Author’s response to reviews

Title: Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial

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Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial.

Dear Professor Doug Altman,

We are pleased to resubmit the revised version of the above-mentioned manuscript. We very much appreciated the constructive suggestions and comments of the editor and the reviewer. We have addressed each of their concerns as outlined below. In addition, we made some updates and changes regarding the study screening tools and authors’ names and institutional affiliations. In particular, we added one author (KP), as he will help us with the laboratory analysis. Moreover, we will now use the 3D-CAM for delirium screening (a revised version of the CAM) and the CAM-S for the quantification of delirium severity (instead of the delirium index). I hope our manuscript now complies with the high standards of *Trials*.

Yours sincerely,

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Comments of referee 1:

• “Major remarks: 1. The null hypothesis is not clearly stated.”

Thank you for bringing up this concern. We have added the following sentence on page 11; paragraph over study outcomes; primary endpoint: “Hence, the null hypothesis states that there is no difference between both groups in the incidence of POD (yes/no) during the first 5 postoperative days”.

• “Major remarks: 2. One problem with xenon anesthesia is the depth of anesthesia and postoperative awareness. This will be assessed by BIS monitoring, though the indicated levels of xenon are quite low (less than 1 MAC). Both xenon and sevoflurane seem to be dosed quite low in the respective subsets.”

Thank you for this important note. We have mentioned in the Methods-section that in both groups, anesthetic concentrations will be titrated according to the clinical observation of vegetative signs for the depth of anesthesia (including heart rate (HR), blood pressure, sweating, etc.) and to the instantaneously registered EEG-monitoring in order to reach a bispectral index (BIS)-value between 40-60.”

Moreover, all patients will be screened postoperatively, one day after ICU-discharge, for the occurrence of intraoperative awareness. This will be performed using the Brice questionnaire.

The following secondary study endpoint has been added to the current protocol:

Page 13: “Incidence of intraoperative awareness as detected by the use of a structured Brice questionnaire [41] that will be performed one day after ICU discharge.”

The concentrations of xenon and sevoflurane that are suggested in our study protocol are based upon our previous experience with both agents in two randomized controlled trials. In none of these trials, patients reported awareness.

In on-pump coronary artery bypass surgery, we previously reported the use of 41% Average xenon concentration (vol%) or 1.0 Average sevoflurane concentration (Stoppe C et al. Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study. British Journal of Anaesthesia. 2013 Aug 14;111(3):406–16.)


• “Major remarks: 3. All patients undergoing cardiac surgery will be enrolled. However, extensive valve surgery could hardly be compared with a patient with two-vessel disease in whom CABG has to be performed in terms of postoperative neurologic outcome.”
We totally agree with the referee regarding this comment. Therefore, we will use a stratified randomization procedure in which the patients will be randomized in two different strata using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (Stratum I: EuroSCORE ≤ 3; Stratum II: EuroSCORE > 3. This was already outlined on page 6 under the paragraph of randomization.

• “Major remarks: 4. Postoperative analgesia should be indicated in view of the potential postoperative hyperalgesia after use of remifentanil.”

We are very grateful for this remark. We have added the following sentences to the paragraph referring to intraoperative analgesia (page 9) “After completion of surgery, the interventional treatment will be stopped, and a bolus of IV piritramide 0.2 mg∙kg⁻¹ will be given. Patients will be transferred to the ICU under mono-sedation with propofol.”

In addition, we describe postoperative analgesia now more clearly than in the previous version. The following text is added on page 6; Intensive care unit treatment: “On the ICU, analgesia will be achieved with a continuous infusion of piritramide, supplemented by systemic acetaminophen (1-2 g, administered IV every 8 hours) during the first postoperative day. Standard tracheal extubation and patients discharge criteria will be applied”.

• “Major remarks 5. Anesthesia is extensively described. However, what about the anesthestic during cardiopulmonary bypass? Xenon will certainly not be continued. What impact has this on the anesthetic management?”

