PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Lateral Episiotomy versus No Episiotomy to Reduce Obstetric Anal Sphincter Injury in Vacuum Assisted Delivery in Nulliparous Women: Study Protocol on a Randomised Controlled Trial
AUTHORS	Bergendahl, Sandra; Ankarcrona, Victoria; Leijonhufvud, Åsa; Hesselman, Susanne; Karlström, Sofie; Kopp-Kallner, Helena; Brismar Wendel, Sophia

VERSION 1 – REVIEW

REVIEWER	Lena Sagi-Dain Senior obstetrician, Department of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel
REVIEW RETURNED	24-Jul-2018

GENERAL COMMENTS	The study aims to examine the important issue of the effect of episiotomy on advanced perineal tears during vacuum delivery. In fact, it might be the first randomized controlled trial with an adequate sample to deeply examine the subject. Since we have conducted a trial examining the avoidance of episiotomy vs. standard care on OASIS in nulliparous women (the EPITRIAL), I have several suggestions for the investigators. We have faced several unexpected difficulties with compliance of obstetric personnel with trial design, as many obstetricians could not handle the deviation from common practice. Thus, continuous education of the personnel is crucial throughout the trial, as well as periodic interim analyses (as planned by the authors). Second, the investigators permit deviation from protocol in "no episiotomy" arm in specific cases, including fetal distress. This also constituted a problem in our trial, since obstetricians in favour of episiotomy seemed to note fetal distress in any case they felt episiotomy was needed. Furthermore, since episiotomy was partially allowed, the obstetric personnel still performed this procedure in "no episiotomy" arm due to other indications. Thus, based on our painful experience, the investigators should consider strictly forbidding episiotomy in "no episiotomy" arm in no case. These are mere suggestions for investigators' consideration. The protocol is finely written and can be accepted in its current form.

REVIEWER	Miranda Davies-Tuck Hudson Institue of Medical Research, Australia
REVIEW RETURNED	07-Aug-2018

GENERAL COMMENTS	Introduction: Will the new swedish guideline launched in 2017 cause issues for recruitment? If guidelines state ML epis, is your control group of no epis feasible?

	Why not also have a media/laternal group? Can you please detail when consent would be obtained? At the time of a VE being needed is not appropriate. Sample size: Authors justify a 50% decrease to prevent harm to women and then describe recruiting double the women to detect a smaller difference? This seems contradictory ? What was the rationale to make the difference to 7.8% when a 50% reduction has already been shown? why would the authors expect a smaller difference? Can the authors describe the method for the interim analysis? The power calculation states a p<0.05 will be used to determine the outcomes of the trial, but with 2 interim analyses this does not make sense?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
"The study aims to examine the important issue of the effect of episiotomy on advanced perineal tears during vacuum delivery. In fact, it might be the first randomized controlled trial with an adequate sample to deeply examine the subject.
Since we have conducted a trial examining the avoidance of episiotomy vs. standard care on OASIS in nulliparous women (theEPITRIAL), I have several suggestions for the investigators. We have faced several unexpected difficulties with compliance of obstetric personnel with trial design, as many obstetricians could not handle the deviation from common practice. Thus, continuous education of the personnel is crucial throughout the trial, as well as periodic interim analyses (as planned by the authors). Second, the investigators permit deviation from protocol in "no episiotomy" arm in specific cases, including fetal distress. This also constituted a problem in our trial, since obstetricians in favour of episiotomy seemed to note fetal distress in any case they felt episiotomy was needed.
Furthermore, since episiotomy was partially allowed, the obstetric personnel still performed this procedure in "no episiotomy" arm due to other indications. Thus, based on our painful experience, the investigators should consider strictly forbidding episiotomy in "no episiotomy" arm in no case.
These are mere suggestions for investigators' consideration. The protocol is finely written and can be accepted in its current form."

