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Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study Protocol

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Abstract

Introduction:

In vasa previa, umbilical blood vessels travel embedded in the fetal membranes between the baby and the uterine cervix, unprotected by either Wharton's jelly or placenta. During rupture of membranes, these vessels can rupture and put the baby at serious risk of severe blood loss and death. Numerous studies are being conducted to improve diagnostic modalities and establish clear management plans to improve pregnancy outcomes. However, the lack of a standardized set of outcomes for studies on vasa previa makes it difficult to compare study findings and draw meaningful conclusions. Through this project, we will be developing a core outcome set for studies on pregnant women with vasa previa (COVasP).

Methods and analysis:

The development of COVasP will involve five steps. The first will be a systematic review, in which we will generate a long list of outcomes based on published studies in pregnancies complicated with vasa previa. The second will involve in-depth interviews with current and former patients, their family members and healthcare providers that care for these patients. This will be followed by a two-round Delphi survey, which will aim to narrow down the long list of outcomes into those considered important by four groups of 'stakeholders': 1) patients, family

members and patient advocates/representatives, 2) healthcare providers, 3) researchers, epidemiologists and methodologists and 4) other stakeholders directly or indirectly involved in the management of these pregnancies such as administrators, guideline developers and policy makers. The fourth step will involve a face-to-face consensus meeting using a nominal group approach to establish a finalized core outcome set. The final step will involve measuring and defining the identified outcomes using a combination of systematic reviews and Delphi surveys.

Ethics and Dissemination

This study as well as consent forms for stakeholder participation have received approval from the Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the Human Research Ethics Committee at The University of Technology Sydney, Australia on 30 July 2019 (UTS HREC REF NO. ETH19-3718). All progress will be documented on the international prospective register of systematic reviews (PROSPERO) and Core Outcome Measures in Effectiveness Trials (COMET) databases.

Keywords

Vasa Previa, Core outcome set, velamentous umbilical cord insertion, stakeholder and patient-reported outcomes

Registration details

http://www.comet-initiative.org/studies/details/1117

Article summary

This protocol describes the development of a core outcome set for studies on vasa previa.

Strengths and Limitations of this study

- This core outcome set will draw from outcomes reported in all experimental and observational studies, as well as case reports and trial registrations, and will not eliminate outcomes from studies that would otherwise be considered at increased risk-of-bias, in order to obtain the most comprehensive initial list of outcomes possible.
- The multinational group of investigators are supported by the International Vasa Previa Foundation and will draw input from numerous international organizations to ensure global representation of all stakeholders.
- Increased emphasis is being placed on the qualitative steps of core outcome set development, in order to ensure that patient-reported outcomes and outcomes related to quality of life, resource use and functioning are considered alongside clinical outcomes.
- This core outcome is being developed as part of the Outcome Reporting in Obstetric Studies (OROS) project (https://www.obgyn.utoronto.ca/oros-project), whose investigators not only have expertise in the conduct of core outcome sets, but are currently setting standards for outcome reporting in obstetric studies.

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Introduction

In normal fetal development, the placenta implants near the top of the uterus and the umbilical cord inserts into the center of the placenta to transport nutrients and oxygen from the mother to the fetus. In some cases, umbilical blood vessels run unprotected outside the umbilical cord and are present in the membranes surrounding the baby. These abnormal vessels can cross the internal opening of the cervix and interfere with the baby's path during labour(1). When the membranes rupture, these abnormal vessels can rupture as well and put the baby at serious risk of severe blood loss and death if delivered vaginally. This condition is called vasa previa and is believed to affect one in 2174 pregnancies.(2) The proximity of fetal vessels to the internal os of the cervix increases the risk of hemorrhage upon spontaneous or artificial rupture of the membranes resulting in serious complications to the fetus, including hypotension, irregular heart rate and fetal death from exsanguination. If vasa previa is not diagnosed prior to labour and vaginal delivery, approximately 40-60% of newborns do not survive.(3, 4) Early diagnosis and the introduction of clear management plans are imperative for improving outcomes in this population. However, there is no consensus on the optimal methods for diagnosis and various aspects of management.

Women who have been diagnosed with this condition have described feeling "like a ticking time bomb" and expressed the reality of "coping with inconsistent information".(5) Preferences of pregnant women with the condition, and outcomes that they consider important have not yet been elucidated. Finally, the cost implications to healthcare systems from inpatient vs. outpatient management and the use of various diagnostic modalities and management protocols have not been determined.

While these issues can be adequately addressed through well-conducted prospective studies, there is uncertainty with regards to the outcomes that should be measured in these studies that are

considered important by pregnant women and other stakeholder groups including healthcare providers, researchers and policy makers. Determining this core set of outcomes that should comprise the bare minimum for inclusion in all further studies is therefore vital.

A core outcome set is a set of outcomes that are considered important by those suffering from the condition, their family members and those involved in their care. Once developed, this minimum set of outcomes should be reported in all clinical studies on the condition.

