Author's response to reviews

Title: Hysteropexy in the treatment of uterine prolapse stage 2 or higher: a multicenter randomized controlled non-inferiority trial comparing laparoscopic sacrohysteropexy with vaginal sacrospinous hysteropexy (LAVA-trial, study protocol)

Authors:

Mèlanie N van IJsselmuiden (m.n.van.ijsselmuiden@isala.nl)
Anne-Lotte WM Coolen (anne_lotte_coolen@hotmail.com)
Renée J Detollenaere (r.j.detollenaere@isala.nl)
Jan den Boon (j.den.boon@isala.nl)
Marlies Y Bongers (m.bongers@mmc.nl)
Geerte van de Pol (g.van.de.pol@gelre.nl)
Astrid Vollebregt (avollebregt@spaarnziekenhuis.nl)
Hugo WF van Eijndhoven (h.w.f.van.eijndhoven@isala.nl)

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Author's response to reviews: see over
Isala Zwolle
Department of obstetrics & gynecology
Postbus 10400
8000 GK Zwolle
The Netherlands

BMC Women’s Health
Biomed Central
236 Gray’s Inn Road
London WC1X 8HB
United Kingdom

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Subject: submission of revised manuscript

Dear Editor,

Enclosed please find the revised manuscript entitled “Hysteropexy in the treatment of uterine prolapse stage 2 or higher: a multicenter randomized controlled non-inferiority trial comparing laparoscopic sacrohysteropexy with vaginal sacrospinous hysteropexy (LAVA-trial)” by Anne-Lotte WM Coolen, Renée J Detollenaere, Jan den Boon, Marlies Bongers, Geerte van de Pol, Astrid Vollebregt, Celine M Radder, Jan Deprest, Hugo WF van Eijndhoven and Mélanie N van IJsselmuinden. This article has been primary submitted in October 2013 for possible publication as research article in BMC Women’s health.

The manuscript has been reviewed by two peer reviewers. We appreciate their effort, their comments are of great value for the study protocol. Therefore, we would like to thank the reviewers.
In this cover letter, we would like to give a point-by-point response to the concerns. The revised manuscript is enclosed.

Referee 1

The only practical question is the great number of validated questionnaires: total 7! The reviewer wonders if the participating women will be able to complete all these questionnaires.

We are aware of the large amount of questionnaires. In the follow up phase patients are asked to fill in 3 questionnaires in the first year postoperatively, and then one questionnaire a year (at 2, 3, 4 and 5 years). Therefore, we believe the questionnaires are spread sufficiently throughout the study period. Furthermore, in our SAVE-U trial (RCT comparing vaginal hysterectomy with sacrospinous hysteropexy) a similar study design has been used, with the same number of questionnaires in the follow-up phase. The study is still ongoing, but no problems with filling in the questionnaires have been reported so far.

Referee 2

1. Discretionary revision, last sentence of background paragraph: the trial hasn’t been conducted yet, change to “plan to conduct the LAVA trial.”

The study was started in August 2013. Therefore, we have not revised the manuscript with respect to this item.

2. Discretionary revision, methods: would add that validated outcome measures are being used.

This is revised in the manuscript (line 62).

3. Discretionary revision, 1st paragraph: 1st reference is outdated. There is already a new ICI published on this topic.

This is revised in the manuscript. We have decided to drop this reference, because it will give no extra information and we would like to keep the background concise.

4. Minor revision 4th paragraph, page 6: left off the word “intestines” after small when describing enterocele.

This is revised in the manuscript (line 104).
5. **Major point, 2nd paragraph, page 7:** While I agree that there is inconclusive evidence and similar results comparing sacrospinous hysteropexy (SSHP) and TVH, the only RCT by Dietz, 2010 (your reference #16) reported a higher rate of apical recurrences in the hysteropexy group 21% versus 3% hysterectomy group (p=0.03). Both groups had high rates of postoperative anterior vaginal wall prolapse (51% vs. 64%). The latter point is important because of how you structure your outcomes for this study and will be discussed later in this review.

We agreed with the reviewer and added these outcomes to the manuscript (line 133-137).

6. **Major point:** I think it is appropriate to structure this as a non-inferiority result if only looking at the apical compartment (recurrent uterine prolapse), but my hypothesis would be that the laparoscopic results will be better based on anterior wall recurrence rates being much higher in the vaginal group resulting in overall more symptomatic prolapse that requires additional treatment with surgery or a pessary.

We agree with the reviewer. For our primary outcome we have chosen to look at the apical compartment only. The difference in change in vaginal axis between the two techniques could hypothetically result in a difference in level 2 support. With lower anterior vaginal wall recurrence rates patients could benefit from the laparoscopic approach. Therefore, anterior and posterior vaginal wall prolapse are secondary outcome measures. These are described in the revised manuscript (line 201-202).

