Author's response to reviews

Title: The use of LiDCO based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: Neck of femur optimisation therapy - targeted stroke volume (NOTTS)

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Author's response to reviews: see over
Professor Charlie Goldsmith  
Trials  

Dear Professor Goldsmith,

22nd August 2011

Re: MS: 1012666617527515  
The use of LiDCO based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: Neck of femur optimisation therapy - targeted stroke volume (NOTTS)

Thank you for the opportunity to revise our manuscript. I have detailed each response below. I have ‘tracked changes’ for all textual changes as requested, though I have taken the liberty of accepting all the minor formatting changes to make it easier to read. I can confirm that all of the authors have approved the changes made to the manuscript.

   Changed as requested.

2. P 2, p 2, l 2. Insert [concealed] between [generated] and [tables].  
   Changed as requested.

3. P 2, p 2, l 4. Rewrite as [> 65 years]. Include a space between the inequality and the number and insert the age units.  
   Changed as requested.

4. P 2, p 2, l 10. Insert [is determined by a blinded team of clinicians] after [stay].  
   Changed as requested.

5. P 2, p 3, l 1. Insert the date of registration as well as the date the first patient was randomized. P 5 claims that patients are being recruited; however, it does not mention the date of randomization of the first patient. Was the first patient randomized on September 9, 2009? Has recruiting ceased? If so, include the date the last patient was randomized.  
   Details added to P 5, p 2, l 3 and P11, p2, l5

6. P 3, p 1, l 2. Insert [United Kingdom [] between [the] and [UK] and []] after the latter.  
   Changed as requested.
7. P 3, p 1, l 7. Insert [likely] between [will] and [increase].
   Changed as requested.

8. P 3, p 2, l 4. Replace [significant] by [clinically important] or some such phrase, reserving
   significant for statistical judgments in clinical trials.
   Changed as requested.

9. P 3, p 2. These facts should be supported by suitable references if they are available.
   References added.

10. P 3, p 2, l 6. Suggest rewriting as [For these reasons most …] as more than one is mentioned.
    Changed as requested.

11. P 4, p 1, l 9. Does R(eference) 18 support all the points raised in the this p? If not, provide
    other Rs as well as it.
    Additional reference added.

12. P 4, p 1, l 9. Claiming the [never been studied] without a viable search strategy is not
    sufficient. This may be the authors’ opinions, and so should be toned down unless a recent
    published search can be cited.
    We have clarified that a repeat literature search based on Venn’s systematic review has
    been undertaken recently.
    Also P 4, p 2, l 2.
    Although we have not undertaken a formal systematic review, we can not find any
    published work on this. The closest is the work by Meyhoff, but that was ‘healthy’
    elective elderly. We have toned down the sentence to make this clearer.

13. P 5, p 2, l 3. Was this the same day the first patient was randomized? See 5.
    Details have been clarified (as for point 5)

14. P 5, p 3. Include the allocation ratio somewhere here. Presumably it is 1:1; if so, say so.
    Changed as requested.

15. P 5, p 3, l 4 to 6. Using the NHFS to stratify the patients looks as if there are
    exactly 2 strata: Low and High risk; however, this should be stated as 2 levels.
    Corrected – see below.
    Also, where do you put those with = 10%?
    NHFS is a discrete score and does not give a risk =10% so the groups can be split above
    and below 10%.

The stratification factor has not been considered in the analysis as it seems as if the NHFS is to
be used continuously and not as 2 categories that are constraints on the randomization.
NHFS is not used continuously – the two levels are NHFS predicted risks above and
below 10% respectively.
We have amended this paragraph: [To achieve equal numbers and balance of important
covariates, randomisation is in blocks of variable size and is stratified according to
predicted 30-day mortality (2 levels). The Nottingham Hip Fracture Score [22 - 24], is used to identify patients with low (≤ 10%) or high (>10%) risk of mortality within 30–days.

16. P 5, p 5, l 6. This statement seems incorrect. The study is not complete until the last patient randomized has been discharged (your primary outcome measure). Otherwise you will not have data on the last few patients and no mention has been made about a censored analysis. It would also be helpful to follow patients until discharge to record any adverse effects that may accrue during the trial and be recorded in their chart.

This has been corrected. [The study intervention is complete at the end of the surgical procedure, though all participants have a follow-up visit the next day to ensure no problems have arisen. The medical notes are reviewed following hospital discharge for in-hospital complications and medication use.] P5 final paragraph.

