PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study Protocol
AUTHORS	D'Souza, Rohan; Villani, Linda; Hall, Chelsea; Seyoum, Meron; Kingdom, John; Krznaric, Michael; Donnolley, Natasha; Javid, Nasrin

VERSION 1 – REVIEW

REVIEWER	Shigeki Matsubara Jichi Medical University, Japan
REVIEW RETURNED	12-Oct-2019

GENERAL COMMENTS	To authors, 1. Not only medical data but also patients-themselves-reported outcomes are involved. Also, opinions of international panel members are planned to be retrieved. These may enrich and standardize the study (core outcome determination). 2. Line 93: "around" center is right. Central, lateral, marginal, and then velamentous insertion of the cord is the classification. Please consider to mention velamentous cord insertion because vasa previa is a subtype of this insertion (Benirschke'a pathology of the human placenta). 3. Line 100 around: Please add the following meaning for the readers: "Vasa previa, one type of velamentous insertion of the cord, is usually observed in case of low-lying placenta. The cord runs on the fetal membrane unprotected between the velamentous insertion site to the placental edge." I mean that you had better write this meaning and not the phrase per se. 4. Lie 240 around: Please state that Delphi members here described "cover" almost all necessary personnel or authorities in order that this outcome-set will be appropriate. I mean that you had better justify that the Delphi members are appropriate. 5. Line 417: issue number looks "5I". I mean if it is "I", OK? 6. Line 439: Official journal,,, should be deleted. We usually do not write it. This is similar that, for example, for OBGYN (grey journal) we do not add "official journal of ACOG". Some journal name is written with small character. Please be consistent.

REVIEWER	Eric Jauniaux University college London
REVIEW RETURNED	19-Oct-2019

GENERAL COMMENTS	The authors are planning to develop a core outcome set for studies on pregnant women presenting with vasa previa (VP). Overall, I think this is an interesting approach and there is a need for standardised set of outcomes to better evaluate the

	epidemiology of VP. Heterogeneity in terminology, diagnosis and confirmation of diagnosis before and after birth is a major issue in obstetrics and this study would certainly contribute to improving the screening and management of vasa previa. I have two main comments about some aspects of the methodology: 1) Systematic review. There have been a couple of relatively recent systematic reviews published the international literature and the authors have submitted one to the AJOG in 2019 (their reference No 2). These are: Incidence of and risk indicators for vasa praevia: a systematic review. Ruiter L, Kok N, Limpens J, Derks JB, de Graaf IM, Mol B, Pajkrt E. BJOG. 2016 Jul;123(8):1278-87 & Systematic review of accuracy of ultrasound in the diagnosis of vasa previa. Ruiter L, Kok N, Limpens J, Derks JB, de Graaf IM, Mol BW, Pajkrt E. Ultrasound Obstet Gynecol. 2015 May;45(5):516-22. Thus it is not clear why they want to perform another systematic review considering that the risk factors, diagnosis and outcomes of VP are already well defined by previous systematic reviews and theirs if it gets accepted for publication. 2) In-depth interviews with current and former patients, their family members and healthcare providers. There are essentially 3 types of outcomes for VP: Cases that are diagnosed antenatally and delivered according by local/national guidelines (usually by C-section at 34-35 wks); cases that are not diagnosed antenatally and results in severe neonatal morbidity/mortality (these cases tend to be those that are registered with the IVPF) and cases that are not diagnosed antenatally but are not associated with fetal/neonatal complications during delivery (near-misses). The latter category is less likely to be reported and thus may create a bias in patient recruitment and thus in outcome evaluation.