During the cardiopulmonary bypass period, the investigational treatment (xenon or sevoflurane) will be discontinued in both groups and replaced with a target-controlled infusion of propofol that will be titrated according to the BIS-monitoring. This is illustrated now more obviously on page 9: “During the CPB period, the investigational treatment will be discontinued in both groups and replaced with a target-controlled infusion (TCI) of propofol with calculated plasma concentrations of 1-2 µg∙ml⁻¹ that will be titrated according to the BIS-monitoring. After completion of surgery, the interventional treatment will be stopped, and a bolus of IV piritramide 0.2 mg∙kg⁻¹ will be given. Patients will be transferred to the ICU under mono-sedation with propofol.” We have also added the following sentences on page 10; latest paragraph over cardiopulmonary bypass: “Furthermore, propofol TCI will be stopped and the investigational treatment will be re-administered”.

• “Minor comments 1. Cisatracurium will be administered during induction of the anesthesia. However, no indication is provided concerning further curarization.”

Page 9: “Cisatracurium will be administered at the induction of anesthesia. Further curarization will be left upon the discretion of the attending anesthesiologist.”
Handling Editor comments:

Thank you for your comments. Below you will find point-to-point answer to your concerns.

1. “The central panel of Figure 1 is not well rendered, and I am not clear what the almost circular arrows are meant to represent. Please amend to make comprehensible.”

We revised the figure illustrating the study visits and screening tools.

2. “Exclusion criteria, "lack of informed consent" cannot be an eligibility criterion. An inability to give informed consent is OK.”.

We did correct the sentence on page 6 as follows: “Inability to give informed consent”.

3. “Inclusion criteria. I do not like the term “Dutch proficiency”, it is rather subjective. Better to say able to read and understand trial material (literature).”

Page 6: We replaced the term “Dutch proficiency” with the following sentence: “Able to read and understand trial materials”

4. “Analysis plan. The primary analysis appears to be Fishers exact test. Is that correct? Much better (and more standard) to use adjusted logistic regression analysis.”

We have forward this question to our statistician Steffen Fieuws, PhD.
His answer: "The test we were planning was not the Fisher’s exact test, but a test based on the exact common odds ratio for a 2x2 table (Mehta, C. R., Patel, N. R., and Gray, R. (1985), "On Computing an Exact Confidence Interval for the Common Odds Ratio in Several 2x2 Contingency Tables," Journal of the American Statistical Association, 80, 969–973.).

However, since one of the sensitivity analyses is based on multiple imputation (which is not straightforward to perform for exact tests), we decided to follow the advice of the reviewer and use the asymptotically valid logistic regression as primary analysis. Hence, the sentence referring to the primary analysis (page 15 has been rewritten as”: For the primary outcome, the incidence of POD, a logistic regression adjusting for the stratification variable EuroScore will be used to compare both groups.

In addition the following words have been added on page 16; “Using a two-sided test for the detection of differences between proportions (with alpha=5% and applying a continuity correction)”
5. “If multiple imputation methods are planned, then give details about what method is to be used; e.g. ICE. Also what is a "non-evaluable" patient? I am unfamiliar with this term...a missing value?”

Steffen Fieuws: “A non-evaluable patient is a patient for whom an evaluation of POD was not possible. Note that the analysis based on the multiple imputation is (only) a sensitivity analysis for the primary analysis. Nevertheless, we have added more detailed information on the imputation model. The sentence dealing with the multiple imputation has been rewritten as follows:

“Second, a multiple imputation approach will be used imputing a POD value for the non-evaluable patients, with as imputation model a logistic regression fitted in both groups separately (Puma et al. 2009) with baseline characteristics as categorical and continuous predictors. 20 imputed datasets will be created and results will be averaged appropriately.”

6. “Non-normally distributed data rather than not normally distributed data.”

Thank you, we have changed the term to non-normally.

7. “Time-to-event analysis is planned, using time from surgery until the occurrence of the event...what event? Please be more specific.”

