Author's response to reviews

Title: The effect of Ultrapro or Prolene mesh on postoperative pain and well-being following Totally Extraperitoneal (TEP)endoscopic hernia repair (TULP): Rationale and Design of the study protocol for a randomised controlled trial

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

Thank you for peer reviewing our submitted manuscript, with ID MS: 1920572794579595. I hereby sent you the revised document. In the accompanying letter, you will find our point-by-point response to the Editorial and Reviewers’ questions and comments. All changes accordingly made in the manuscript itself are highlighted with the ‘track changes’ option in MS Word.

Hopefully, this allows for a smooth continuation of the submission process.

Thank you in advance,

Yours sincerely,

Nelleke Schouten
Answer to referee and editorial comments:

Editorial requests:

- If applicable, please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

   Answer: We included an Acknowledgment section at the end of the manuscript. Furthermore, the declaration of competing interests and financial disclosure section was adjusted to include not only the authors, but also the person(s) mentioned in the Acknowledgment section.

Comments of the Reviewer:

The authors supply a well written protocol. The design seems rigorous and the statistical methods seem appropriate for the design. There are several minor issues to consider, as follows:

1. The design compares 2 types of mesh – lightweight and heavyweight – within a specific choice of surgical approach (TEP). The primary outcomes are postoperative pain and well-being, but there is no mention of effectiveness, apart from recurrences as a secondary endpoint up to 3 years after the outcome. The concern would be twofold:
   a) If the lightweight is shown to be superior to the heavyweight in terms of pain, the heavyweight might be better than the lightweight in terms of recurrence (for TEP).

   Answer: Generally, the recurrence rate is considered the most important outcome ‘parameter’ in inguinal hernia repair in terms of effectiveness, since that is what a mesh is supposed to do; to prevent recurrences.

   We agree with the reviewer that what he mentioned at a) is a possibility, since heavyweight meshes create maximum mechanical stability and promote the formation of scar tissue, while the properties of the lightweight mesh aim to improve integration in the abdominal wall and prevent the formation of scar tissue. On the other hand, other (smaller) studies comparing the outcomes of a heavy- and lightweight mesh in inguinal hernia repair, - the recurrence rate being the primary outcome variable - found no significant differences in the recurrence rate. Following this, we hypothesize that the lightweight mesh is not associated with a higher recurrence rate. Nevertheless, if the outcome of this study proves to be that the heavyweight mesh is better than the lightweight mesh in terms of recurrences, but the lightweight mesh is shown to be better in terms of preventing postoperative pain, the findings of this study will still be valuable, since large studies with a long(er) follow-up addressing this problem, are limited.
and b) That although the trial is designed to compare the two meshes within TEP, how can the design give reassurance that this was the right surgical approach – i.e. as above, the lightweight is better than the heavyweight (all round, in terms of pain and effectiveness) but that possibly the heavyweight would be better for a different non-TEP surgical approach?

Answer: Strictly, the design of this study cannot give any reassurance that this is the (only) right surgical approach, since the aim of this study is to compare the two meshes within the endoscopic TEP technique.

What we, -based on the literature,- do ‘know’ however, is that endoscopic hernia repair techniques are (in experienced hands) associated with significantly less postoperative pain and an earlier return to normal activities compared to conventional (i.e. open, such as Lichtenstein, hernia repair). Furthermore, TEP is preferred over Transabdominal Preperitoneal (TAPP) hernia repair, since it is less invasive and associated with if fewer visceral injuries (see Introduction section). In addition, a few recent (smaller) suggesting that lightweight meshes may be associated with less chronic postoperative pain compared to a heavyweight meshes are conducted both in patients undergoing open Lichtenstein repair as in patients undergoing endoscopic hernia repair. Ideally, a TEP with lightweight mesh would be an appealing surgical technique in the prevention of chronic postoperative pain.

2. Describing the trial as double blind is a bit confusing – the authors then subsequently make it clear that the patient and the clinical assessor of outcomes are blinded, but that obviously the surgeon performing the operation cannot be blinded. I would describe that as a single blind with blinded assessment of outcomes, not double blind.