REVIEWER	L. Ruiter Academic Medical Center, Amsterdam, the Netherlands
REVIEW RETURNED	30-Oct-2019

GENERAL COMMENTS	In this submission the authors present a proposal for defining a core outcome set in vasa previa. I am pleased to see that over the past years there is increasingly attention for this complication with such high risks of fetal morbidity and mortality. Also, the effort and attention for the impact of this diagnosis on pregnant women and their partners is very important. However, I do have some remarks as stated below. Regarding incidence and risk indicators for vasa previa, why do the authors refer to a poster from which the paper is submitted but not yet accepted/published. Why not refer to papers/studies that are already published containing this information? Line 112: Authors state that issues on diagnosis and management protocols can be adequately addressed through well-conducted prospective studies. Can authors explain in which way we will be able to do so? Do the authors have an idea of how to perform prospective research in this field?

	The incidence of vasa previa is low, so to perform a prospective study with any effecf size one must perform a very(!) large study which must continue for a certain amount of (many) years. For example, I think we must start with the process of prenatal diagnosis. Most important outcomes in these are presence of prenatal diagnosis and fetal survival and in the existing literature most studies on vasa previa do report those outcomes already. Furthermore, what will be the exact advantage of having a core outcome set? I would like to see this more specified. I think it is very important to strive for uniformity in studies, however, in my opinion a core outcome set can only be useful when methods to perform prospective research are known and clearly defined and I think this is debatable in the case of vasa previa. With the current manuscript I am not yet convinced that a core outcome set will certainly improve healthcare in women with a pregnancy complicated by vasa previa.

REVIEWER	Catanzarite, Val San Diego Perinatal Center USA
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	The authors propose an interesting methodology for determining a core set of outcomes for vasa previa. However, there are several concerns with the paper as it stands. 1. In the first paragraph, the first few sentences are incomplete. The normal placental location is not just at the fundus of the uterus; it can be anterior or posterior, and even with a placenta that extends to the fundus, there can be vasa previa. The key point here is that vasa previa is a condition in which fetal vessels run within the membranes over or near the cervix, regardless of placental location, and the authors should so state. A methodology question in all studies of vasa previa is "how close is too close". Not sure if the authors wish to address this in the introduction; hopefully this would come up in the course of the study. 2. In Step 2, Stakeholder consultation, the authors skip the important step of stating what is already known about the problem. The series of cases regarding vasa previa should give several indices of what is important to researchers and clinicians, including survival, gestational age at delivery, hospital stay, etc. 3. The recruiting mechanism is of key importance. Concrete examples: A. Current but undelivered pregnancy with vasa previa. B. Nonsurvival vs. survival. It makes sense that what matters most to a woman who lost her baby to vasa previa (most of whom will be in the no-prenatal-diagnosis group) would value certain outcomes (e.g., live healthy baby) above all. C. Uncomplicated vs. complicated course-- a woman diagnosed prenatally with vasa previa, who had a completely uncomplicated course and delivered electively at 34 weeks after a prolonged

	hospital stay may feel differently-- that a valued outcome would be no hospitalization. D. Ditto for women whose babies had serious complications from prematurity, or for women who required emergency rather than elective timed deliveries. I wonder whether "a maximum of 20" for the initial phase is enough, and whether it would be better to use two distinct groups in phase 1-- women with prenatal diagnosis and women without. Step 3- Delphi methodology. Line 239 indicates that the pilot would include at least 1 from each stakeholder group. Is this adequate? LIne 245. One stakeholder group is identified as being researchers whose publications were included in a yet-to-be-published article (reference 19). Is the article out yet? Otherwise it is hard to determine whether this would be adequate. Step 5. "Two to five representatives from each stakeholder group" is too nebulous. Suggest that the authors choose a concrete number from each group and give an explanation of the choices. Since the final meeting is a consensus development workshop, results would be potentially affected by, for example, having 5 epidemiologists, 5 researchers, and only 2 patients (or the reverse). Overall, this looks like a great idea, but the proposal would benefit from being better specified and the article accordingly revised.

REVIEWER	Sheila Turner University of Southampton UK
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	This study seems well thought through, and it is good to see this type of work being undertaken. I wish you every success.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Shigeki Matsubara, Jichi Medical University, Japan

Not only medical data but also patients-themselves-reported outcomes are involved. Also, opinions of international panel members are planned to be retrieved. These may enrich and standardize the study (core outcome determination).