We have now described the event more specifically on page 15 and 16: “Time-to-events (occurrence of POD) will be assessed from end of surgery until the occurrence of POD. Patients will be censored if they do not experience POD at the time of the last follow-up. To obtain the cumulative distribution curves for the POD times, Kaplan-Meier estimates will be used and groups will be compared using the stratified log-rank test.

8. “Please add more details about the longitudinal analysis; e.g. GEE or mixed-effects model etc.”

It has already been mentioned on page 16 that the used model is a multivariate regression model (i.e. a true multivariate model, not a multiple regression model, often mistakenly referred to as multivariate model in many biomedical article). Hence, this is nor a mixed-effects model, neither a model using GEE methodology. To avoid any confusion, we have added a reference.

In the paragraph on the linear model for the longitudinal measurements, the following reference is added (page 16): using a direct likelihood approach, (Molenberghs and Kenward, 2007, Section 14.4.)
9. “In my experience, the allowance for loss to follow-up in most RCTs is between 10-20%. The authors inflate the sample size by a very small amount only, how do they justify this?”

Indeed, in many RCTs with long-term follow-up, the loss-to-follow up is higher than 5%. However, in our study the primary outcome refers to the post-operative period of 5 days and not to a long-term endpoint. For the majority of patients the evaluation of POD during this postop period will be possible. Only for e.g. deceased patients, patients transferred to another centre and extremely sedated patients no POD evaluation will be available. Based on previous experience this percentage of patients will not exceed 5%.

10. “If sample size recalculation is to be attempted then the authors will need to provide details of how this is to be implemented, and importantly, by whom. An independent study data monitoring and safety committee (DMEC) should be established at study initiation and they should discuss and agree a strategy with the study steering committee. Please provide details.”

The following part has been added (page 16) in the description of the sample size re-estimation to provide more details:

“Since the SSR is fully blinded (i.e. the group allocation is not known), this analysis can be performed by a member of the study steering committee. Applying the assumed relative risk (relative reduction of the POD by 50%) on the overall POD rate, the power will be recalculated. For example, suppose that the overall POD rate after inclusion of 50 subjects in each group equals 24%, instead of the expected 30% (40% and 20%, respectively). Based on the assumed 50% relative reduction, this corresponds to 16% and 32% for xenon and sevoflurane, respectively, which would require 123 patients in each group instead of 91 patients to maintain 80% power. Based on this information, the study steering committee will decide on extending the accrual time. Note that based on the result of the SSR, the planned sample size will only be maintained or increased (not lowered).”
Editorial requests:

1) “Please ensure the title conforms to journal style for study protocol articles. The title should follow the format “________: study protocol for a randomized controlled trial.” Please note that the title in the submission system should match that of your manuscript.”

The title was already written according to the journal style

2) “Can you please add the email address of each author to the title page.”

Email address of each author has been added to the title page.

3) “Please include the date your study was registered with your trial registration number at the end of the Abstract.”

The trials registration date is mentioned now: (13-05-2015).

4) “Please include the names of all ethical bodies that approved your study in the various centres involved. If you do not wish to list them all in the Methods section, please include the list as an additional file and refer to this in the Methods section.”

The ethics committee at the University Hospitals Leuven, Belgium, approved the study. This has already been mentioned in the methods section. (Please see ethics committee approval documents, English and Dutch version)

5) “Please move the funding details from the competing interest section to the acknowledgement section.”

Funding and acknowledgment sections have been changed as follows:

Competing interests
SR has received an unrestricted research grant from Air Liquide, Belgium. MC received lecture and consultant fees from Air Liquide Santé International, a medical company involved in developing clinical applications for medical gases, including the noble gas xenon.

Acknowledgements
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6) “Please mention each author individually in your Authors' Contributions section. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.”

The author's contribution section has been re-written:
SR is the principle investigator of this trial. All authors contributed to the study design and protocol. LA and SR drafted the manuscript with contribution from MVDV, MC, GM, BM and KM. SF will perform the statistical analysis. KP will perform the laboratory examinations. All authors critically revised the manuscript draft, read and approved the final version.