Reviewer's report

Title: IVC CLAMP: Infrahepatic Inferior Vena Cava Clamping during hepatectomy - A randomised controlled trial in an interdisciplinary setting [NCT00732979]

Version: 2 Date: 28 April 2009
Reviewer: Charlie Goldsmith

Reviewer's report:

1. Will the study design adequately test the hypothesis? No. In my opinion it will not. The authors need to consider stratifying by the type of surgery the surgeon will conduct. In addition, I felt that having this study done at one center will make it difficult to replicate since so often the authors comment on the standards of the centre will be employed. This means, to my mind, that both an anesthetist and a surgeon will need to check over the clinical description to see that it is adequately described to be reproducible if the study is successful.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing? The key issue for me is that the reliability, validity and responsiveness of the measurement tools are not articulated in the Protocol. There is detail asked for in the comments below.

3. Is the planned statistical analysis appropriate? No. The authors have not provided for blocking in the analysis nor have they provided adequate sample size to take into account blocking and the covariates. The analysis of covariance that they propose does not check its validity, and this should be done before it should be believed.

4. Is the writing acceptable? No. Many times the authors write in the present tense and since this is a Protocol, I suggest it should be consistently put either in the present tense or the past tense. I found it difficult to read as if it is present tense.

Specific comments:

1. Title page: There is no email address for Heike Elbers. This name should be added to the list at the bottom of the page.

2. Page 1, Abstract, Methods/Design, last line: Replace “parameters” by “variables”. A parameter is a characteristic of a distribution of a variable and not another name for a variable.

3. Continuation of page 1, Background, para 1, lines 1 and 2: Rather than talking about "within the last two decades", the actual years should be stated so that if this article is published it does not go out of date as the paper ages.

4. Continuation of page 1, Background, para 1, second last line: Suggest
inserting “the” between “drawbacks” and “optimal”.

5. Continuation of page 1, Background, para 2, second last line: Since “or” logically includes “and”, drop “and/”.

6. Continuation of page 1, Existing evidence and need for the trial, line 2: Replace “results” by “search found”. We are not given the benefit of the search strategy that is used here, so its completeness is impossible to judge. The authors also should tone down their use of “this is the first study” since we have no way to judge whether their literature search had the possibility to uncover other RCTs in this area.

7. Page 2, para 1, line 3: Suggest dropping “that”.

8. Page 2, para 1, line 4: Replace “suggests” by “suggested”.

9. Page 2, para 1, last sentence: How do you know that this search strategy provided that there is no other one known since there is no completeness measure applied to their search strategy? The authors might want to reword this to say as far as they can tell from the look of the literature, there is no other study, so that it conditions it by what they did in their search strategy.

10. Page 2, last para, second last line: Drop “and/”.

11. Page 4, Immediate Preoperative Care, beginning with para 2: The authors need to consistently handle numbers and units. There should always be a space between the number and the units. This occurs in a variety of places throughout the text and should be made consistent. For example, page 4, Immediate Preoperative Care, para 2, line 1, there should be a space between “80” and “mg”, with other examples throughout the text.

12. Page 5, Intraoperative care, para 1: The details of the randomization are inadequate to judge its credibility, including what has been provided in later text on page 9. This reviewer found it was not adequate to replicate the randomization schedule.

13. Page 5, Intraoperative care, para 1, line 8: Drop “and/”.

14. Page 5, last para, last line: Make “patient” plural and drop the word “only”.

15. Page 6, para 1, line 6: Drop “in order” in front of “to” as the words are redundant in English.

16. Page 6, para 2, lines 5 and 7: The authors are proposing to use within-surgery measures as covariates in their covariance analysis. This is something that is done after randomization so does not meet the conventional definition for a covariate. These seem to be time-dependent and are more towards the outcome end of things rather than a covariate at the beginning of the study. Consequently I think the authors need to call attention to this fact and be checking the validity of these by checking for interaction between these covariates and the two treatment groups before they do the testing.

17. Page 6, last para: In the opinion of this reviewer, having things written as “according to local standards” needs to be checked out by both anesthetists and surgeons so that it is adequately reproducible. This reviewer is not in a position to judge these, but this information should be looked at carefully by card-carrying
clinicians.

18. Page 7, under Study objectives and endpoints, para 1, last line: Replace “parameters” by “variables”.

19. Page 7, under Study objectives and endpoints, para 2: Since blood loss is a primary outcome measure, it is unclear whether the person who is doing the collecting will be blind to the procedure being compared in the trial. Does this person know by what goes on during the procedure which one is being done? It may not be possible to blind this nurse as to the treatment group. Will this person know the hypothesis being tested?