7. **Major revision, 1st paragraph study design page 9:** The authors indicate that “follow-up after one year will be done by an physician not involved in the surgery.” Why not have 6 month and 1 year exams be done by someone other than the surgeon? The 1 year exam is the primary outcome and will contain significant bias if done by the surgeon. I strongly suggest that the 1 year exam be done by someone other than the surgeon.

This has been a grammatical mistake: the 6 month, 1 and 5 year exam will be done by someone other than the surgeon, since that will be our primary endpoint. It has been revised in the manuscript (line 185-186).

8. **Major revision recommended, 1st paragraph of primary and secondary outcomes, page10:** The primary outcome is unclear throughout the paper. It sounds like POP-Q for uterine prolapse that is stage 2 (point C at or below -1) constitutes a failure. However it also mentions “symptoms or redo surgery in the case of uterine descent.” Do the authors mean that someone with recurrent stage 2 uterine prolapse that is not symptomatic or does not undergo reoperation would not be considered a failure? That is what this sentence implies. I would argue that the authors should have a composite outcome.
Success should be those with anatomic descent of the apex at or above the mid-vagina (C < TVL/2), no prolapse in any compartment (anterior or posterior walls) beyond the hymen (since that is where symptoms occur), and no reoperation for recurrent prolapse or pessary use. Failure of any one of these areas would constitute a failure. Since a woman could be included with the cervix 1 cm internal to the hymen, I do not think her surgery would be considered successful if she ended up with the cervix 2 cm internal to the hymen and the anterior wall 3 cm beyond the hymen. Yet, by the study criteria, that would not be considered a failure. Please reconsider how you define your primary outcome so that it is meaningful and relevant.

This study is powered on the apical compartment. Anterior and posterior vaginal wall prolapse are secondary outcomes. We agree with the reviewer that our primary endpoint is not specific. We decided to use a composite outcome, according to Barber et al (2009, ref #20). We specified our primary endpoint in the revised manuscript (line 196-200).

9. **Major revision recommended for inclusion/exclusion criteria of 3rd and 4th paragraphs, study population page 10:** Is any abnormal cervical smear considered an exclusion criteria (ASCUS with high risk HPV negative) or those with cervical dysplasia? What about those with high risk HPV but normal cervical smears? The authors need to be more specific about what abnormal ultrasound findings of the uterus and ovaries will be excluded. Will a small asymptomatic fibroid that is 2 cm be excluded? The authors specify abnormal uterine bleeding. Does this mean menorrhagia, menometrorrhagia, and dysmenorrhea? What about postmenopausal bleeding? I would suggest that any recent postmenopausal bleeding even with a negative workup in the past year be excluded since Frick’s article suggests a high rate of unanticipated abnormal pathology in this population. Will the authors include or exclude those women with cervical elongation? There is a study by Lin et al indicating a 10 fold increased risk of failure in women with cervical elongation undergoing SSHP. While it is difficult to quantify cervical elongation, I would suggest that the authors leave this to the discretion of the enrolling surgeon but exclude those felt to have elongation or the need for cervical shortening/partial trachelectomy. Those patients may be better served with a TVH. Alternative is to mandate surgical shortening but not as clean for the study.

We agree with the reviewer and specified the exclusion criteria in the revised manuscript (line 212-221). Whether or not elongation should be an exclusion criterion is still unclear. In our SAVE U study group (sacrospinous hysteropexy n=103) the cervical length was not an independent risk factor for recurrence. We think it is a great suggestion to leave this to the discretion of the surgeon. Certainly, in case of clear elongation without any prolapse of the uterine corpus the surgeon should consider partial trachelectomy or TVH.
10. Minor revision, first paragraph of randomization, page 11: I agree with stratifying or block randomization according to centre but wouldn’t do this for severity of prolapse/POP-Q stage as there should be no difference between groups in a RCT that is adequately powered and done correctly.

The LAVA-trial has started in August 2013, we already randomize for severity. Therefore, we can’t change this item. We agree that, when the study is powered adequately and performed correctly, stratifying for severity will not be necessary. However, we would like to make sure that the two study arms will be homogenous and that the severity of prolapse will be equally distributed in the two study arms. Therefore, we have chosen to stratify for severity of prolapse as well. Furthermore, our local ethical committee required stratifying for severity of prolapse.

11. Major revision, first paragraph of randomization, page 11: The authors need to add details here about when the randomization will take place. Implied in the discussion regarding sample size that randomization is done before the operating room so that 10% will likely drop out because they are not happy with their assignment. Please state when randomization will be done, by whom, and how subjects that withdraw after randomization will treated.

This is specified in the revised manuscript (line 237-246). Patients will hear the result of the randomization shortly after the randomization procedure. We already started to enroll subject and we included 26 subjects so far. Until now, no withdraw because of unhappiness with the assignment occurred.

12. Minor revision, data collection, 2nd paragraph of this section, page 11: who will administer validated quality of life questionnaires at baseline and postop visits.

The validated questionnaires will be administered by the participating hospitals (baseline and 6 weeks postoperative) and by the coordinating hospital (6 months postoperative and yearly thereafter). This is added to the revised manuscript (line 273-275).