17. P 5, p 6, l 3 and 4. Subjects randomized should not be able to have you delete their fact/date of death (if it happens) and the date of their discharge as these are important to the proper analysis of your data.

However, other secondary data might be erased. It seems to this reviewer that the former 2 variables should be available for all who are randomized. It might be helpful to have ruling on this form your ethics committee, so as not to allow patients randomized to compromise your study credibility. See P 6, last p for more details where this is relevant. Allowing patients to opt out once randomized means you cannot do an intent-to-treat (ITT) analysis on your primary outcome.

We have clarified this. [Data on time to discharge and postoperative mortality are collected routinely and separate from this study. These outcome data are therefore available for all randomised participants.] P6, p1

18. P 6, p 1, l 2. Replace [significant] by [large] or some other suitable phrase.

Changed as requested.

19. P 6, last p, l 3 to end and p 1 on next P. Suggest having a selected use of the data, instead of complete withdrawal, ie, 1) death date and discharge date, 2) all other relevant outcomes, and then 3) the remaining data not used for the study outcomes.

In accordance with REC approval and the Data Protection Act, we are able to collect death / discharge date. We have amended as follows (P7 p1): [If the patient declines, date of discharge and postoperative mortality data are collected as part of routine clinical management and so will be available for analysis.]

20. P 7, p 2, l 1. Replace [parameters] by [variables]. A parameter is a characteristic of a distribution of a variable in a population and not another name for a variable in a sample, as used in this trial. Also P 7, p 4, l 6 and 7.

All changed as requested.

21. P 7, p 2, l 4. The manufacturer of LiDCOplus should be specified with a location.

Changed as requested.
22. P 7, p 2 and 3. Too many items are stated without references. Please try to cite suitable references for the things stated here.
   References added as requested.

23. P 8, p 1, l 4. Please cite the manufacturer’s guidelines.
   Reference added as requested.

24. P 8, p 3, l 7. Suggest replacing [significantly] by [clinically important].
   Changed as requested.

25. P 8, p 3. Are the discretionary interventions recorded? This could lead to serious co-interventions. If they are recorded, then there is a possibility to take them into account in the trial report.
   Yes, these are recorded, the text has been amended accordingly.

   Cited as requested.

27. P 8, p 5, l 4. Cite the pathway.
   This is a local clinical pathway and is therefore not citeable as such.

28. P 8, p 5, l 8 and 9. Is this report citable?
   Data from this audit have been published previously – the references are cited.

29. P 9, p 3. It is not clear that the stratification factor is considered in all analyses, since there is a lack of the correct analyses that take this into account. Also, no references are provided for unusually analyses. Consideration should be given to multiple imputation for missing data and suitable censored analyses for things like death and incomplete data. Sensitivity analyses will likely not be powerful enough to measure the impact of changes specified here. Any choices such as these should be documented with suitable references.

   We have simplified the analysis plan. The stratification at randomisation is to minimise imbalance in co-variates (30-day mortality high vs low) but the analysis is simply on the basis of the two groups – control and intervention.

   We agree with the reviewer that sensitivity analyses are not appropriate in this sample size and have removed reference to these.

   As detailed above we do not envisage incomplete data for the primary outcome measure due to the nature of clinical data recording.

   We have discussed the issue of the effect of pre-discharge death on the primary outcome at length with our statisticians. The analysis will be based on patients surviving to discharge. In hospital mortality is approximately 5% so for this sample size we would expect around 6 in hospital deaths in total. We do not feel that more complex analyses are necessary for such a small number of censored events.

   The paragraphs have been revised to:
[Data will be analysed by the research team in conjunction with a medical statistician, using latest versions of SPSS software. There will be no interim analysis.

From previous examination of the Nottingham Hip Fracture Database (which has over 7000 patients) it is expected that the primary outcome, length of stay (LOS), will be normally distributed following a log transformation. Following transformation these data will be analysed using ANOVA. The primary outcome measure is time until declared medically fit for discharge. This is expected to follow a log normal distribution so the log transformation will be used to normalize the data allowing the use of parametric tests. Following transformation these data will be analysed using ANOVA. Length of acute hospital stay, superspell (total time in hospital including rehabilitation) will be analysed similarly.

The secondary outcomes of complications, residence and place of discharge will be treated as categorical and differences between the groups will be examined using Fisher’s exact test or Chi Squared test. Mortality outcome will be analysed using Kaplan-Meier mortality curves and log rank tests, and further analysed using Cox regression to allow for covariates.