The goal of this study is to gather patient and other stakeholder input regarding the outcomes important to them, and use this to create a set of outcomes for studies involving vasa previa and pregnancy which provide researchers in future studies a list of outcomes that must be reported, in order to improve the translational value and clinical usage of such research. This project will reduce bias in outcome reporting, enable meta-analysis of published data to inform decision-making, and provide an empiric basis for inclusion of stated outcomes based on input from relevant stakeholders.

Methods and analysis

The protocol for this Core Outcome Set for studies on Vasa Previa (COVasP) is registered on the Core Outcome Measures in Effectiveness Trials (COMET) website. It is guided by the COMET handbook(6) and complies with the Core Outcome Set – Standardized Protocol Items (COS-STAP) statement.(7) As with other core outcome sets being developed as part of the University of Toronto's Outcome Reporting in Obstetric Studies (OROS) project (https://www.obgyn.utoronto.ca/oros-project), COVasP will be developed in five distinct steps, involving qualitative and quantitative research methods, as outlined in Figure 1.(8, 9)

Step-1: Systematic Review:

A systematic literature review will be undertaken to explore all reported outcomes in published studies involving pregnant women with vasa previa, and will generate a preliminary list of outcomes that are deemed important and hence reported by researchers. The protocol for this systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, is available on the international prospective register of systematic reviews - PROSPERO (CRD42018087837).

Study selection: Five bibliographic databases - Medline, Embase, Cochrane, PubMed and Clinicaltrials.gov will be searched from inception. All interventions and exposures will be included. Randomized or non-randomized studies, prospective and retrospective cohort studies, case-control studies, case series, case reports, qualitative research, as well as economic evaluation studies and decision analyses will be included in the search. We will exclude letters to the editor, commentaries, editorials, conference abstracts that do not describe clinical outcomes and reviews that do not report on outcomes or contain original research.

Data Extraction: Extracted information will include details on study characteristics such as publication year, number of participants, study type, number of included pregnancies, as well as individual and composite outcomes and their definitions, components and measurement instruments when available.

Quality Assessment: As the purpose of this review is to identify reported outcomes and not to determine the effectiveness of management strategies, no assessment of the study's methodological quality will be performed. Similarly, as the aim of this systematic review is to identify all reported outcomes in order to generate a long-list of outcomes to inform the development of the core outcome set, and there is no validated tool to assess the quality of

outcome reporting, it was decided a priori that the quality of outcome reporting of included studies would not be assessed.

Analysis and presentation of results: The proportion of studies reporting each outcome and the components will be documented. No subgroup or sensitivity analysis is proposed.

Step 2: Stakeholder Consultation

In addition to identifying outcomes reported by researchers, we aim to understand what maternal and perinatal outcomes are considered important by women with a diagnosis of vasa previa, their family members, health care providers and researchers. Qualitative methodology provides a scope for all relevant stakeholders to discuss their views on important outcomes, and contributes to the robustness of core outcome set development by identifying the new outcomes that were not reported in the literature, exploring why the outcomes are considered important, and understanding the scope and priority of the outcomes.(10) Our systematic literature review found only three qualitative studies on vasa previa; that were conducted with the women,(5) midwives(11) and obstetricians.(12) However, none specifically focused on identifying the outcomes that could inform the development of COVasP. Hence, we will conduct a descriptive-interpretive qualitative research study(13) with the relevant stakeholders in high-income countries.

Inclusion criteria: We will include women who have had a diagnosis of vasa previa (current or previous) and their partners, health care providers who have cared for women with a diagnosis of vasa previa, and health care professionals who have been involved in conducting research or development of a policy/guideline in relation to vasa previa that are above the age of 18 and able to give informed consent and participate in an interview in English language. Women and their

partners will be excluded if they (or their partners) had been diagnosed with vasa previa that was not confirmed at a later stage during pregnancy or birth.

Sampling: Women and their partners will be recruited through an established partnership with the International Vasa Previa Foundation - IVPF (http://vasaprevia.com). The IVPF is an all-volunteer charity created to promote awareness and provide support and advocacy to the general public and professionals regarding vasa previa. Earlier this year the IVPF sent out an 'Expression of Interest' email to their members which was also shared on social media in relevant peer support groups as a means of recruitment. To ensure that the views of women with different experiences and backgrounds are represented, specific criteria (age, type of conception, time of diagnosis, and country where care was received) will be selected to provide maximum variation sampling as outlined in Table 1.(10) Healthcare providers and researchers will be recruited through email using a study flyer, via contact lists assembled by the study investigators. As is the norm with qualitative research, the exact sample size will be determined once data collection and analysis are commenced.(14) We will conduct up to 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.