- `Line 93: “around” center is right. Central, lateral, marginal, and then velamentous insertion of the cord is the classification. Please consider to mention velamentous cord insertion because vasa previa is a subtype of this insertion (Benirschke’a pathology of the human placenta).

  Authors’ response: We thank the reviewer for this comment, and acknowledge the relationship between vasa previa and non-central cord insertions (velamentous and

marginal). In consideration of this comment and those by Reviewer 4, we have modified the introduction, and have included the suggested reference, as well as the second edition of the Manual of Pathology of the Human Placenta by RN Baergen.

- Line 100 around: Please add the following meaning for the readers: “Vasa previa, one type of velamentous insertion of the cord, is usually observed in case of low-lying placenta. The cord runs on the fetal membrane unprotected between the velamentous insertion site to the placental edge.” I mean that you had better write this meaning and not the phrase per se.

Authors’ response: We have modified the first paragraph of the introduction, as well as the abstract, to incorporate the reviewer’s suggestion, while staying true to the definition of vasa previa, provided by Benirschke’s Pathology of the Human Placenta.

- Line 240 around: Please state that Delphi members here described “cover” almost all necessary personnel or authorities in order that this outcome-set will be appropriate. I mean that you had better justify that the Delphi members are appropriate.

Authors’ response: We have included the reviewer’s suggestion in lines 307-308 of the revised manuscript.

- Line 417: issue number looks “5l”. I mean if it is “l”, OK?

Authors’ response: The font has been appropriately changed. This should now read 51 and not 5l.

- Line 439: Official journal,,, should be deleted. We usually do not write it. This is similar that, for example, for OBGYN (grey journal) we do not add “official journal of ACOG”. Some journal name is written with small character. Please be consistent.

Authors’ response: The entire reference list has been formatted for consistency.

Reviewer 2: Eric Jauniaux, University college London

The authors are planning to develop a core outcome set for studies on pregnant women presenting with vasa previa (VP). Overall, I think this is an interesting approach and there is a need for standardised set of outcomes to better evaluate the epidemiology of VP. Heterogeneity in terminology, diagnosis and confirmation of diagnosis before and after birth is a major issue in obstetrics and this study would certainly contribute to improving the screening and management of vasa previa. I have two main comments about some aspects of the methodology:

1) Systematic review.

There have been a couple of relatively recent systematic reviews published the international literature and the authors have submitted one to the AJOG in 2019 (their reference No 2). These are: Incidence of and risk indicators for vasa praevia: a systematic review. Ruiter L, Kok N, Limpens J, Derks JB, de Graaf IM, Mol B, Pajkrt E. BJOG. 2016 Jul;123(8):1278-87 & Systematic review of accuracy of ultrasound in the diagnosis of vasa previa. Ruiter L, Kok N, Limpens J, Derks JB, de Graaf IM, Mol BW, Pajkrt E. Ultrasound Obstet Gynecol. 2015 May;45(5):516-22. Thus it is not clear why they want to perform another systematic review

considering that the risk factors, diagnosis and outcomes of VP are already well defined by previous systematic reviews and theirs if it gets accepted for publication.

Authors' response: We thank the reviewer for this comment. The systematic review that is proposed for purpose of developing the core outcome set is much broader, in that it is not restricted to larger cohort studies that report on the prevalence of vasa previa and its risk factors, but also includes case reports and smaller case series, since the intention is to identify all clinical, radiologic and patient-reported outcomes that have been published in the literature, and to determine how these outcomes have been measured. The objectives of the two systematic reviews, and therefore the inclusion criteria are vastly different, as we have attempted to describe in Step-1.

2) In-depth interviews with current and former patients, their family members and healthcare providers. There are essentially 3 types of outcomes for VP: Cases that are diagnosed antenatally and delivered according by local/national guidelines (usually by C-section at 34-35 wks); cases that are not diagnosed antenatally and results in severe neonatal morbidity/mortality (these cases tend to be those that are registered with the IVPF) and cases that are not diagnosed antenatally but are not associated with fetal/neonatal complications during delivery (near-misses). The latter category is less likely to be reported and thus may create a bias in patient recruitment and thus in outcome evaluation.