All secondary variables will the presented using appropriate descriptive statistics. In addition to the calculated values, confidence intervals and odds-ratios will be presented when appropriate. All clinical information including all adverse events will be presented in full. All secondary analyses will be interpreted with caution as the sample size calculation is based on the primary outcomes only. However, the level of power associated with secondary results will be investigated.]

30. P 9, p 4. These analyses also do not take the stratification into account and are more complicated than stated as a result. Software such StatXact can handle these analyse using stratification while SPSS can not currently.

As discussed above, the stratification is to minimise co-variate imbalance. The data are not being analysed according to strata and we apologise for the confusion in the previously submitted text.

31. P 9, p 4, l 11. Unpaired t test does not take the stratification into account. ANOVA could. This has been corrected.

32. P 10, p 2, l 3. Rewrite as [p = 0.05] rather than [p # 0.05].

We are slightly unsure what is meant here as the pdf has inserted # symbols. We have changed to p=0.05.

33. P 10, p 2. My use of PASS version 11 determined that a sample size of 60 per group would be needed, and the inflation for dropouts should be 60/0.9 = 66.6 or 67 before inflating for stratification. This reviewer suggests adding 1 to get 68 per group or 136 for the trial. If this is challenged, the authors should cite suitable software used to get their sample size, and a case why they did no take dropouts into account properly as well as the inflation for stratification.

We have corrected the typographical error and the rounding of SD.
Length of acute hospital stay in our unit is consistently around 17 days (SD 4.9 days), so to find a 3 day reduction in LOS in survivors would require 58 patients in each group with 90% power and p = 0.05.

34. P 10, p 3. This p has not mentioned ITT analysis. This means you have to analyse all who are randomized with no other criteria. Otherwise your testing is not valid. Other analyses could also be done and should be specified, i.e., as per protocol, etc.

This has been clarified:

[Safety set: All randomised participants who received LiDCOplus monitoring during surgery receive at least one dose of the study drug.

Full Analysis set: All randomised participants, who received LiDCOplus monitoring during surgery and for whom at least death and discharge date are available.

Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

Efficacy will be assessed on both the full analysis set and the per protocol set.

Safety summaries will be performed on the safety set]

35. P 10, p 6. Provide Rs for these.
   References added.

36. P 11, p 1. Provide dates either here or on P 2 or 5. See earlier issues.
   Date added as requested.

37. P 11, p 2, l 5. Replace [significant] by [important].
   Changed as requested.

   Changed as requested.

39. P 11, p 3. Mention the blinding of your team to get more credit for this with length of stay.
   We have added ‘Both these outcome measures are collected by members of the research team blinded to treatment allocation.’

40. P 11, p 3, l 6. Replace [significant] by [clinically important].
   Changed as requested.

41. P 11, p 5, l 2. Replace [significant] by [important].
   Changed as requested.

42. P 12, p 1. Suggest mentioning your choice of LiDCOplus again.
   Changed as requested.

43. P 12, p 2, l 1. Replace [significant] by [important].
   Changed as requested.
44. P 12, p 2, l 8. Suggest that you delete [significant].
   Changed as requested.

45. P 12, p 3, l 2. Replace [significant] by [high].
   Changed as requested.

A random sample of 10 Rs was checked for citation accuracy. Also this reviewer
likes to see issue numbers as they make the R easier to find on many databases.
   Issue numbers added as requested.

46. P 13, R 4 seems to require payments so could not be verified.
   We have changed this reference to the more contemporary National Hip Fracture
   Database.

47. P 13, R 12, l 3. Insert [(1)] after [88].
   Changed as requested.

48. P 13, R 13 seems correct.

49. P 13, R 14, l 2. Insert [(1)] after [92].
   Changed as requested.

50. P 14, R 18, l 1. The fifth author is [Grounds], and in l 3, insert [(6)] after [9].
   Changed as requested.

   Changed as requested.

52. P 14, R 22, l 2. Insert [(3)] after [79].
   Changed as requested.

53. P 14, R 26, l 1. The authors are [Hamilton TT, Huber LM, Jessen ME] and on
   l 2 insert [(4)] after [74].
   Changed as requested.

   Changed as requested.

55. P 15, R 35, l 2. Insert [(5)] after [75].
   Changed as requested.

We look forward to hearing from you.

Yours sincerely,

Iain Moppett (on behalf of the authors).