Consent: Information regarding the aims of the study and the process of interview will be provided to interested individuals in writing by means of a participant information sheet, highlighting that participation is voluntary. Individuals will be given an opportunity to contact the researchers to receive more information before they make an informed consent to participate in an interview. Only individuals who provide written and/or verbal consent will be interviewed.

Data collection: All interviews will be conducted online or over the phone. Upon commencement of the interview, the interviewer will confirm that the participant has read the

participant information sheet and consent form and obtain verbal consent. The interviewer will then request certain demographic details, which the participants may or may not choose to answer. Demographic details will vary slightly depending on stakeholder group but include: age, occupation, education, ethnicity and descriptions of their experiences with vasa previa or number of years working with this population, as appropriate. After a brief introduction, and providing a description of the project and explanation of what constitutes health outcomes the interview will commence. The interviews are designed to be semi-structured and conversational using a topic guide (Appendix A). The goal is to ensure that the participant feels comfortable sharing their views and experience while ultimately eliciting health outcomes important to the participants that can then further inform our core outcome set development. During the reflective and iterative process of data collection and analysis, the topic guide may be refined and/or expanded to include the issues raised by earlier participants. One experienced qualitative researcher will conduct all the interviews by telephone or online. The interviews will be audio-recorded and transcribed verbatim.

Data analysis: Thematic data analysis(15) taking a descriptive interpretive approach(16) will start after the first interview. The data will be imported into NVivo V.12 software, which will assist with data management and analysis. Transcripts will be read and coded by a qualitative researcher (NJ) who conducted the interviews. The codes, emerging categories and the related quotes will be discussed with the research team, that includes at least one physician that cares for pregnant women with vasa previa, to reach agreement. Information and outcomes obtained through this qualitative data analysis will be used to develop a list of outcomes deemed important by the participants, which will inform the subsequent Delphi study.

Step-3: **Delphi Methodology:**

Steps 1 and 2 generate a long list of outcomes considered important by researchers, women and other stakeholders involved in their care. The Delphi process that follows, is designed to achieve convergence of opinion on these outcomes, in an iterative and sequential manner.(17) For this step, we will identify four groups of 'stakeholders': 1) women, family members and patient advocates or representatives, 2) healthcare providers, 3) researchers, epidemiologists/ methodologists and core outcome set developers, and 4) other stakeholders directly or indirectly involved in the care of pregnant women such as administrators, guideline developers and policy makers. The Delphi survey will be developed by grouping the long list of outcomes (obtained through steps 1 and 2) into domains based on a published taxonomy.(18) Lay-language summaries will appear alongside complex medical outcomes. The survey will be piloted with at least 10 people including one person from each stakeholder group. After piloting, the survey will be made available online (through links on social media) and widely distributed through identified listservers of relevant organizations, including but not restricted to the Cochrane Pregnancy and Childbirth Group (30 members), the Global Obstetric Network (237 members), Core Outcomes in Women's and Newborn Health (CrOWN) initiative (77 members), corresponding authors of publications on vasa previa included in a recent systematic review,(19) IVPF, United Kingdom Obstetric Surveillance System (UKOSS) https://www.npeu.ox.ac.uk/ukoss, UK Vasa Praevia Raising Awareness Trust (http://vasapraevia.co.uk), Australasian Maternity Outcomes Surveillance System (AMOSS) https://www.amoss.com.au, Perinatal Society of Australia and New Zealand (PSANZ) https://www.psanz.com.au and Vasa Praevia Support and Awareness Ireland (https://www.facebook.com/vasapraeviasupportandawarenessIreland). We will aim to recruit at least 25 individuals from each stakeholder group to ensure an appropriate degree of

representation. An online approach using DelphiManager™ software will be employed, to ensure privacy, feasibility, cost effectiveness and reliability, while facilitating global representation.(6) Upon signing an online consent form and completing a brief demographic questionnaire, participants will be required to score each outcome on a 9-point Likert Scale based on its perceived degree of importance. Scores of 1 to 3 will be considered as 'not essential'; 4 to 6, 'important but not critical'; and 7 to 9, 'critically important for inclusion'.(6) Participants will also be presented with a text box for them to enter any outcomes they deem important, which might not have been included in the list provided.

Analysis: In order to mitigate respondent fatigue in the second round, outcomes assigned scores of 1-3 by >70% participants from all stakeholder groups and 7-9 by <30% will be removed from the next round. In order for an outcome to be removed, it is essential that the above criteria are met by all stakeholder groups individually. Should an outcome fulfil criteria for removal by three stakeholder groups, but not by patients, that outcome would still be retained for the second round. All outcomes entered into text boxes, if deemed (by the COVasP investigators) as distinct from those presented, will be included into the second round. Upon completion of first-round analysis, an invitation will be sent out to all members requesting participation in the **second round.** Each member scoring outcomes in the second round will have access to mean scores for the entire group as well as those for individual stakeholder groups, to enable them to decide on whether they would like to retain their original score, or modify it based on the total- and individual group scores from the first round. Email reminders will be sent out to ensure that at least 85% of respondents complete both surveys, to prevent attrition bias. In the final analysis, all outcomes that were scored 7-9 by >70% of participants from each stakeholder group and 1-3 by <30% will automatically be included into the core outcome set. All other outcomes, stratified

under 'important but not critical' or 'critical' will be considered at a consensus group meeting. Each participant will be asked whether they would like to and be able to attend the face-to-face consensus meeting in Toronto, Canada.

