Author's response to reviews

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

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Author's response to reviews: see over
Dear Editors,

Thank you very much for considering our article entitled “IVC CLAMP: Infrahepatic Inferior Vena Cava Clamping during hepatectomy – A randomised controlled trial in an interdisciplinary setting [NCT00732979]" for publication in Trials. The reviewer’s comments were very helpful in improving the manuscript in form and content. We followed these comments and the advice they offered strictly and hereby present a revised manuscript for re-submission. In particular, we followed the statistical advice, increased sample size and modified the covariance analysis. Revised passages are highlighted yellow.

Please find our point-by-point response to the referee comments and editorial comments below.

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.

   We are grateful for this hint. The email address of Heike Elbers was added to the list of email addresses

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.

We replaced “parameters” by “variables”.

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“within the last two decades”, the actual years should be stated so that if this article is published it does not go out of date as the paper ages.

We included a date. We are grateful for this comment, as it is helpful in making the manuscript more precise.

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

We inserted “the” between “drawbacks” and “optimal as suggested.

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

We dropped “and/” as recommended.

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.

We replaced “results” by “search found” as proposed by the reviewer. In the revised version of the manuscript we, moreover, do not state that “this is the first study”.

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

We dropped “that”.

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

We replaced “suggests” by “suggested”.
We replaced “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.

*We fully agree with the reviewer that we cannot exclude that there is already another similar study. We searched the Medline database and in addition searched the reference lists of related articles on hepatic vascular control. Furthermore, we contacted experts in the field of hepatic surgery. We are therefore confident that there is no prospective randomized trial comparing the same interventions as in our present study. In the revised version of the manuscript we provided more details on our literature search. However, as we still cannot be sure that we missed a relevant study we followed the reviewer’s recommendation not to state “this is the first trial”.*

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

*We dropped “and/” as suggested.*

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.

*We are grateful for this comment that helped to improve the form of the manuscript. In the revised version of the manuscript we left a space between the number and the units.*

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.

*We agree with the reviewer that our previous description of the randomization lacked details. In the revised version of the manuscript we provided further details that will help to replicate the randomization schedule.*

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

*We dropped “and/” as suggested.*

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

*In the revised version of the manuscript we replaced “patient” by “patients” and dropped the word “only”.*

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

*We dropped “in order” as recommended.*

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.

*We are grateful to the reviewer for this advice and we fully agree to check the validity of the covariates by checking for possible interaction between them and the intervention groups. Following the reviewer’s recommendation we modified our statements in the revised version of the manuscript as follows: The transection technique is documented and considered as a factor in covariance analysis and the interaction with intervention will be*
tested. While routine use of portal triad clamping is not recommended, the final choice to use portal is left at discretion of the executing surgeon and the need for portal triad clamping is documented as a secondary endpoint."

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.

*In our protocol patients’ anaesthesiological and surgical treatment within the trial are described in detail. Even though we mention that patients’ care will be in accordance to the standards at our the our institution, we provided very detailed discription how these standard look like. This will allow the readers to transfer the results of the trial to their own institution.*

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

*We replaced “parameters” by “variables” as recommended.*

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?

*We agree with the reviewer that it is not possible to blind people who actually attend the operating room to the allocated intervention. As patients may experience hemodynamic instability during clamping of the inferior vena cava, the surgeon ususally tells the anaesthetist when he starts the clamping maneuvre. Hence, it is not possible to blind people in the operatig room. However, the study nurse is not aware of the tested hypothesis as are the anaesthetists. As blood loss is also assessed within routine clinical practice the amount of blood loss assessed by the*
study nurse is compared to that determined by the anaesthesiologist to minimize assessment bias.

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.

We thank the reviewer for this comment as assessment of outcomes has not been described in sufficient detail in the initial version of the manuscript. All secondary endpoints are assessed and documented by an independent study nurse who is blinded to the allocated intervention. We added this information to the revised version of the manuscript. The secondary endpoints chosen in the present trial are very common outcomes in randomized and non-randomized clinical trials in the field of surgery. For IVC CLAMP they were chosen in accordance with recently published randomised studies in the field of liver surgery. Although we are not able to provide measurement properties of these outcomes such as reliability, validity and responsiveness, we are confident that these rather simple endpoints in their presented form provide valuable information about the compared interventions as they already did in previous studies.

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

We replaced “parameter” by “variable” as suggested.

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.

