Reviewer's report

Title: BIOLAP: Biological versus synthetic mesh in laparo-endoscopic inguinal hernia repair: Study protocol for a randomized multicenter, self-controlled clinical trial

Version: 0 Date: 18 Aug 2018

Reviewer: Felix Hüttner

Reviewer's report:

I appreciate the opportunity to review this manuscript. The trial addresses an important topic and a wide evidence gap that needs to be closed.

However, the current manuscript will need some substantial revisions before being potentially suitable for publication in Trials. The points that have to be addressed are listed in tabular form in the following:

- General comments:

  # The manuscript needs some language editing. I would recommend revision by a native speaker.

  # I would recommend to use the term "trial" throughout instead of "study" for the current research.

- Title: I would recommend to include the word "inguinal" or "groin" in the title to clarify what types of hernia are considered within the trial. In the current form, one could not tell if the trials assesses groin hernia repair or e.g. ventral hernia (by laparoscopic IPOM technique).

- Abstract: The abstract needs some substantial rework since it reports some information that is not necessary in an abstract whereas it omits some points that should be mentioned (e.g. principal eligibility criteria, setting/what type of hospitals, randomization details etc.). Even though the current manuscript is not a report of results, I would recommend the authors to orient themselves e.g. in the CONSORT extension for abstracts of trials assessing non-pharmacological interventions, regarding what needs to be reported in the abstract and what does not need to be reported here.

- Abstract: The last two sentences of the discussion are basically the same. Please delete one of them.
- Background: I would recommend moving the first paragraph of this section to the end of the section. The background section should lead the reader towards the objective of the trial not start with the objective.

- Background 3rd paragraph: in the description of treatment options for inguinal hernia, the authors should also mention watchful waiting, which represents a viable treatment option especially for oligosymptmoatic groin hernia in men. Another option would be to revise the sentence to clarify that the authors only list the surgical treatment options e.g. "if surgical treatment is indicated/planned, patients can be treated by either primary open repair, ....".

- Background 4th paragraph: the authors should reconsider their literature search: they state that only one study compares biological to synthetic mesh in open inguinal hernia repair. This is not true; to my knowledge there are at least 4 RCTs comparing biological mesh to synthetic mesh in open inguinal hernia repair and even a meta-analysis of these trials (Fang et al. ANZ J Surg 2015; PMID: 26183816).

- Furthermore, some of these trials and the meta-analysis showed a significantly higher rate of seroma formation in the biologic mesh group. This should also be mentioned as potential disadvantage of the biological mesh group.

- Methods: I would recommend to separate the combined headers (e.g. "aim of the study/primary and secondary outcomes" to e.g. "aim of the trial" next header "primary and secondary endpoints"). Furthermore, I would recommend to adapt the order of the points to the usual and widely accepted order, for example: aims, trial design, participants/eligibility criteria, randomization/operations for minimising bias such as blinding etc, interventions, outcomes, safety measures, sample size, statistical analyses...

Additionally, the authors mix it up in some parts, for example mentioning some details of the randomization (telephone-based randomization) in the "Intervention"-section instead of the "Design"-section.

- Methods: The current description of trial specific features is insufficient. How was the random sequence generated, how was allocation concealed? Were only patients blinded or also outcome assessors, statisticians etc.?

- Methods: Since the trial is already recruiting, the participating centres should be stated explicitly in the methods section.
- Methods/Intervention: Glue fixation is left up to the discretion of the individual surgeon/Center. If glue fixation is performed, is it prespecified that it has to be performed on both sides in the individual patient? If not this may represent a relevant source of bias.

- Methods: Considering the primary endpoint: Is it planned to assess whether patients are dependent of pain medication? Since the trial is self-controlled this should not have a major impact on the primary endpoint; nevertheless, it would still be interesting and relevant to know how many patients are still dependent on pain medication due to groin pain at the individual points of time.

- Methods: The sample size calculation for the primary pain endpoint is based on a difference of 0.5 points on the VAS scale. How clinically relevant would the authors judge a difference of 0.5 in VAS? Could you provide any literature discussing clinical relevance of the amount of change in VAS?

- Methods: On the other hand I have concerns about the sample size assumptions for the recurrence endpoint. The authors set a non-inferiority margin of 3%; considering the expected frequency of 5% recurrences during 2 years of follow-up this would represent a 60% increase of recurrent hernias. As frequency of recurrences increases over time it could be possible that the gap between the two procedures would even grow over time to an even larger amount.

- Methods: More detail should be provided for secondary endpoints, e.g. complications: which complications will be assessed? how are they defined?

- How are safety aspects managed within the current trial? Is there some kind of serious adverse reporting? Is there a DSMB or comparable board overseeing safety and conduct of the trial?

- The self-controlled design of the trial has several clear benefits, but one major confounding factor is not adjusted for by the current design: it is well known that several preoperative factors represent risk factors for postoperative pain such as preoperative groin pain or size of the hernia (c.f. Magnusson et al. Surgery 2014; PMID: 23973111). Patients with bilateral hernia usually do not have the same preoperative symptoms or hernia size on both sides. In fact in a lot of cases the contralateral hernia is only discovered incidentally during the preoperative work-up. Randomization cannot completely adjust for that and this fact is not considered in the analysis. Considering the worst case scenario if by chance one type of mesh will in most cases be randomized to the symptomatic side, this could substantially distort the results and limit their validity.
- SPIRIT checklist: the authors filled the checklist with "not applicable" in several places. In my opinion most of these points are applicable to the current trial (e.g. "role of the sponsor and funder", "relevant concomitant care" -> e.g. glue fixation, "unblinding options", "data collection methods", "confidentiality/data protection"...). I would request the authors to substantially revise the checklist and the manuscript considering the checklist respectively. Some points are already addressed in the text and just need to be filled in the checklist and others need to be amended to the text.

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An article of importance in its field

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**Statistical review**

Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.
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No