Missing Data and Attrition: Participants will be given clear outlined expectations of timelines and a six-week window to complete each round of the survey. We will clearly stipulate in the original invitation to participate that those that do not complete the first round will not be invited to the second round. Should the response rate not achieve 80%, a level deemed acceptable by published recommendations(6), additional interventions will be implemented, guided by measures adopted by other COS developers. Telephone calls, emails, personal reminders and extension of the survey deadlines may be used to improve the response rate. Any feedback after the first round regarding obstacles when completing the survey in its entirety will be noted and addressed before the second round.

Step 4: Consensus meeting

Two to five representatives from each stakeholder group that express interest in participating will be selected at random to attend the face-to-face consensus meeting, aimed at reaching consensus on the core outcome set. We will use a **nominal group technique** (NGT), a structured variation of a small-group discussion, to reach consensus on the final core outcome set.(20) NGT gathers information by asking individuals to respond to questions posed by a moderator, and then asking participants to prioritize the ideas or suggestions of all group members. The process prevents the domination of the discussion by a single person, encourages all group members to participate, and results in a set of prioritized solutions or recommendations that represent the group's

preferences. This consensus meeting will occur over a half-day and will be conducted in keeping with the specifications laid out by the Evaluation Research Team at the Centre for Disease Control.(20) The first step will involve the moderator presenting outcomes that need to be discussed, and encouraging each participant to work independently and silently. This will be followed by encouraging group members to engage in a round-robin feedback session to concisely record each outcome (without debate at this point), followed again by a discussion on each outcome to determine clarity and importance. Here, there will be an opportunity for members to express their understanding of the logic and the relative importance of the outcome. The final step will involve a vote wherein participants will vote privately to prioritize the outcomes. Participants will vote using an electronic device to ensure anonymity. The votes will be tallied to identify the outcomes that are rated highest by the group as a whole. The moderator will establish what criteria are used to prioritize the ideas. To start, each group member will select the five most important outcomes from the list and write one idea on each index card. Next, each member ranks the five ideas selected, with the most important receiving a rank of 5, and the least important receiving a rank of 1. After members rank their responses in order of priority, the moderator will create a tally sheet on the flip chart with numbers down the left-hand side of the chart, which correspond to the ideas from the round-robin. The moderator will collect all the cards from the participants and ask one group member to read the outcome number and number of points allocated to each one, while the moderator records and then adds the scores on the tally sheet. The outcomes that are the most highly rated by the group are the most favoured group outcomes in response to the question posed by the moderator. The entire process will be audio-recorded.

Step 5: Measuring/defining core outcomes

Upon selection of a final list of core outcomes, we will employ the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) to assess measurement tools/ definitions for included outcomes based on four criteria: validity, responsiveness, reliability and interpretability.(21) We will begin the process by listing measurement instruments and/or definitions for outcomes where universal agreement exists. For outcomes where there is a lack of agreement on measurement instruments or definitions, we will conduct systematic reviews to determine all currently used instruments and definitions. This will be followed by Delphi surveys involving relevant stakeholder groups as required, to determine the most appropriate definition or measurement instrument for each identified core outcome where systematic reviews are inconclusive.(22)

Patient and Public Involvement

Although the steps of developing a COS as standardized, we will involve patients and other stakeholders in steps 2-4, first through recruitment followed by interviews, the Delphi survey and a consensus meeting. The purpose of their involvement is to determine what outcomes related to vasa previa are most important to them. The design of the study encourages stakeholders to consider outcomes related to domains such as functioning, resource use, satisfaction, compliance, healthcare delivery and mental health concerns in addition to the clinical and physiological outcomes most commonly reported in research studies. We have taken steps to ensure that these outcomes considered important by patients are represented in the final COS. We aim to involve patients in ensuring that the COS is disseminated widely through the IVPF webpage and also through social media, in addition to ensuring knowledge translation to

clinicians and researchers. The findings of each step of COVasP development will be published on the Outcome Reporting in Obstetric Studies website (https://www.obgyn.utoronto.ca/oros-project), enabling ongoing feedback from patients and the public.

Discussion

COVasP aims to provide researchers and clinicians with a systematically-derived list of outcomes, incorporating preferences of patients and other relevant stakeholders, which will form the minimum standard required to be collected, measured and recorded as a baseline in all clinical studies on vasa previa. Input from various stakeholder groups will enhance the quality and relevance of future studies on vasa previa, and go a long way in improving outcomes that are considered most important by those that are affected by this rare but morbid obstetric condition.