Answer: We concur with the reviewer that describing this trial as double blind is a bit confusing. However, although the operating surgeon is not blinded (quite obviously, as you mentioned) for the type of mesh used, the surgeon who does the follow-up of the patient is (since the type of mesh is not mentioned in the operating chart and patients are examined at the outpatient clinic by another than the operating surgeon. The clinical assessor of outcomes (or coordinating investigator) is also blinded for the mesh type. After consulting with the Medical Ethical Committee, we ‘chose’ therefore to describe the trial as double-blind, instead of a single blind trial with blinded assessment of outcomes. Hopefully, this response is satisfactory to the reviewer.

3. Page 2 – the authors state they are undertaking ‘a complete efficacy ... assessment’ – I read this as a pragmatic trial (albeit single centre) and would have expected to see the trial described as estimating effectiveness, not efficacy?

Answer: We apologize for the erroneous use of the term effectiveness, since that is what we meant, not efficacy. After I checked the dictionary, I realized the different meanings of both words. The text is adjusted where appropriate.
4. On the other hand, there are just 4 surgeons in a single high volume centre, all of whom are described as being expert. So is this why the authors are describing it as an efficacy and not an effectiveness trial – it is delivered in the hands of expert surgeons, and so despite an inclusive set of patients, the findings may not be easily generalized from this single centre, expert surgeon setting?

Answer: The endoscopic TEP technique is a hernia repair technique with a long(er) learning curve. Expertise is therefore a prerequisite in performing TEP repair. What 'you' therefore often see, is that centers offering a TEP repair do this in an expert surgeon setting. Although a criticism might be that the findings of this study may not be easily generalized to all other TEP hernia repairs (including those performed by inexperienced surgeons), we do believe it can be generalized from our centre to most other centers performing TEP hernia repair. Following this, minor revisions have been made to the Discussion paragraph.

5. It would be useful to give more details of the patient characteristics e.g. average age, proportion working etc?

Answer: patient characteristics will be described in detail in the final version of the manuscript, i.e. after analyzing the results. However, it is possible to give some details, such as (indeed) the average age, average ASA-score and proportion working.

6. Page 5 – the authors state that they give ‘... preliminary results (updated until July 1st, 2011)’ – these are not so much results, as achieved recruitment targets. Although this is informative, it could be confused as being the final recruitment – I would have included a ‘950 target’ version as well / instead of?

Answer: We have chosen to include an estimated ‘950 target’ version instead of the previously submitted version with results until July 1st, 2011. In addition, the term ‘preliminary results’ is changed in ‘expected recruitment targets’.

7. Page 5 ‘The block size is 8 patients’ – generally, not considered a good idea to broadcast the block size while recruitment is ongoing.

Answer: Thank you for your advice. We deleted the sentence in the manuscript.

8. Page 5 ‘The patient, investigator and surgeon involved in the follow up’ – what is the difference between the investigator and the surgeon? That is, who is the investigator here?

Answer: In the entire manuscript, with the investigator, the ‘clinical assessor of outcomes’ is meant (i.e. the author of this manuscript, N. Schouten). The surgeon is one of the four surgeons specialized in TEP hernia repair, in this manuscript therefore never referred to as the investigator or clinical assessor of outcomes.

9. The authors state (Page 7) ‘The type and amount of analgesics used during the first post-operative week are kept in a pain diary’ – so in terms of analysis, are the primary comparisons of pain going to be adjusted for analgesic use? Or as a secondary supporting analysis?

Answer: We planned the comparisons of pain to be adjusted for analgesic used as a secondary supporting analysis. This is added to the ‘Statistical methods’ section.
10. Page 7 ‘IPQ, BPI, CCS, VAS, SFP, SF-36, EQ-5D’ – spell out what these Instruments are?

Answer: Since these instruments are already spelled out and described in the paragraph ‘Questionnaires’, I put this paragraph before the paragraph where a ‘timeline’ of the follow-up is described. Following this, the instruments are spelled out first.

11. Page 8 – type ‘Severe pain VAS 4-6’ – should be 7-10?

Answer: Severe pain is indeed corresponding to a VAS score of 7-10. The text was adjusted accordingly.

In addition to the above mentioned comment, one minor revision has been made; VAS should be NRS (numerical rating scale) since that is what we used. The term VAS implies a visual score instead of a numerical one.