been managed in a site-specific section of the consent form. We have modified the protocol only to allow different sites to monitor glucose in different ways.

C4. Vitamin C, Thiamine, and Steroids, each get a special ethical approval or together? Please clarify.

R4. Approval was sought from the central IRB at Johns Hopkins University for the combined use of Vitamin C, thiamine, and hydrocortisone, as it is the effect of this three-drug cocktail on patients with sepsis that we seek to test.

C5. When combined with three drugs, how to get the appropriate dosage?

R5. Thank you for this question. You are correct that it is not clear in the literature what the optimal dose is for any of the three drugs in the setting of sepsis. There is certainly a precedent for the use of hydrocortisone at a dose of 50 mg IV every 6 hours from several randomized controlled trials. However, the best dosing regimen for thiamine and vitamin C are not clear. Our dosing is based on the trials by Marik et al. (Ref #17) and Donnino et al. (Ref #49), and with insight from co-authors Fowler and Levin, both of whom are leading authorities on Vitamin C. However, as we have emphasized in the limitations section of the manuscript (page 26, paragraph 2, second limitation, line 14 from top of page), there is limited phase II data to guide dosing. If we see a benefit using the dosing regimen used by Marik et al, the next logical question will be which component of the cocktail is most important and at what dose is the greatest benefit observed (page 26, paragraph 2, last complete sentence on page). In contrast, a negative result to the trial could raise questions about inadequate dosing. These are limitations we have acknowledged.

C6. What are the possible drug interactions and adverse events among these drugs? How to deal with them?

R6. We do not know of any significant interactions between the three drugs other than the potentially beneficial synergistic effects detailed in the introduction of the manuscript (bottom page 4 – page 6). However, we have a structured process for reporting adverse events and it is possible that any significant negative interactions, were they to occur, would be identified in review of these events. The details of adverse event reporting are on pages 16 – 18.

If there is suspicion of a significant adverse event related to drug interaction during the study, it would be managed by stopping the study drugs and reporting the event in accordance with our
adverse events reporting protocol. We have emphasized this detail on page 18, lines 7 – 8 in the revised manuscript.

C7. This clinical trial used three drugs simultaneously, respective mechanism of action is completely different, how to evaluate the clinical effect of drugs? Synergy or superposition? How to clarify the mechanism?

R7. Thank you. As we have mentioned in the discussion, this is an important limitation of this study (page 26, paragraph 2, fourth limitation, 6th line from bottom). We will not be able to say with any level of confidence which component is most effective. Our approach is to first clarify if the combined regimen improves outcomes. If it does, the next step would be to clarify which of the three components, or combination of components, is most important. We have described in the introduction (bottom page 4 – page 6) our understanding of the mechanism by which each drug may improve patient outcomes.

C8. Exclusion Criteria should include upper age limit.

R8. We agree that age has been demonstrated to be an important variable in predicting outcomes over time. However, because the primary outcome of the study is a short-term outcome (VVFDs at day 30 after randomization), and because this is a randomized trial in which age should be evenly distributed between groups, we did not define an upper age limit as an exclusion. However, we will certainly report the age distribution of patients enrolled in each arm of the trial so we will be able to detect any disparity were it to occur.

Reviewer #3: No comments required response.

Peer Review: The Vitamin C, Thiamine, and Steroids in patients with Sepsis (VICTAS) Protocol: A prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial

General comments

This protocol publication describes a study planned to address the question of whether the combined therapy of intravenous vitamin C, thiamine and hydrocortisone provide clinically meaningful outcome benefits for the treatment of patients with sepsis and in particular vasopressor dependent and/or respiratory support dependent sepsis.

C9. Since the publication of a small before and after single centre study which demonstrated a very large effect size using this treatment regimen the critical care community globally has been
polarised between those who wish to implement this so-called metabolic resuscitation of sepsis and those who consider the findings implausible. Therefore, this is a key clinical research question which will be addressed by these investigators.

Although as they state there are several other randomised trials recruiting or in set up trying to address the same question this study will be the largest.

My comments below are all positive & I do not have any recommendations to improve this manuscript further.

R9. Thank you! We greatly appreciate your time and detailed consideration of this manuscript.

Major comments

Although the research questions is not novel as it was brought to attention globally by the publication mentioned above & as mentioned many other similar trials are underway the adaptive study design is a novel approach.

The background section clearly defines the scale of the sepsis problem and the biological rationale for each component of the regime. The aims of the study are clearly stated.

The outcome measures and justification for them are well described and are appropriate. Particularly novel will be the detailed late follow of neuropsychological outcomes of sepsis survivors.

The target population is appropriate as are the eligibility criteria and represent those that most clinicians would wish to target with this therapy if it is proven beneficial.

The allocation concealment & randomisation procedures described are robust and the study will benefit from being multi-cantered.

Although it's a phase 3 efficacy study the trial is pragmatic in design allowing local clinical practice part from the protocolised drug regime. This will make the study results more generalisable.

The outcomes measures are clinically meaningful, clearly defined and objective to measure.

The tertiary outcomes will add more interesting and useful information as will the vitamin C pharmacokinetic modelling - particularly as by the authors own admission they are jumping to this phase 3 study without doing a phase 2 dose finding study. There is therefore a chance that the intervention is unsuccessful due to inadequate dosing as all participants receive the same dose.
However, the study which has prompted all the investigations used the same protocol & found the exceedingly large effect size. At least if that were to be the case the pharmacokinetic information would be able to suggest if dosing is inadequate.

Adaptive trial designs are regularly discussed by critical care trialists & are very topical including the use of Bayesian analysis however they are rarely embarked on in practice due to the challenges of predicting funding requirements, complexity of the statistics etc…

This trial design is especially important for this research question as the community will be eager to implement the strategy if there is proven benefit given the low risk & cost and the volume and severity of illness of the target population.

The descriptive of the multiple interim analyses & rules for stopping or continuing are logical and sensible however I do not have sufficient statistical expertise to advise whether the statistical tests at each time point are correct.

The adaptive design allows early stoppage if clear benefit thus preventing unnecessary wastage of research resources, costs & exposing more participants to usual care who may benefit from the intervention while at the same time allowing progression to a large sample size to be confident more subtle benefits are not missed by a study that is to small. Again, given the factors mentioned above even small advantages would probably be worth standardised implementation into guidelines.

Data collection is adequately prescribed visually on the GANNT chart & handling of missing data is appropriate as is monitoring to minimise this.

Minor comments

The writing is clear, and the manuscript is well organised following the layout of the SPIRIT guidelines for trial protocols.

The title is adequately descriptive of the study.

IRB approval is confirmed and the references are relevant and timely.