Author's response to reviews

Title: SodiUm SeleniTe Admistration IN Cardiac Surgery (SUSTAIN CSX(R)-trial): study design of an international multicentre randomized double-blinded controlled trial of high dose sodium-selenite administration in high-risk cardiac surgical patients

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Author's response to reviews: see over
Dear Professor Altmann, dear Professor Furberg, dear Professor Grimshaw and dear editors,

Please find attached the revised version of the manuscript entitled “SodiUm SeleniTe Adminstration IN Cardiac Surgery (SUSTAIN CSX®-trial): study design of an international multicentre randomized double-blinded controlled trial of high dose sodium-selenite administration in high-risk cardiac surgical patients”, which we would like to submit as an original revised contribution to the journal “Trials”.

We were grateful for the opportunity to improve our paper and very much appreciated the valuable and encouraging suggestions given by you and the reviewers. Please find attached our revised manuscript and the point-by-point reply to the two reviewers. We hope our work now complies with the high standards of the journal.

Thank you for considering our work.

Sincerely yours,

Christian Stoppe, MD and Daren Heyland, MD
Editorial requests:

1. Please replace ‘BD’ with ‘BM’ in the Authors’ Contributions section.

Response: Done

2. Please update the additional file title and legend section.

Response: Done

Referee #1:

Reviewer’s report:

The authors present a study protocol of using high dose sodium-selenite in cardiac surgical patients in a multicentre randomized double-blinded trial.

As we know is sodium selenite a potent radical scavenger, but there a few data on using selenium perioperatively. Therefore this study is justified and important an may gain new knowledge in this field.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Response: We appreciate the valuable comments given by referee #1

Referee #2:

The protocol is well written and considers many factors, which will impact on the quality of the trial. There are in my opinion a few issues, which should be discussed:

- Beside approval by the ethic committee the trial possibly should also be sent to a FDA-like institution of the according country.

Response: The present study has already been approved by Health Canada and the “Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)” in Germany. We will include this information in the methods section:
The present study (study protocol, patient information and informed consent) is approved by the ethic committee of RWTH Aachen University (Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen, ethic vote EK 249/13) and Queens University (Kingston, Canada). Furthermore it has been approved by Health Canada and the “Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)” in Germany. Written informed consent from the patient and treating anaesthesiologist or surgeon will be obtained before enrolment in the study.

- It is not obvious to the reader why a pilot is performed. It seems more appropriate to elaborate a very detailed protocol before starting the trial in the different centers. If the authors insist on this pilot will data of these patients be included in the analysis of the following large trial?

Response: We thank the reviewer for pointing out this obvious misleading explication. The present protocol has been reviewed, discussed and presented on several meeting with experts in the field of cardiology, cardiac surgery, anesthesia and nutrition. Nevertheless we aim to confirm the feasibility of the planned study with respect to:

1) Recruitment of trial patients. Successful recruitment will be defined as >2 patients per month per site on average. A recruitment of 2-3 patients/month is considered as reasonable given the high numbers of competing studies in the field of cardiac surgery, missed patients, and consent failure rates, all of which might limit our ability to enrol all of these potentially eligible patients. We expect to monitor success with recruitment throughout the study and make revisions to the recruitment procedures and eligibility criteria as necessary.

2) Adherence to protocol. Successful adherence will be defined as ≥90% of prescribed intervention being administered across all patients. Preliminary estimates of non-administration of the trial intervention are needed, along with experience with behavioural strategies that maximize exposure to the intervention.

3) Contamination. Success will be defined if <5% of patients have any non-study open-label intravenous selenium, in either group, during their hospital stay. Intravenous selenium is not currently the standard of care in any participating center but this outcome is important because contamination introduces risk of bias. A careful evaluation of the threat of contamination is key and mitigating strategies need to be identified.

After completion of the pilot study, we will analyse these data as a cohort without unblinding the patients’ randomization assignment in order to evaluate the feasibility of our study protocol. We will then go on with recruitment of patients for the definitive trails and roll the pilot study into the group to group analysis of the definitive trial. We now have include this section in the manuscript.
It is well known that anesthesia as well as sedation on the intensive care unit can impact on the outcome (volatile anesthetics, propofol, opioids, dexmedetomidine, etc.). It is highly recommended to develop an according protocol for all centers.

Response: We appreciate this valuable suggestion. During our last meeting we have intensively discussed the issue with the cardiovascular surgeons and anaesthesiologists. However, given the small differences between institutions and overall consensus about anaesthesia in cardiac surgery between the members, we have decided to leave it to the discretion of the attending physician. However, we will carefully revise these thoughts and try to standardize some key procedures (such as use of volatile anesthetics etc.,...)

- A data safety monitoring board is crucial and should be established.

Response: We thank the referee for this valuable comment. Indeed we have not yet established a data safety monitoring board, but will do so after initiation/extension to the definitive trial. We now have concluded this information into the present manuscript: “While a data safety monitoring has not yet been established for the pilot trial, it will be implemented for the definitive trial.”

- Which institution will be involved in the monitoring of the trial?

Response: The monitoring of sites will be performed by the Clinical Evaluation Research Unit (CERU) at the Kingston General Hospital, Ontario, Canada (for the Canadian sites) and by the Clinical Trial Center (CTC) Aachen at RWTH Aachen University, Germany.

We now have included this information in the methods sections.

- Based on the complex character of the study it is highly recommended to include a statistician.

Response: We totally agree with this suggestion. Andrew Day (listed as co-author on the manuscript) has performed the sample size calculations and is responsible for the statistical analysis.