List of Abbreviations

COSVasP – Core Outcome Set for Studies on Vasa Previa

COMET – Core Outcome Measurement in Effectiveness Trials

CROWN – CoRe Outcomes in Women's and Newborn Health

COSMIN – COnsensus-based Standards for the selection of health Measurement INstruments

IVPF - International Vasa Previa Foundation

NGT – Nominal Group Technique

OROS – Outcome reporting in Obstetric Studies

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - Prospective Register of systematic reviews

Ethics and dissemination

This study as well as consent forms for stakeholder participation have received approval from the Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the Human Research Ethics Committee at The University of Technology Sydney, Australia on 30 July 2019 (UTS HREC REF NO. ETH19-3718). The findings of the systematic review, patient interviews and final COS will be published in open-access journals and presented at national and international obstetrics and maternal-fetal medicine conferences. All progress will be documented on the PROSPERO, COMET and CROWN databases and made freely available through the IVPF webpage. Corresponding authors of studies included in the systematic review and participants in the qualitative interviews, Delphi surveys and consensus group meetings will be provided with a copy of all publications related to COVasP, to encourage its dissemination and use in future studies on the topic.

Author Contributions

RD conceived the idea, has experience with mixed-methods study design and development of core outcome sets and is the principal investigator and the founder of the Outcome Reporting in Obstetric Studies (OROS) project. NJ designed the qualitative research components of the study. LV, CH and MS helped with drafting various aspects of the manuscript. JK is a Maternal-Fetal Medicine Physician with clinical expertise in the management of vasa previa. MK, ND and NJ represent the International Vasa Previa Foundation. NJ, RD, JK, MK and ND secured funding for the study. All authors contributed to and approved the final version of the manuscript prior to submission.

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Competing Interests

MK and ND are directors and NJ is a member of the International Vasa Previa Foundation that has provided part funding for this project. RD has received speaking honoraria from Ferring, Canada for presentations unrelated to this project. Other authors have no conflict of interest.

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None

Data statement

The data for all steps of this project will be published in a data repository which will be made available on the OROS webpage - https://www.obgyn.utoronto.ca/oros-project

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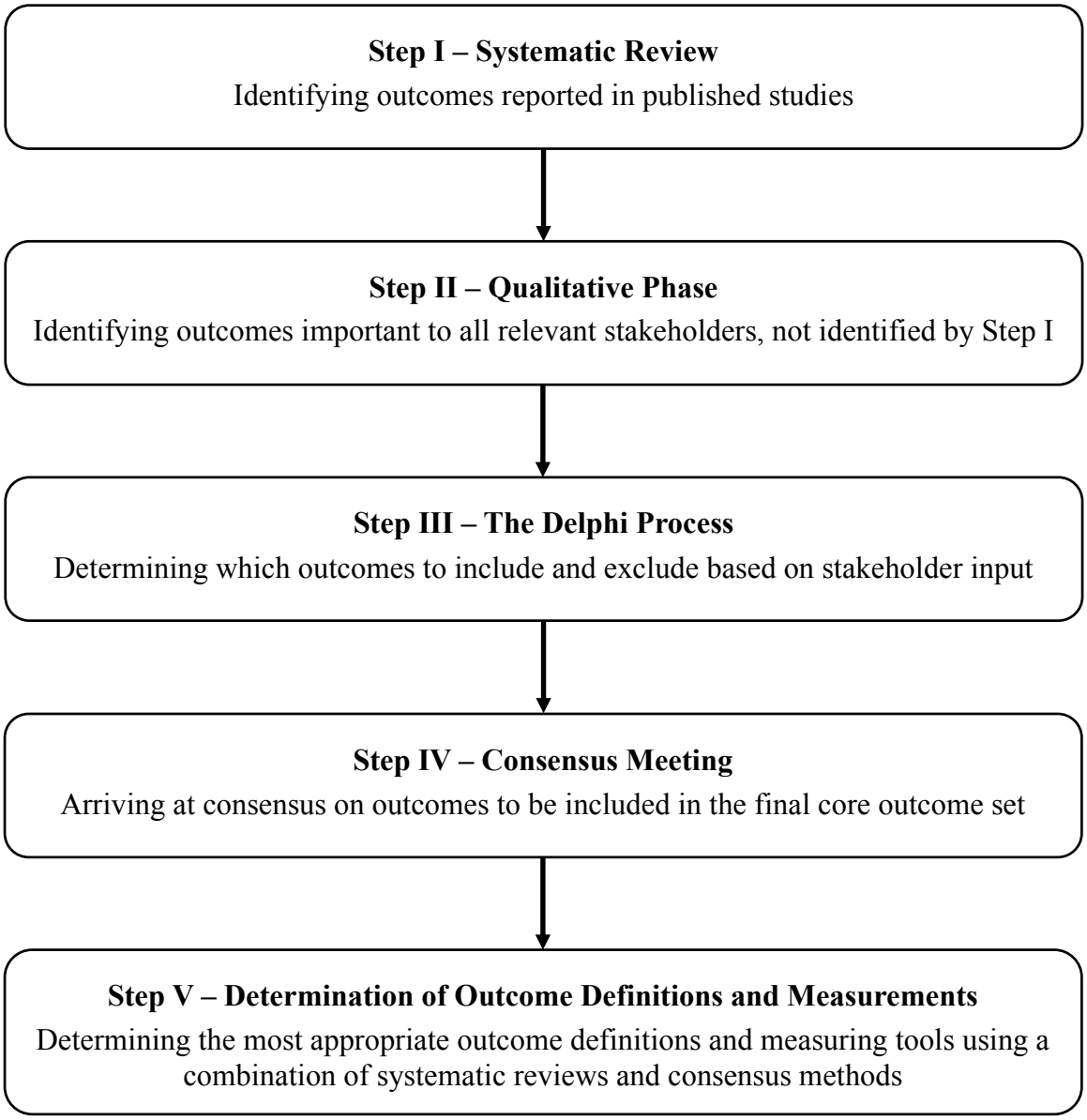
Table 1. Sampling matrix for purposive sampling of women with a history of vasa previa

