Reviewer’s report

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

Version: 0 Date: 13 Jan 2019

Reviewer: Anton Krige

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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.

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.

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.

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