Authors' response: We agree with the reviewer that the input from pregnant persons not diagnosed antenatally, and that have no complications during childbirth (near-misses), will not be represented either through the IVPF or any other manner of recruitment. However, as the intent of developing a core outcome set, is to inform outcome reporting and measurement on studies on vasa previa, we do not anticipate that this group will have any specific outcomes to report, that will not already have been covered by the other two groups, including those related to screening, diagnosis, management, resource-use, mental health, quality of life and long-term outcomes. We have however, added a section to the revised manuscript, to ensure that we include participants with as diverse a range of experiences, as possible.

Reviewer 3: L. Ruiter, Academic Medical Center, Amsterdam, the Netherlands.

In this submission the authors present a proposal for defining a core outcome set in vasa previa. I am pleased to see that over the past years there is increasingly attention for this complication with such high risks of fetal morbidity and mortality. Also, the effort and attention for the impact of this diagnosis on pregnant women and their partners is very important. However, I do have some remarks as stated below.

Regarding incidence and risk indicators for vasa previa, why do the authors refer to a poster from which the paper is submitted but not yet accepted/published. Why not refer to papers/studies that are already published containing this information?

Authors' response: We opted to go with the most recent review on the topic, which included studies published since 2015, and provided a slightly different estimate (0.46 per 1000, as opposed to 0.60 per 1000). At the time of citing this review, we had hoped that the conference paper would be accepted by the time the current paper is published. Since this is not yet the case, we have included the earlier systematic review and its estimate in the revised manuscript.

Line 112: Authors state that issues on diagnosis and management protocols can be adequately addressed through well-conducted prospective studies. Can authors explain in which way we will be able to do so? Do the authors have an idea of how to perform prospective research in this field? The incidence of vasa previa is low, so to perform a prospective study with any effect size one must perform a very(!) large study which must continue for a certain amount of (many) years.

Authors' response: Prospective studies do not necessarily refer to single-centre randomized controlled trials, which indeed would take many years to complete, with a condition as rare as vasa previa.

In contemporary obstetrics and obstetric medicine, the rarity of a clinical condition is seldom a contraindication to conducting prospective research. Even for the rarest of conditions, international registries have now been established through RedCap, in order to prospectively gather data. Prospectively-gathered data through international registries, has numerous advantages over single-centre retrospective studies and has helped inform clinical practice in areas such as heart and lung transplants in pregnancy (https://ishlt.org/registries/overview), among others. Prospective multicentre studies on vasa previa, conducted under the auspices of organizations such as The International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) are an opportunity that similarly need to be tapped.

Registry-based studies are not the only prospective studies that can be conducted in this area. Observational studies and randomized trials using varied designs, including cluster randomized trials can be used to effectively answer questions with regard to the universal vs. risk-factor-based screening for vasa previa, inpatient vs. outpatient management during the second trimester of pregnancy, or routine vs. targeted use of corticosteroids. Depending on the primary outcome, and the number of sites involved, many of the clinical questions can be answered effectively using prospective research.

Prevalence studies, conducted using retrospective data have their flaws. Prospectively-gathered data using a policy or universal screening vs. targeted screening, over a finite period, would be able to give a much better idea of the true prevalence of the condition, and risk factors.

Finally, prospective research also includes qualitative research – knowing how our patients may be affected by universal screening for vasa previa, or prolonged hospitalization, for example. Serial interviews conducted in real-time, could bring to light many aspects of care that are currently overlooked, and could add considerably to the existing body of literature gathered by the authors from past experiences of patients. These studies, as the authors have shown, helps also with the identification of barriers and challenges to the implementation of care, an important aspect to consider, to ensure the success of clinical programs.

