Author’s response to reviews

Title: “Is dangling of the lower leg after a free flap reconstruction necessary? A study protocol for a large multicenter randomized controlled study.”

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Author’s response to reviews:

Dear Dr. Tharmanathan, Dear Reviewers,

Thank you very much for reviewing our article and for your comments. I am convinced these comments improved the quality of the paper. I have uploaded version two of the manuscript with "track changes".

Hereby our point-to-point response to your comments:
1. Please revise the title of the study and point out that this is the study protocol and not the results of the actual study itself. At present the title is misleading.
   - We have changed the title to: “Is dangling of the lower leg after a free flap reconstruction necessary? A study protocol for a large multicenter randomized controlled study.”

2. Please revise the introduction in the same regard and point out that this is just the protocol.
   - We changed the last sentence of the introduction clearly stating that we are presenting our study protocol in this article.
3. Please revise the first sentence of objectives and make it more precise. At present the sentence is too long and confusing.
   - We simplified this sentence.

4. What is the standard of care in the participating centres at the moment? If the standard of care is the non-dangling protocol the authors should mention that, if the standard of care the authors should mention that as well. Furthermore, if the standard of care is something entirely different I wonder why dangling wasn't compared to the standard of care.
   - The standard of care in all centers is the dangling protocol presented in our article. Worldwide there are a lot of different dangling protocols but almost everyone does use a form of a dangling protocol.

5. Please provide some parameters when the study will be terminated due to adverse events. This should be mentions in the method section.
   - We added a sentence at the end of the paragraph "recruitment, consent and withdrawal" of the method section.

6. At present the discussion is very short. I believe it would help if the authors discuss the potential benefits that can come from doing the study and compare the proposed study design with the other studies that were conducted regarding this question.
   - Thank you for this comment. We added an explanation of the potential benefits/clinical impact that this study can have in the discussion.

7. The authors designed the study as a non-inferiority trial. However, I wonder, if both treatments are equivalent, what are possible reasons that would lead to actually implement a dangling protocol. What is the benefit of a dangling protocol if the study shows that both treatments are comparable? I think that should be briefly explained in the discussion. In particular, if the hypothesis is confirmed, what will be the clinical impact of the study.
   - Worldwide patients undergo a version of a dangling protocol. However we believe that that is not necessary. With a non-inferiority design we will test our hypothesis that a non-dangling protocol is not inferior to a dangling protocol. If our study supports our hypothesis our conclusion will be that a dangling protocol is not necessary anymore.

8. Regarding the PCOT measurement, how many patients are needed to achieve statistical relevant results? If I understand correctly only once center will perform these measurement. Are enough patients expected to be enrolled in this one center? What is the necessary sample size? If only a handful of patients are expected to get this measurement and feasibility of the statistical analysis is questionable I believe it is unethical to do these measurements. Especially because they are the only invasive measurements. Please explain and revise manuscript accordingly.
   - The goal of our POCT measurements is not to show a statistical significance and therefore there is no sample size necessary. We only want to get more insights in the gaseous changes internally in the free flap during dangling. We expect to include about 10-15 patients in our POCT measurements. The goal is to present a curve of these values before and directly after dangling. This will be completely new and very interesting information since this has never been done before. We added sentences about our POCT measurements in the method section paragraph "point of care tests" and in the discussion.