Author’s response to reviews

Title: Study protocol: a single-blind, multi-center, randomized controlled trial comparing Dynamic Intraligamentary Stabilization, Internal Brace Ligament Augmentation and Reconstruction in individuals with an acute anterior cruciate ligament rupture: LIBR study

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Version: 1 Date: 19 Sep 2019

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1. The NCT webpage states that an estimate 100 participants would be recruited, while this study protocol states 48. Please provide an explanation for this. These concerns are related to sample size issues that could arise.

On clinicaltrials.gov we adjusted the ‘estimated enrollment’ to 96 and in the section ‘intervention model description’ we clarified that for study 1 N=48 and for study 2 also N=48. We agree that 48 participants per study is quite small but this number was a balance between what was feasible in recruiting 28 months in 2 centers that are sufficiently familiar with the new techniques and a sample size that would give us the opportunity to find a clinically meaningful difference.

2. Discuss why no "Early" patient group has been included in Study 1, which would be a ACL-reconstruction surgery group deferred until 5 weeks post-injury. It makes sense to me that both new treatments should be compared to conventional treatment.
We agree that this would be the ideal scenario but a design choice we did not make for several reasons. The main reason is that if all the patients would have to be recruited in a 3 instead of 2 times 2 arms comparison, 78 patients would have to be recruited within the 4 weeks after the ACL rupture. Due to patient and doctors referral delay, many of the patients with a ruptured ACL report to our orthopedic departments after 4 weeks and therefore could not be included. We expected the early patient group (0-4 weeks) to be more challenging to recruit compared to the 5-12 weeks post rupture group; 78 patients within 0-4 weeks would not be feasible.

Another reason is that the patient blinding could be more difficult. For both the 0-4 and 5-12 weeks groups, after inclusion a date of surgery will be chosen, afterwards the randomization will be performed. If first the randomization will be performed and afterwards the date of surgery is chosen with the patients, it could give a clue which type of surgery the patient will receive.

3. Consider how good use of matching/co-variates can be used for data analysis purposes. Will you small sample size even allow for this? A biostatistican should be consulted.

We agree that with this small dataset of 48 participants matching will be challenging so this is why we originally have added if possible to line 412 but we now have removed this from the analysis.

For the comparisons of the randomized groups within a study the randomization ensures a valid comparison between treatment groups, the addition of covariates to the model will allow us to add sensitivity to the results.

For the comparisons of the non-randomized groups between studies the covariates will be important and as numbers are small we will start by ANCOVA models where only one covariate is added to the model. In case confounding factors come up we can combine and add more than one covariate to the model. We are aware of the fact that the sample size will not allow to fit a model with all the covariates at the same time but we will try to infer the effect of the covariates from the ANCOVA models and combining models with reasonable numbers of variables. We also believe that it is advantageous that we have repeated measurements of the outcomes over time which will give us more power with these small numbers to detect effects.

Ella Roelant, co-author of this article is our statistician at the Antwerp University Hospital.

We adapted this in the protocol, see page 18-19 section ‘Analysis of the secondary outcomes’.