Response to reviewer 1:
Thank you for your thoughtful suggestions and for sharing research experience. It is true that obstetric personnel's preferences for or against episiotomy is a challenge in this and previous similar trials. In our setting, the objection is instead *against* performing routine episiotomy. The use of episiotomy is very restrictive in Sweden since over 20 years, to the point that many employees have never performed an episiotomy. Swedes are prone to follow rules and have adhered to the recommendation of a restrictive use of episiotomy. To date, the enrolled study sites have an episiotomy rate below or at the national average. The generally low episiotomy rate is why Sweden has some advantage as setting for the trial, to ensure the quality of the comparison group. During the initiation of the trial, we have needed to clarify that episiotomy is allowed in cases of severe fetal distress to ensure that fetal well-being is not jeopardized. In all, we do not expect it to be a problem to refrain from episiotomy, but rather to accept the trial design including routine use in one arm. We calculate an "ideal" episiotomy rate of 10% in the "no episiotomy" group. This has been updated on page 12, lines 235-238. As both intention-to-treat and per-protocol analyses will be made, we will be able to adjust for some cross-overs between groups. We now also plan to perform a safety analysis when 100 women have been randomised to ensure adherence to protocol and collate serious adverse events (page 17, lines 360-362).

Reviewer 2:
"Introduction: Will the new swedish guideline launched in 2017 cause issues for recruitment? If guidelines state MLepis, is your control group of no epis feasible?

Why not also have a media/laternal group?

Can you please detail when consent would be obtained? At the time of a VE being needed is not appropriate.

Sample size: Authors justify a 50% decrease to prevent harm to women and then describe recruiting double the women to detect a smaller difference? This seems contradictory ? What was the rationale to make the difference to 7.8% when a 50% reduction has already been shown? why would the authors expect a smaller difference?

Can the authors describe the method for the interim analysis? The power calculation states a p<0.05 will be used to determine the outcomes of the trial, but with 2 interim analyses this does not make sense?"

Response to reviewer 2:
The new Swedish guideline does not explicitly recommend episiotomy, but "to consider" episiotomy at vacuum delivery in nulliparous women. This has not been interpreted by attending physicians as to actually change practice, but just to consider performing an episiotomy. The guideline authors have knowledge, but are not part, of the EVA-trial and wanted to await results from the trial before phrasing it as a recommendation or not. To make this clearer, the word "consider" has been put in italics (page 7, line 113) and we have rephrased lines 400-402 on page 18.

We have decided to use lateral, not mediolateral, episiotomy because current research has shown that the terminology is often mixed up and when actually comparing the two techniques the difference is not that evident. Nordic obstetricians mostly use lateral technique and we believe that the technique is easier to learn to perform correctly. This has been further elaborated on page 8, lines 141-143 and 157.

Consent is obtained in antenatal care, but can also be obtained during labor if the woman has received adequate pain relief, as stated on page 10. This is *not* done at the decision to perform a vacuum, other than in exceptional cases. Some words have been added to clarify this (page 10, lines 200-201).

The sample size has been calculated to reject the null hypothesis (no difference between the groups) if the difference is at least a reduction from 12.4 to 6.2% OASIS. Since OASIS is a serious complication, several reviewers during the planning phase of the trial recommended a larger sample size to avoid a beta error, regarding a 30-40% reduction as clinically relevant. We felt that the risk-benefit balance might not be in equipoise, especially if recruitment is slow due to strong personnel preferences favoring restrictive use of episiotomy. We settled on a pragmatic solution and decided to aim for a first sample size of 355 women in each group (344 including 3% missing outcome, for example failed vacuum cesareans). This has previously been explained on page 16.

The interim analyses will be made to ensure that it is ethically defendable to continue the trial. The first interim analysis after 350 women have been randomised will reveal the unlikely event that a very large difference is apparent between the allocation groups, like in the Dutch register studies (12.4 vs 2.5%). In this analysis, we have set the p-value to 0.01 to minimize the risk of making an alpha error and erroneously decide to discontinue the trial prematurely. The second interim analysis is actually more of a preliminary final analysis with the same intention to check if the trial should go on or not. Only if recruitment is quick and easy, and a clinical equipoise between routine or no episiotomy still prevail, we will continue until all 1400 women have been included. This has previously been explained on page 17.

VERSION 2 – REVIEW

REVIEWER	Dr. Miranda Davies-Tuck Hudson Institute of Medical Research, Australia

REVIEW RETURNED	12-Oct-2018

GENERAL COMMENTS	The authors have addressed my questions.