Author's response to reviews

Title: The effects of continuous prostacyclin infusion on regional blood flow and cerebral vasospasm following subarachnoid haemorrhage. Design and rationale for a randomized, blinded, placebo-controlled, clinical pilot trial

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Author's response to reviews: see over
Dear Editors-in-Chief Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell

Thank you for qualified and constructive criticism. We found the comments from the reviewers most relevant and helpful and have improved the manuscript accordingly. Attached is our revised manuscript with highlighted changes and below a point-by-point response to the reviewers comments.

Sincerely,

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Point-by-point response

1. The paper and background focus on vasospasm, but the SAH trials community regard delayed ischaemic neurological deficit (DIND) as the key concept now. It is the DIND that results in neurological impairment, death and disability. Vasospasm is only the presumed cause of arterial narrowing as imaged by angiography, or altered cerebral blood flow velocity on Doppler ultrasound. Not all patients with vasospasm develop impaired perfusion or DIND. Not all with DIND have vasospasm. The antiplatelet effects of prostacyclin may also be relevant to preventing ischaemic deficits. This should all be mentioned in the introduction which should discuss the complex relationship between vasospasm and DIND in much more detail. The Dutch group in Utrecht have published a great deal on the topic, and I am surprised their work has not been mentioned at all.

We agree that although the complex relationship between vasospasm and DIND is mentioned in the discussion, the introduction should discuss this as well. Changes has been made accordingly in background.

2. DIND is a secondary outcome, and will be important in any phase III trial. The authors should cite the key paper by Vergouwen1 here as well and give the definition of DIND to be used in the study, and the process by which it will be determined for patients in the trial. This has been added in the section “outcome measures”.

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3. More details of the process of randomisation are needed. Exactly how will nurses access the list and how will security of the allocation list be maintained?
This is now described in the manuscript.

4. There is no stratification / minimisation to reduce imbalance, so will the analyses be adjusted for baseline covariates or not? If yes, how?
We will adjust the analysis of covariance with baseline covariates: age, previous neurological status and baseline values for mean rBCF in affected ROIS. This is now described in the manuscript.
If yes, how?
The randomization is not stratified.

5. What adverse events will be recorded? What will the process for reporting SARs and SUSARs be?
The section “Advers reactions” has been added to the manuscript, describing this issue.

6. Is there a data monitoring committee? If not, will there be any independent review of the accumulating safety data?
The trial is monitored by The GCP unit at Copenhagen University Hospital, however, we did not establish a DSMC due to the limited trial period and sample size, this is now described in the manuscript.

7. The rationale for the dose selected is extremely brief and should be expanded.
The rationale for the dose described in “discussion” has been re-written and expanded.

8. Which institution is acting as the sponsor for the trial?
Principal investigator is acting as sponsor (sponsor-investigator).

9. How is the trial funded, and what role does the funding source have in the trial?
The trial is funded by Copenhagen University Hospital research fund which is a non-for profit funding with no influence on the trial protocol, conduct or analysis whatsoever.

10. How will GOS be analysed (dichotomous, sliding dichotomy, ordinal or other)? There is a good case to use an ordinal analysis to maximise statistical efficiency
We thank the reviewer for this suggestion and we certainly will aim for an ordinal analysis which is now stated in the manuscript

11. The statistical analysis plan should be set out in much greater detail before the code is broken (though it does not need to be included at this stage, the journal may be sympathetic to publishing the SAP as a follow-on to the protocol).
We agree with the reviewer that an analysis plan should preferably be published before the database is analysed. We will aim to do that as a follow-on to th