These are some of the examples of how prospective studies can be conducted in the area, to inform clinical practice and health policy.

For example, I think we must start with the process of prenatal diagnosis. Most important outcomes in these are presence of prenatal diagnosis and fetal survival and in the existing literature most studies on vasa previa do report those outcomes already.

Authors' response: Through the development of core outcome sets, it has become apparent that there are considerable differences in what clinicians, researchers, patients and policy makers view as important outcomes. As outlined in the manuscript, outcomes in medical research are broadly categorized into five core areas – mortality/survival, morbidity (clinical/physiological), functioning (life impact), resource use and adverse events.

The reviewer mentions two outcomes as most important with regard to prenatal diagnosis. One of these (fetal survival) is in the broad area of mortality/survival. The second (presence of prenatal diagnosis) is what would be considered an intermediary/radiologic/surrogate outcome, not belonging to any of these categories.

The reviewer is right that most studies only report on these outcomes. However, to a patient, prenatal diagnosis has wider implications – how this diagnosis affects her quality of life and her mental health from the need for prolonged hospitalization or resource utilization for the hospital and the healthcare system, are seldom reported. Yet, these outcomes (albeit less important to clinicians and researchers, and hence seldom reported), are important to other stakeholders such as policy makers in publicly funded health systems, and most importantly to patients and families, the greater good of whom, all clinical research should be directed towards.

Medicine has often been criticized for doing a excellent task of keeping patients alive, but without consideration of the quality of that life. While fetal survival is an important outcome, to a mother and a family, arguably, 'intact survival' may be a more important outcome. The survival of an extremely premature infant that spends months in the neonatal intensive care unit and is finally discharged with serious disabilities, may be an outcome that most obstetricians will not consider, due to the scope of their practice, but to a neonatologist and to families, this outcome might have different connotations.

It is to this end that emphasis is being placed on patient-reported outcomes and the outcomes considered important to other stakeholders involved in the care of patients, and to their incorporation into clinical studies.

In summary, it would be premature to state that prenatal diagnosis and fetal survival are the only outcomes or the most important outcomes in studies on vasa previa. The qualitative work done by the authors, with patients of vasa previa, midwives and obstetricians, suggest that there are other outcomes that affect patients, carers and healthcare systems, that are not reported in published studies. The purpose of developing a core outcome set, is to ensure that clinical studies in the area of vasa previa, no longer make the error of only reporting outcomes that only clinicians or researchers consider important, but open the gates to including patient-reported outcomes in clinical studies.

Furthermore, what will be the exact advantage of having a core outcome set? I would like to see this more specified. I think it is very important to strive for uniformity in studies, however, in my opinion a core outcome set can only be useful when methods to perform prospective research are known and clearly defined and I think this is debatable in the case of vasa previa. With the current manuscript I am not yet convinced that a core outcome set will certainly improve healthcare in women with a pregnancy complicated by vasa previa.

Authors' response: While we have attempted to answer this question in response to the reviewer's previous comment, a few points need to be re-emphasized. The qualitative research the authors have conducted in the area has highlighted the disconnect between what outcomes patients and various clinicians/ researchers consider important. As the reviewer has rightly stated, clinical research tends to report on measurable outcomes, which in some instances are clinical (fetal survival) but in other instances may be intermediary such as laboratory markers and radiologic findings (presence of prenatal diagnosis), regardless of the clinical consequences of the outcome. This is true not only in regard to the example stated by the reviewer, but with most aspects of the diagnosis and management of vasa previa.

We have shown through several publications (unrelated to vasa previa), how clinical studies often do not report on the other core outcome areas, especially life impact, resource use and adverse consequences of interventions and diagnosis. Yet, these are important parameters which shared decision-making is based on, and we therefore believe, must be appropriately reported and measured, in order to be able to fully interpret study findings. The Outcome Reporting in Obstetric Studies (OROS) Group, of which the authors are members, is committed to improving outcome reporting in obstetric studies in two main areas – (1) ensuring that a set of core outcomes, determined by patients and other stakeholders involved in their care, are consistently reported and measured, in order to enable comparison between studies and the making of meaningful clinical conclusions and (2) ensuring the comprehensiveness of outcome reporting, whereby studies whenever possible, report on outcome related to both mother and baby, in all five core outcome areas, as identified earlier. Given the rarity of vasa previa, ensuring that core outcomes are consistently and comprehensively reported in all studies, is critical. The development of a core outcome set, developed through established methodology is instrumental in making this possible.