20. Page 7, under Study objectives and endpoints, last sentence: Who will measure these endpoints? The measurement properties of all of these are not listed anywhere in the text or cited as to be credible. Measurement properties such as reliability, validity and responsiveness should be implemented in the Protocol.

21. Page 7, under Sample size, line 1: Replace “parameter” by “variable”.

22. Page 7, under Sample size, line 4: Who decided that 280 ml was a minimum clinically important difference? The authors have not considered the block size of 8 that they are planning to use; indeed, 47 patients is not a multiple of 8 and so should be adjusted to do a complete block as articulated later on on page 9, when they talk about block randomization. Whoever wrote these sections should make this consistent. Also, the sample size does not properly consider all of the issues in a sample size calculation that the authors should articulate. They are in other sections, such as the fact that it is a two-tailed alternative and that it appears to be a t-test when in fact blocking has not taken into account with a regular analysis of variance that should be done here. In addition, the authors do not talk in the analysis section about how they are going to handle any violation of assumptions needed in the statistical analysis.

23. Page 8, para 2: The authors are incorrect that these covariates would not decrease the power. In fact, there would be a loss of at least two degrees of freedom and possibly four to check validity which, with this small sample size, could change the power of the study. So there should be an inflation of sample size to take covariates into account.

24. Page 8, under Statistical analysis, para 1, line 3: Replace “population” by “patients”.

25. Page 8, under Statistical analysis, para 2, lines 1 and 2: Drop “means of” in two instances because these words are redundant in English.

26. Page 8, last para, second last line: Replace “population” by “patients”. There should also be a more detailed description of what kind of sensitivity analysis will be done. This is currently inadequate.

27. Page 9, para 1: Using opaque envelopes that are not numbered and cannot measure the integrity of the implementation of the randomization schedule should be avoided. The authors should number the envelopes consecutively and make a master list where patients are entered indelibly and make sure that the envelope corresponds to the number of the patient entered. It is possible for a
nurse to open up multiple envelopes and apply whichever one they want unless the system has been set to give exactly one envelope for each patient so that the randomization integrity is kept in tact. The current description on the top of page 9 is a problem.

28. Page 11, para 1, line 1: Suggest the authors drop the claim that this is first—their literature review does not justify this.

29. Page 11, para 1, line 4: Drop “means of”.

30. Page 11, para 1, line 6: Drop “significantly”. The word significantly should be reserved for a statistical analysis.

31. Page 11, para 2, line 1: Drop “for the first time”.

32. Page 11, para 2, line 3: Drop “and/”.

33. Page 11, para 3, line 2: Replace “parameter” by “variable”.

34. Page 12, para 1, line 5: Drop “In order” and capitalize “To”.

35. Page 12, para 2, line 2: Drop the “s” from “helps”.

36. Page 12, para 2, line 6: Drop “in order” and capitalize “To”.

37. Page 12, para 3: Allowing the surgeons to do three different common techniques is a weakness of this study. The authors should consider stratifying by the preference of the surgeon and making this part of the structure of the design to make sure that this does not unbalance things unnecessarily and so be a comparison of technique rather than the methods that they are designing into this trial.

38. Page 12, last para, line 2: Drop “represents the first study to” and add an “s” to “compare”. The authors have not justified the search strategy adequately to make this claim.

39. Table 1: For the third bullet of Inclusion criteria, provide a reference to the ASA score. Similarly under Exclusion criteria, provide a reference to the NYHA stages. For “Renal insufficiency”, insert a space between “2” and “mg”, and “For female patients” replace “and” by “or” between “pregnancy” and “lactation”.

40. Table 3: Insert a space between the inequalities and the numbers and also between the numbers and the units in each case. For the “Minimum hemoglobin” the conversion should be “0.621”.

41. Table 4 re Secondary outcomes: These should be referenced.

42. Table 4, page 17: Drop “only” on the first line.

43. Table 5: The footnotes referring to Table 5 should be to Table 6.

44. Table 6: The intervention seems to use three columns for Visit 2, so it is unclear what should be measured. If it is meant to be all three times after induction prior to first incision, before resection, and after resection as three separate times when all of these measure are made, that should be made clear. It is not clear in the opinion of this reviewer.

45. References: For the most part the references are accurately cited except ref 15, which is “28:1082-1087” and ref 16, for which the author’s name is Miller RD,
it is the 6th edition, and Elsevier is in New York NY.