Author's response to reviews

Title: Design and rationale for the 6S - Scandinavian Starch for Severe Sepsis/Septic Shock trial - A double-blinded, randomised clinical trial comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis

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Author's response to reviews: see over
To the editors of *Trials*

We are grateful for the opportunity to improve and resubmit our paper, and hope that you will find the revised manuscript suitable for publication in *Trials*.

The revised manuscript, which has been changed according to the issues raised by the reviewer, has been uploaded to the website as requested.

Our response to the comments from the reviewer is given below.

On behalf of the authors

Sincerely yours

Anders Perner, MD, PhD.

Response to prof. Goldsmith:
Thanks for your thorough review through which the manuscript has been improved.

1. Done

2. Thank you for the suggestion, but in some of the Scandinavian countries consent from both physician and next of kin is needed; in others consent from only next of kin is needed. Therefore we have kept AND/OR as it appeared in the original manuscript.

3. Done.

4. Done.

5. We appreciate the suggestion, but this is a pragmatic trial, so concomitant medication will not be registered except for the use of potentially nephrotoxic drugs. The use of nephrotoxic drugs will be included in the secondary analyses.

To clarify this, we have added a sentence to the revised manuscript (P6, p2, l10-12):
‘As this is a pragmatic trial, concomitant medication will not be registered except for the use of potentially nephrotoxic drugs (see below).

6. The DSMC will decide on statistical criteria as outlined in the Charter. To clarify this we have added ‘see Additional file 3 for details’ to P 7, p 2, l 10 of the revised manuscript.

7. The analysis plan was made according to ICH-CGP Guidelines E9, which states that the crude unadjusted analysis is the primary analysis. To clarify this we have added ‘according
to the ICH guidelines’ after the text describing the analysis plan, P 8, p 6, final line in the revised manuscript.

8. Done

9. Done

10. You are right, but these variables will be used to characterise the full trial cohort. We chose a 4-h window around the time of randomisation to get data from more patients. Most of these variables are recorded in 2-4 hour intervals, so using a 2-h period prior to randomisation would result in more patients without data. Clearly this precludes us from baseline comparisons of these variables.

11 – 14. Done

15 – 22. Thank you and sorry for the errors in reference. They have been corrected.

23. Done.

24. We appreciate your point. However, to us the term [deranged] implicitly refers to the value deviating the most from the stated normal reference values (i.e. 36°C ≤ temperature ≤ 38 °C; pulse ≤ 90/min; respiratory frequency ≤ 20/ min; PaCO2 ≥4.3 et cetera.) The term [deranged] is incorporated into the screening forms of the eCRF. To our knowledge, no investigator or trial staff has questioned the meaning of the term [deranged], indicating that the term is actually well understood in a screening context. After thorough consideration, we have thus chosen not to change the phrasing.

25. Done

26. In principle you are right, but the charter states ‘DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the 6S trial.’

Therefore, committee members have to judge - using the above definitions - if a member encounters conflicts of interest during the trial period. We find this to be a fair, and at the same time simple, construction.

27-30. Done