PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a protocol for a randomised controlled trial.
AUTHORS	Baekelandt, Jan; De Mulder, Peter; Le Roy, Ilse; Mathieu, Chantal; Laenen, Annouschka; Enzlin, Paul; Weyers, Steven; Mol, Ben; Bosteels, Jan

VERSION 1 – REVIEW

REVIEWER	Daniel Steinemann Claraspital, Basel, Switzerland
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This is a well designed study on a hot topic. The removal of specimen in adenxectomy by the transvaginal route is very appealing. I do have some concerns regarding the primary endpoint. The authors assume that in 5% of cases a conversion of the technique - meaning from transvaginal to laparoscopy (removal by enlarging the umbilical incision) will be required. What would be the conversion/failure of the technique in the comparison Group? Conversion to open surgery? This is two very different Kind of conversions and you should better define the type of conversion and differ between pre-emptive and reactive conversion. Furthermore I believe that this endpoint is not important. Most patients would easily agree to take a 5% risk of getting a laparosopic instead of NOTES surgery if the alternative would be laparoscopy with mini-laparotomy. If you would instead take postoperative pain and especially postoperative recovery as a primary end point this would be far more important.

REVIEWER	Karl Jallad Cleveland Clinic, Ohio, USA
REVIEW RETURNED	07-Jul-2017

GENERAL COMMENTS	This is a randomized controlled trial assessing NOTES adnexectomy for benign pathology compared to laparoscopic excision. Overall the study is well written and the study objectives are well defined. The abstract is accurate and the study design appropriate to answer the questions. This is an important study because it is evaluating a new technique that has the potential to change the approach to adnexal surgery.

	The authors have made significant changes and improvements and the 5th version is appropriate for publication. Here are minor comments. 1- Consider providing slightly more information regarding the NOTES procedure. Type of scope used, 0 deg, 30 deg, flexible? 2- “Cefazolin and metronidazole are administered during the procedure”. Are they given prior to skin incision? If yes, consider specifying. Choice of antibiotic is based on hospital protocol, surgeon preference or specific guidelines? Same for decision of giving an additional dose post op. 3- Are the questionnaires validated in English or in the Dutch? Please clarify. 4- Just to clarify, the primary outcome is to assess women successfully treated by removing one or both adnexa without spill? In the initial version, it seems that you were switching between removing one or both adnexa without spill and removing adnexa without conversion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: I do have some concerns regarding the primary endpoint. The authors assume that in 5% of cases a conversion of the technique - meaning from transvaginal to laparoscopy (removal by enlarging the umbilical incision) will be required. What would be the conversion/failure of the technique in the comparison Group? Conversion to open surgery? This is two very different Kind of conversions and you should better define the type of conversion and differ between pre-emptive and reactive conversion.

Response: Conversion means that due to technical reasons the allocated technique as randomized was not used. This applies to both the control or intervention group. If a woman is randomized to undergo NOTES but treated by laparoscopy or laparotomy, this is a conversion. If a woman is randomized to laparoscopy, but treated by open surgery or NOTES, this is a conversion.
We have used data from an RCT by Wang et al: they reported a 2.4% failure rate to remove dermoid cysts by laparoscopy assisted colpotomy. A systematic review with meta-analysis comparing single port versus conventional laparoscopic surgery for benign adnexal disease reported a 0% conversion rate from laparoscopy to laparotomy. This additional reference has been added to the manuscript. Based on these two sources, we imputed a 5% failure rate as a sensible cut-off for designing a non-inferiority trial.

Comment: Furthermore I believe that this endpoint is not important. Most patients would easily agree to take a 5% risk of getting a laparosopic instead of NOTES surgery if the alternative would be laparoscopy with mini-laparotomy. If you would instead take postoperative pain and especially postoperative recovery as a primary end point this would be far more important.