Reviewer 4: Val Catanzarite MD PhD, San Diego Perinatal Center, USA

The authors propose an interesting methodology for determining a core set of outcomes for vasa previa. However, there are several concerns with the paper as it stands.

1. In the first paragraph, the first few sentences are incomplete. The normal placental location is not just at the fundus of the uterus; it can be anterior or posterior, and even with a placenta that extends to the fundus, there can be vasa previa. The key point here is that vasa previa is a condition in which fetal vessels run within the membranes over or near the cervix, regardless of placental location, and the authors should so state.
A methodology question in all studies of vasa previa is "how close is too close". Not sure if the authors wish to address this in the introduction; hopefully this would come up in the course of the study.

Authors' response: We thank the reviewer for this comment. In keeping with the suggestions of this reviewer and Reviewer 1, we have modified the introduction, to better reflect the definition of vasa previa.

2. In Step 2, Stakeholder consultation, the authors skip the important step of stating what is already known about the problem. The series of cases regarding vasa previa should give several indices of what is important to researchers and clinicians, including survival, gestational age at delivery, hospital stay, etc.

Authors' response: Since this publication is a study protocol, we have refrained for publishing results of the systematic review of case reports, series and observational studies. This will be published separately. The reviewer however, is correct that Step-2 could benefit from a mention on what is already known about the problem, and why it is important to conduct this step. We have added the following sentence to the revised manuscript. "…However, these studies were focussed on eliciting experiences of patients and midwives, identifying barriers and challenges to care, and determining variations in opinions and clinical practice. None specifically focused on identifying the outcomes that could inform the development of COVasP."

3. The recruiting mechanism is of key importance.
Concrete examples:
A. Current but undelivered pregnancy with vasa previa.
B. Non-survival vs. survival. It makes sense that what matters most to a woman who lost her baby to vasa previa (most of whom will be in the no-prenatal-diagnosis group) would value certain outcomes (e.g., live healthy baby) above all.
C. Uncomplicated vs. complicated course-- a woman diagnosed prenatally with vasa previa, who had a completely uncomplicated course and delivered electively at 34 weeks after a prolonged hospital stay may feel differently-- that a valued outcome would be no hospitalization.
D. Ditto for women whose babies had serious complications from prematurity, or for women who required emergency rather than elective timed deliveries.
I wonder whether "a maximum of 20" for the initial phase is enough, and whether it would be better to use two distinct groups in phase 1-- women with prenatal diagnosis and women without.

Authors' response: We thank the reviewer for this extremely insightful comment. It is definitely our intention of including current and former patients, with as varied experiences and backgrounds as possible, as we have stated. We had considered including some of the subgroups mentioned by the reviewer, in Table 1, but sub-stratification into too many groups made numbers in each group seem very small. Since we are committed to obtaining as diverse a representation as possible, and since, the groups mentioned by the reviewer are vital to ensuring that we obtain a comprehensive account of outcomes, we have explicitly included these sub-groups into the revised manuscript.

With regard to the maximum of 20 interviews, we had based this off two qualitative studies conducted with patients with vasa previa and healthcare professionals caring for them, wherein data saturation was attained after the conduct of 14 and 20 interviews respectively. The reviewer is correct in stating that 'a maximum of 20' sounds restrictive, and it is certainly not our intention to terminate interviews upon

attainment of a number, without attaining data saturation. For the same reason, we also do not intend to restrict numbers to ten in each group. We have therefore made the following modification to the revised manuscript, "Based on interviews we have conducted with patients and healthcare professionals in this area, wherein data saturation was attained after the conduct of 14-20 interviews, we anticipate that we will conduct approximately 20 patient interviews and 10-12 interviews with clinicians/researchers until data saturation is reached and no new outcomes are identified in two successive interviews."