Criteria	**Target number of participants**
Method of conception	
In vitro fertilization	3-5
Spontaneous conception	10-12
Pregnancy affected by vasa previa	
<5 years ago	6-8
>5 years ago	6-8
Time of diagnosis of vasa previa	
During pregnancy	10-12
During labor and childbirth	3-5

Continent	
North America	6-8
Europe	6-8
Australasia	6-8
Africa	1-3
South and Central America	2-3
Target total	20

Figure Legend

Figure 1 – Steps in the development of a core outcome set for studies on vasa previa


Step I – Systematic Review
Identifying outcomes reported in published studies
Step II – Qualitative Phase
Identifying outcomes important to all relevant stakeholders, not identified by Step I
Step III – The Delphi Process
Determining which outcomes to include and exclude based on stakeholder input
Step IV – Consensus Meeting
Arriving at consensus on outcomes to be included in the final core outcome set
Step V – Determination of Outcome Definitions and Measurements
Determining the most appropriate outcome definitions and measuring tools using a combination of systematic reviews and consensus methods

COVasP – Interview Guide

ID number	
Interview date	
Country	
Date/ Year of diagnosis of vasa previa	
Age	
Sex and Gender	
Education	
Profession	
Ethnicity	
Marital status (of women with vasa previa)	
Parity	
Method of conception (In vitro fertilization /spontaneous)	

Introduction

- Explain the objectives of the study to potential participants.
- Check whether they have any questions and answer their queries.
- Check if they are still happy to participate in research.

COVasP – Interview Guide

Women and family members

1. Could you describe your experience of vasa previa in your own words?
2. Do you recall being told about the diagnosis vasa previa? What was your reaction?
3. Can you tell me about any questions that you/ your partner sought answers to when you were diagnosed with vasa previa?
4. As you/ your partner progressed through the pregnancy, were there any specific considerations or concerns that arose?
    - Which of these have been the most important to you?
5. Can you tell me about the care that was offered to you/ your partner?
6. Can you tell me what extra monitoring you/ your partner received during pregnancy?
    - How did you feel about this extra monitoring?
    - How did you decide on undertaking this extra monitoring?
7. Tell me about the birth plan that was offered to you/ your partner?
    - How did you feel about this?
    - How did you decide on undertaking this?
8. Think about when you/ your partner had vasa previa during your pregnancy, and how you might decide if the care for vasa previa has worked?
9. When it comes to your baby specifically, what did you think most about? What aspects of their health did you take into consideration?
10. Overall in terms of your (partner's) health, or your baby's health, what matters most to you?
11. Is there anything that you have been thinking about in relation to pregnancy and having a child, that you feel did not get addressed?
    - (If yes), can you please tell me more about it?

COVasP – Interview Guide

12. What are the main pieces of advice you would share with a friend with vasa previa?
    - Probe: we're interested in hearing about any aspect of your care, health or well-being.
13. In your opinion, what is an outcome?
14. What outcomes do you think are essential and should be measured?
    - Probe: These outcomes may be related to you (your partner) and/or your baby
15. Can you tell me if your opinion on what is important has changed over time?
16. Is there anything else you would like to add?
17. Would you be interested in an online survey a few months from now?

Other Stakeholders

1. Based on experience, what are some considerations you typically have while caring for women with vasa previa?
2. What aspects of mother's or baby's health matter most to you when caring for these women?
3. What outcomes influence your management of women with vasa previa?
4. What are some concerns and negative or positive experiences that these women typically share with you?
5. What are the main pieces of advice you would share with a colleague who does not care for this population as frequently as you do?
6. In your opinion, what is an outcome?
7. What outcomes do you think are essential and, therefore, need to be measured in research?
    - Probe: These outcomes may be maternal and/or fetal/neonatal
    - Do you discuss any of these with women? (If yes) Which one?
8. Is there anything else you would like to add?
9. Would you be interested in participating in an online survey a few months from now?