Response: We have defined the successful removal of the adnexa by the technique as randomized as the primary outcome of effectiveness. This outcome measures in how many women the technique as allocated by a random process rather than surgeon’s or patient’s preference can be effectively carried out without spill or without having to convert to another technique. We have designed a non-inferiority study based on the superiority of the laparoscopic technique for removing adnexa over the classical open surgery approach by laparotomy.

Reviewer: 2

This is a randomized controlled trial assessing NOTES adnexectomy for benign pathology compared to laparoscopic excision. Overall the study is well written and the study objectives are well defined. The abstract is accurate and the study design appropriate to answer the questions. This is an important study because it is evaluating a new technique that has the potential to change the approach to adnexal surgery. The authors have made significant changes and improvements and the 5th version is appropriate for publication.

Here are minor comments.

1- Consider providing slightly more information regarding the NOTES procedure. Type of scope used, 0 deg, 30 deg, flexible?

Response: The following sentence is added: In both groups a 30° rigid endoscope is used. See page 9 of the
revised manuscript.

2- “Cefazolin and metronidazole are administered during the procedure”. Are they given prior to skin incision? If yes, consider specifying. Choice of antibiotic is based on hospital protocol, surgeon preference or specific guidelines? Same for decision of giving an additional dose post op.

Response: The requested change has been made:
In accordance with hospital protocol, the anaesthesiologist will administer cefazolin 2g and metronidazole 1.5g IV prior to incision for prophylaxis against infection to all women of both treatment arms. See page 9 of the revised manuscript.

3- Are the questionnaires validated in English or in the Dutch? Please clarify.

Response: The two questionnaires were validated in Dutch and presented to the participants in their mother tongue.

4- Just to clarify, the primary outcome is to assess women successfully treated by removing one or both adnexa without spill? In the initial version, it seems that you were switching between removing one or both adnexa without spill and removing adnexa without conversion.

Response: The proportion of women successfully treated by removing one or both adnexa without spill by the allocated technique as randomized will be measured as the primary outcome of effectiveness.

VERSION 2 – REVIEW

REVIEWER	Daniel Steinemann, MD Claraspital AG, Department of Visceral Surgery, Basel, Switzerland
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	I am still concerned about the Primary endpoint. You argue that a conversion is a consequence of a technical problem. In NOTES you consider a conversion a change from NOTES to laparoscopic or to open and in the laparoscopic Group the change to open surgery. I believe that you are wrong here. In NOTES it is quite frequent that you intraoperatively decide that the removal of the organ/tumor (adnexe) through the vagina is not possible due to a very large specimen or due to a small and atrophic vagina. There will be no attempt to remove the organ transvaginally. This would be a conversion and failure of the technique in your description. I would call it a "preemptive conversion". Nowadays when NOTES is established preemptive conversion account for the far most of conversions in NOTES (see also Bulian DR, Ann Surg 2010). Preemptive conversion is not afflicted with morbidity. The step from NOTES to mini-laparotomy is a small step for the patients and they usually easily agree with this intraoperative decision. However, you compare all this kind of "harmless conversions" to the conversion from laparoscopic-assisted resection to open resection (which is rare and mostly due to a intraoperative complication). Therefore the comparison is 1) unfair and 2) clinically irrelevant. I am convinced that you are planning to perform a very important and very well designed RCT and it is a pity when you choose a irrelevant primary endpoint as this will distort the findings of your study.

REVIEWER	Karl Jallad Lebanese American University Rizk Hospital, Lebanon
REVIEW RETURNED	04-Sep-2017

GENERAL COMMENTS	Overall, all points have been addressed and necessary changes have been made. This version is appropriate for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Daniel Steinemann, MD
Institution and Country: Claraspital AG, Department of Visceral Surgery, Basel, Switzerland
Competing Interests: I do have no competing interests.

I am still concerned about the Primary endpoint. You argue that a conversion is a consequence of a technical problem. In NOTES you consider a conversion a change from NOTES to laparoscopic or to open and in the laparoscopic Group the change to open surgery.