13. Discretionary revision, major point to be considered but does not necessarily require revision, last paragraph page 11: Collection of a postop pain diary by VAS is a great idea. How will the authors make sure that the patients are completing the pain diary regularly rather than just filling it out the day before the 6 week visit. There will be significant recall bias if the patients are not completing them on a regular basis. The authors should consider a way to collect this at shorter intervals. Maybe mail in the daily
diary at 2 weeks and then collect pain scores once a week for 2-6 weeks that is submitted at 6 weeks. Do you really need a daily pain diary after 2 weeks?

The pain diary is not daily during 6 weeks: in the first two weeks, we ask to fill in a VAS score and pain medication daily, then the interval will be 2-weekly (thus at 4 and 6 weeks). We agree that there is a risk of recall bias. To prevent a recall bias as much as possible, we decided to phone the patients two and four weeks after surgery as a reminder to fill in the diary. This is added to the revised manuscript (line 266-267).

14. Minor revision suggested, paragraph 1, page 12: Be specific regarding the exam data (POP-Q) and validated questionnaires that will be collected at each time interval.

This has been revised in the manuscript (line 270-272).

15. Discretionary revision/question, paragraph 2 of interventions section page 12: It is a good idea to have all investigators perform at least 20 of “each” to eliminate the learning curve. Will a participating surgeon be required to perform both of the procedures or could they partner with another surgeon so that one does the laparoscopic and the other does the vaginal procedure?

The participating surgeon is not required to perform both of the procedures. It is allowed that they partner with another surgeon: one surgeon performs the laparoscopic and one performs the vaginal procedure. A few participating hospitals act in this manner, because most surgeons have their own field of experience. This has been added to the manuscript (line 291-294).

16. Discretionary revision, paragraph 1, page 13 in section on laparoscopic sacrohysteropexy: Will the surgeon be able to run the graft further down the anterior and posterior walls of the vagina into the vesicovaginal and rectovaginal space? I suggest the authors consider dissecting the bladder further off the anterior wall and running the grafts down further to decrease the risk of anterior vaginal wall recurrences. We use a slightly different technique similar to that shown in a video published by Dr. Paraiso at the Cleveland clinic. This technique allows better proximal anterior vaginal wall support similar to that observed with laparoscopic sacrocolpopexy.

We agree that anterior and posterior vaginal wall support is better after running the grafts further down. The description in the protocol comprises a minimum of fixation of the graft. The surgeon is allowed to run the graft further down the walls. This information is added to the manuscript (line 310-311).
17. Minor revision suggested, end of paragraph 1, page 13: I suggest making an anterior and/or posterior colporrhaphy mandatory if there is any prolapse of the anterior or posterior vaginal walls at or beyond the hymen after the study procedure is completed. This is the most likely location of failures in this study.

In our original protocol, we have decided to leave the decision for complementary surgery to the surgeon. Although, we believe it is exceptional that the vaginal wall after the study procedure still exceed the hymen, we agree that in such case a colporrhaphy is necessary. This is added to the manuscript (line 317-318).

18. Discretionary revision suggested, 1st paragraph statistical analysis section for sample size, page 14: I believe that they will have at least a 10% attrition from being unhappy with the treatment allocation with more lost to follow up over the 1 and 5 year study period. Maybe there is better follow-up in a European population because of the health care system.

In our SAVE-U trial, patients were included and randomized for vaginal hysterectomy or vaginal sacrospinous fixation. In this study (which is still ongoing), 208 participants are enrolled in the study. Similar to the LAVA trial, the follow up phase is 5 years. At this moment, there are 9 patients lost to follow up in this study.

We already enrolled 26 participants in the LAVA-trial, there has been no attrition from being unhappy with the treatment allocation so far. Therefore, the 10% margin at least in our study population seems correct.

19. Major revision, last paragraph page 14, data analysis: This again concerns the primary outcome. Be specific. Sounds like a purely anatomic outcome. However, again states with symptoms. If using symptoms, need to specify what validated measure. No symptoms of vaginal bulging and protrusion on a validated questionnaire would be recommended, such as the Pelvic Floor Distress Inventory 20 question #3.

We agree with the reviewer. We specified the primary outcome in the revised manuscript (line 358-362, see also point 8).

20. Discretionary revision: I suggest that the authors also add another secondary outcome to track. They should follow uterine issues such as bleeding, cervical dysplasia, etc and the need for a subsequent hysterectomy.

We agree that this is an interesting secondary outcome. Therefore, we have added this to the study protocol (line 204-205).
The revised manuscript has been approved by all authors and has never been published, or under the consideration for publication elsewhere.

Thank you for receiving our revised manuscript and considering it for review. We appreciate your time and look forward to your response.

Sincerely,

Mèlanie van IJsselmuiden
MD/coordinating investigator LAVA-trial
Isala Zwolle The Netherlands
m.n.van.ijsselmuiden@isala.nl
+31 38 424 4692