Core Outcome Set-STAndardised Protocol Items: The COS-STAP Statement Checklist

TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	1a	P1
Abstract	1b	Provide a structured abstract	1b	P2-3
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	2a	P5-6
	2b	Describe the specific objectives with reference to developing a COS	2b	P6
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	3a	P5
	3b	Describe the intervention(s) that will be covered by the COS	3b	P6
	3c	Describe the context of use for which the COS is to be applied	3c	P6
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	4	P8,9,11
Information sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	5a	P6-10
	5b	Describe how outcomes may be dropped/ combined, with reasons	5b	P12-13
Consensus process	6	Describe the plans for how the consensus process will be undertaken	6	P13-14
Consensus definition	7a	Describe the consensus definition	7a	P12-13
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	7b	P12-14
ANALYSIS			
Outcome scoring/ feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	8	P12-13
Missing data	9	Describe how missing data will be handled during the consensus process	9	P13
ETHICS and DISSEMINATION			
Ethics approval/ informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	10	P17
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	11	P17
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	12	P18
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	13	P18

BMJ Open

Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study Protocol

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Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study Protocol

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Abstract

Introduction:

Vasa previa is a condition where fetal blood vessels run unprotected in the membranes, outside the umbilical cord, and cross the internal opening of the cervix. During rupture of membranes, these vessels can rupture and put the baby at serious risk of severe blood loss and death. Numerous studies are being conducted to improve diagnostic modalities and establish clear management plans to improve pregnancy outcomes. However, the lack of a standardized set of outcomes for studies on vasa previa makes it difficult to compare study findings and draw meaningful conclusions. Through this project, we will be developing a core outcome set for studies on pregnant women with vasa previa (COVasP).

Methods and analysis:

The development of COVasP will involve five steps. The first will be a systematic review, in which we will generate a long list of outcomes based on published studies in pregnancies complicated with vasa previa. The second will involve in-depth interviews with current and former patients, their family members and healthcare providers that care for these patients. This will be followed by a two-round Delphi survey, which will aim to narrow down the long list of outcomes into those considered important by four groups of 'stakeholders': 1) patients, family

members and patient advocates/representatives, 2) healthcare providers, 3) researchers, epidemiologists and methodologists and 4) other stakeholders directly or indirectly involved in the management of these pregnancies such as administrators, guideline developers and policy makers. The fourth step will involve a face-to-face consensus meeting using a nominal group approach to establish a finalized core outcome set. The final step will involve measuring and defining the identified outcomes using a combination of systematic reviews and Delphi surveys.

Ethics and Dissemination

This study as well as consent forms for stakeholder participation have received approval from the Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the Human Research Ethics Committee at The University of Technology Sydney, Australia on 30 July 2019 (UTS HREC REF NO. ETH19-3718). All progress will be documented on the international prospective register of systematic reviews (PROSPERO) and Core Outcome Measures in Effectiveness Trials (COMET) databases.

Keywords

Vasa Previa, Core outcome set, velamentous umbilical cord insertion, stakeholder and patient-reported outcomes

Registration details

http://www.comet-initiative.org/studies/details/1117

Article summary

Strengths and Limitations of this study

- This core outcome set, which is being developed by a multi-national group of investigators that comprise the Outcome Reporting in Obstetric Studies (OROS) project (https://www.obgyn.utoronto.ca/oros-project), are supported by the International Vasa Previa Foundation, and will draw input from numerous international organizations to ensure global representation of all stakeholders.
- COVasP will draw from outcomes reported in all published studies and trial registrations, and will not exclude outcomes from studies that are at increased risk-of-bias, in order to obtain the most comprehensive initial list of outcomes.
- Increased emphasis is being placed on the qualitative steps of core outcome set development, in order to ensure that patient-reported outcomes and outcomes related to quality of life, resource use and functioning are considered alongside routinely-reported clinical outcomes.