Comment: I believe that you are wrong here. In NOTES it is quite frequent that you intraoperatively decide that the removal of the organ/tumor (adnexe) through the vagina is not possible due to a very large specimen or due to a small and atrophic vagina. There will be no attempt to remove the organ transvaginally. This would be a conversion and failure of the technique in your description. I would call it a "preemptive conversion". Nowadays when NOTES is established preemptive conversion account for the far most of conversions in NOTES (see also Bulian DR, Ann Surg 2010). Preemptive conversion is not afflicted with morbidity. The step from NOTES to mini-laparotomy is a small step for the patients and they usually easily agree with this intraoperative decision. However, you compare all this kind of "harmless conversions" to the conversion from laparoscopic-assisted resection to open resection (which is rare and mostly due to a intraoperative complication). Therefore the comparison is 1) unfair and 2) clinically irrelevant.

I am convinced that you are planning to perform a very important and very well designed RCT and it is a pity when you choose a irrelevant primary endpoint as this will distort the findings of your study.

Answer:
We thank the reviewer for this criticism. We do understand his viewpoint from a clinical perspective. We do however strongly disagree with the comment that the conversion rate is an irrelevant primary endpoint. The primary aim of the planned intervention trial is to assess the efficacy/effectiveness and safety of vNOTES versus laparoscopy for performing adnexectomy. Efficacy/effectiveness deals with the answer to the questions: “Can the technique work under very controlled circumstances?” “Does the technique offer to the patient what it promises to do?” So if an RCT aims to compare the effectiveness of two antidiabetic drugs, both drugs under comparison should be studied for their capacity to offer metabolic control of the glycaemia of the study participants. For studying the efficacy/effectiveness of NOTES versus laparoscopy for doing adnexectomy, both techniques should be compared for being able to have the adnexectomy done by the allocated technique. Therefore the conversion rate was chosen as the primary outcome measure of efficacy/effectiveness. We do agree that a conversion from laparoscopy to open surgery may have a far larger impact on the overall patient’s wellbeing than a “pre-emptive conversion”. In a “scientific” research setting, it is quite unambiguous to count as a conversion every case that was not treated by the allocated technique. So a case allocated to vNOTES that was treated subsequently by laparoscopy with or without mini-laparotomy is a conversion. A case allocated to vNOTES treated by open surgery is a conversion. A case allocated to laparoscopy but treated by vNOTES is a conversion. We do agree that the impact of the conversion in each example is different but for the sake of unambiguity we preferred to keep things simple. Neither the reason to do the conversion nor the impact of the technique of conversion were taken into account. This does not imply that this does not matter at all. To our judgment it was necessary to keep definitions simple to avoid ambiguity. We are quite confident that this choice is in the interest of an objective comparison between both techniques. Moreover, we hypothesise that there is no difference between both techniques for the primary outcome (non-inferiority design).

We have defined several secondary outcomes that are highly relevant for women undergoing gynaecological surgery. We have 4 years and over 600 cases clinical experience with vNOTES and we hypothesised upfront that vNOTES may be superior to laparoscopy for decreasing operating time, decreasing postoperative pain and decreasing length of hospital stay. We wanted to test these observational data by a pilot RCT to prove in an objective way that there is indeed a difference. Meanwhile the hysterectomy trial (HALON) has been successfully completed and data are being submitted for publication.

We feel that reviewer 1's remark is important and that this issue wasn't addressed enough in our previous submission. Therefore we have added the following to the discussion:
An intraoperative decision to remove an adnexa via laparscopy and not via vNOTES due to e.g. a large specimen or an atrophic vagina may better be defined as a preemptive conversion, as it has less clinical implications than a conversion from laparoscopy to laparotomy. However, for the sake of unambiguity in this trial we decided to count as a conversion every case that was not treated by the allocated technique, whether the conversion was preemptive or not.

Reviewer: 2
Reviewer Name: Karl Jallad
Institution and Country: Lebanese American University Rizk Hospital, Lebanon
Competing Interests: None declared

Comment: Overall, all points have been addressed and necessary changes have been made. This version is appropriate for publication.

Answer:
We thank reviewer 2.