*We thank the reviewer for these important comments. The decision to chose 280 ml as minimum clinically important difference was made based on clinical considerations. Nowadays, liver resections can be carried out frequently without any transfusion. In various studies is has been shown that blood transfusion increase the risk of poor perioperative as well as long–term oncological outcome. As 280 ml represents the amount of one packed red blood cell unit this amount of blood loss was chosen to define the minimum clinically important difference. In the revised version of the manuscript we provided the required details on the sample size calculation. Furthermore, we increased the group size to 48 which is a multiple of 8.*

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.

*We agree with the reviewer that inclusion of additional factors would decrease power. Taking into account the possible loss of power by using one additional factor in the analysis of covariance, another 8 patients per treatment group are randomised. The continuous covariates applied in this analysis do not decrease the power and therefore are not considered in the sample size estimation. As randomisation is carried out before laparotomy an intraoperative drop–out rate of 30% is assumed to consider possible intraoperative findings preventing hepatic resection (e.g. extrahepatic disease such as peritoneal carcinomatosis, technically inoperable disease, severe liver cirrhosis etc). Thus we increased the the total sample size to 144 patients.*
24. Page 8, under Statistical analysis, para 1, line 3: Replace “population” by “patients”.

   *We replace “population” by “patients” as suggested.*

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.

   *We dropped “means of” in both instances*

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.

   *We replaced “population” by “patients”. Furthermore, we provided a more detailed description of the sensitivity analyses as suggested*

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.

   *We are grateful to the reviewer for this comment as we agree that our previous description of the randomization procedure might have been misleading. Indeed, patients in the present trial are randomised using opaque and sealed envelopes that are consecutively numbered. All patients screened as well as those included and randomised in the study are entered in a consecutive list. Envelopes are opened upon entrance of the*
patient in the operating room. In the revised version of the manuscript we provided a more detailed description of the randomization schedule.

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

   We fully agree and dropped the claim as suggested. Please see also our response to comment #9.

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

   We dropped “means of”.

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

   We followed this advice and dropped the word “significantly”.

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

   We dropped “for the first time” as recommended.

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

   We dropped “and/”.

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

   We replaced “parameter” by “variable”.

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

   As suggested by the reviewer we dropped “In order” and capitalized “To”.

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

   We dropped the “s” from “helps”.

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

   We dropped “in order” and capitalized “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.

We are grateful to the reviewer for this comment allowing us to explain our study design in more detail. At our institution liver resections are commonly performed using the stapler hepatectomy technique. For this reason this technique is recommended in our protocol. However, there are cases where stapler hepatectomy is not feasible or associated with increased risk for the patient (e.g. tumors adjacent to major vasculature). To prevent further drop-outs alternative techniques may be used in these scenarios. As we and others could show that there is no statistically relevant difference in blood loss during liver resection using different resection techniques, we are confident that allowing three different transection techniques does not strongly unbalance the results. However, to further minimise potential confounding, we limited the number of allowed techniques. Furthermore, the actual transection technique is considered as a factor in the analysis of covariance and the sample size is adapted to prevent loss of power.

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.

We dropped “represents the first study to” and add an “s” to “compare” as previously explained.

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.”
We thank the reviewer for the advice to provide references for the ASA and NYHA score. We followed this advice and provided these references in the revised version of the manuscript. Furthermore, we inserted a space between "2" and "mg" for "Renal insufficiency" and replaced "and" by "or" between "pregnancy" and "lactation" "for female patients".

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”.

As recommended by the reviewer, we inserted a space between the inequalities and the numbers and also between the numbers and the units in each case. We also changed the conversion factor for the “Minimum hemoglobin” to “0.621”.

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

The secondary endpoints are chosen in accordance with recently published randomised trials in the field of hepatic surgery. In the revised version of the manuscript we provide references to these studies.

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

We dropped “only” on the first line.

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

We kindly disagree on this comment. The footnotes referring to Table 5 provide details on the actual variables that are assessed on each visit. However, details on the laboratory tests are provided in Table 6 (please see the cross-reference in Table 5 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 measures are made, that should be made clear. It is not clear in the opinion of this reviewer.
We are grateful for this comment. We revised the table to make the time points of the performed laboratory tests more clear.

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.

We thank the reviewer for these hints. In the revised version of the manuscripts these inaccuracies were corrected. However, for Elsevier Churchill Livingstone Philadelphia is given as city.

We hope that our revised version of the manuscript meets the high standards of Trials and we look forward to further notice. Please do not hesitate to contact us in case you have any further questions.

Thank you very much for your consideration.

Best regards,

Jürgen Weitz