Step 3- Delphi methodology. Line 239 indicates that the pilot would include at least 1 from each stakeholder group. Is this adequate?

Authors' response: We understand the reviewer's concern regarding piloting the survey on a small group of ten participants. However, we must clarify the following:

1. ***For purposes of the survey, we will be using the software DelphiManager, as stated in the manuscript. This software has been successfully used for numerous core outcome set surveys, including two by our group, and details with regard to formatting, font, display etc. have been pre-approved.***
2. ***All outcomes obtained through the systematic review and interviews, will be retained, and will not be reduced based on piloting.***
3. ***Many of the lay language summaries for common clinical outcomes have already been piloted as part of Delphi surveys conducted for core outcome set development for conditions such as obesity, iron deficiency anaemia, venous thromboembolism and cardiac disease in pregnancy, and are unlikely to need changing.***
4. ***The only purpose of the piloting the Delphi survey is to ensure that the lay-languages summaries created for outcomes unique to studies on vasa previa, are reviewed by representatives of all stakeholder groups, so that we are able to make modifications based on comments obtained, prior to launching the formal survey.***

We believe that a total of 10 members that includes at least one per stakeholder group, would therefore be sufficient for this step. We have clarified this in the revised manuscript.

Line 245. One stakeholder group is identified as being researchers whose publications were included in a yet-to-be-published article (reference 19). Is the article out yet? Otherwise it is hard to determine whether this would be adequate.

Authors' response: We understand the reviewers concerns with regard to this reference. Although not yet published (revisions to the manuscript have been submitted at the time of this submission), we can confirm that this systematic review includes 160 studies, representing every case report, series, and observational study published on the topic. Therefore, it is our hope that every researcher in the area will be contacted, and asked to participate in the Delphi survey.

Step 5. "Two to five representatives from each stakeholder group" is too nebulous. Suggest that the authors choose a concrete number from each group and give an explanation of the choices. Since the final meeting is a consensus development workshop, results would be potentially affected by, for example, having 5 epidemiologists, 5 researchers, and only 2 patients (or the reverse).

Authors' response: Once again, we understand the reviewer's concerns, and have re-written this entire section, to reflect its intent, and the manner in which the final core outcome set will be arrived at. We aim to explain this, below:

(a) All outcomes scored as 'critical for inclusion' (scores 7-9 on the second Delphi round), by 70% of all stakeholders, as well as by 70% of patients alone, will be retained and included in the final core outcome set, and will not be debated. Outcomes scored as 'not important' (1-3) by 70% of stakeholders, will automatically be eliminated. The only outcomes that will be debated at this meeting are those that are scored 4-6 (important but not critical).

(b) We acknowledge that 2-5 representatives from each stakeholder group seems nebulous. We added this number, as it is impossible to ensure the presence of a pre-specified number of stakeholders, especially patients, for a face-to-face consensus meeting, for a condition that is so rare. Developers of core outcome sets for obstetric conditions have not included between 14 and 29 participants in this step. In keeping with the comments of the reviewer, we have changed "two-to-five representatives" to ensuring 'equal representation' of each stakeholder group, without specifying a number.

We have added this to the revised manuscript and have also added details on how we intend to present our results, to ensure greater transparency.

Overall, this looks like a great idea, but the proposal would benefit from being better specified and the article accordingly revised.

Authors' response: Once again, we thank the reviewer for these very insightful comments, and hope that the revised manuscript that incorporates these recommendations, meet the reviewer's approval.

Reviewer 5: Sheila Turner, University of Southampton, UK

This study seems well thought through, and it is good to see this type of work being undertaken. I wish you every success.

Authors' response: We thank the reviewer for her encouraging comments.