Word count: 3577

Introduction

In approximately 7% of all singleton pregnancies, the umbilical cord inserts close to the edge of the placenta (marginal insertion), and in 1% of cases, a more extreme variation is encountered, wherein the umbilical cord inserts at the apex of the membranous sac (velamentous cord insertion).(1) In both these instances, fetal blood vessels could run unprotected outside the umbilical cord, in the membranes surrounding the baby; and when these membranous vessels cross the internal opening of the cervix, preceding the presenting fetal part, the condition is referred to as vasa previa(1, 2). Spontaneous or artificial rupture of the membranes around the time of childbirth, could result in a rupture of these vessels, putting the baby at risk of severe blood loss, hypotension, anaemia, and death by exanguination. Vasa previa is believed to affect one in 1,667 – 2,174 pregnancies [0.46 – 0.60 per 1000 pregnancies].(3, 4) If vasa previa is not diagnosed antenatally, and prior to the onset of labour and vaginal delivery, approximately 40-60% of newborns do not survive.(5, 6) Early diagnosis and the introduction of clear management plans are imperative for improving outcomes. However, there is no consensus on the optimal approach to antenatal diagnosis as well as various aspects of antenatal and peripartum management(7). As a result, women who have been diagnosed with vasa previa have described feeling “like a ticking time bomb”, and expressed the reality of “coping with inconsistent information”.(8) Preferences of pregnant women with the condition, and outcomes that they consider important have not yet been elucidated. Finally, the cost implications to healthcare systems from inpatient vs. outpatient management and the use of various diagnostic modalities and management protocols have not been determined.

While these issues can be adequately addressed through well-conducted prospective studies, there is uncertainty with regard to the outcomes that should be measured in these studies

that are considered important by pregnant women and other stakeholder groups including healthcare providers, researchers and policy makers. Determining this core set of outcomes that should comprise the bare minimum for inclusion in all further studies, is therefore vital. A core outcome set is a set of outcomes that are considered important by those suffering from the condition, their family members and those involved in their care(9).

The goal of this study is to gather patient and other stakeholder input regarding the outcomes important to them, and use this to create a core outcome set for studies on vasa previa which provide researchers with a list of outcomes that must be reported in all future studies, in order to improve its translational value and clinical relevance. This project will reduce bias in outcome reporting, enable meta-analysis of published data to inform decision-making, and provide an empiric basis for inclusion of stated outcomes based on input from relevant stakeholders.

Methods and analysis

The protocol for this Core Outcome Set for studies on Vasa Previa (COVasP) is registered on the Core Outcome Measures in Effectiveness Trials (COMET) website. It is guided by the COMET handbook(9) and complies with the Core Outcome Set – Standardized Protocol Items (COS-STAP) statement.(10) As with other core outcome sets being developed as part of the University of Toronto's Outcome Reporting in Obstetric Studies (OROS) project (https://www.obgyn.utoronto.ca/oros-project), COVasP will be developed in five distinct steps, involving qualitative and quantitative research methods, as outlined in Figure 1.(11, 12)

Step-1: Systematic Review:

A systematic literature review will be undertaken to explore all reported outcomes in published studies involving pregnant women with vasa previa, and will generate a preliminary list of outcomes that are deemed important and hence reported by researchers. The protocol for this systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, is available on the international prospective register of systematic reviews - PROSPERO (CRD42018087837).

Study selection: Five bibliographic databases - Medline, Embase, Cochrane, PubMed (non Medline and in-process) and Clinicaltrials.gov will be searched from inception. All interventions and exposures will be included. Randomized or non-randomized studies, prospective and retrospective cohort studies, case-control studies, case series, case reports, qualitative research, as well as economic evaluation studies and decision analyses will be included in the search. We will exclude letters to the editor, commentaries, editorials, conference abstracts that do not describe clinical outcomes and reviews that do not report on outcomes or contain original research.

Data Extraction: Extracted information will include details on study characteristics such as publication year, number of participants, study type, number of included pregnancies, as well as individual and composite outcomes and their definitions, components and measurement instruments when available.

Quality Assessment: As the purpose of this review is to identify reported outcomes and not to determine the effectiveness of management strategies, no assessment of the study's methodological quality will be performed. Similarly, as the aim of this systematic review is to identify all reported outcomes in order to generate a long-list of outcomes to inform the development of the core outcome set, and there is no validated tool to assess the quality of

outcome reporting, it was decided a priori that the quality of outcome reporting of included studies would not be assessed.

Analysis and presentation of results: The proportion of studies reporting each outcome and the components will be documented. No subgroup or sensitivity analysis is proposed.

Step 2: Stakeholder Consultation

In addition to identifying outcomes reported by researchers, we aim to understand what maternal and perinatal outcomes are considered important by women with a diagnosis of vasa previa, their family members, health care providers and researchers. Qualitative methodology provides a scope for all relevant stakeholders to discuss their views on important outcomes, and contributes to the robustness of core outcome set development by identifying the new outcomes that were not reported in the literature, exploring why the outcomes are considered important, and understanding the scope and priority of the outcomes.(13) Our systematic literature review found only three qualitative studies on vasa previa; that were conducted with the women,(8) midwives(14, 15) and obstetricians.(7) 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. Hence, we will conduct a descriptive-interpretive qualitative research study(16) with the relevant stakeholders in high-income countries.

Inclusion criteria: We will include women who have had a diagnosis of vasa previa (current or previous) and their partners, health care providers who have cared for women with a diagnosis of vasa previa, and health care professionals who have been involved in conducting research or

development of a policy/guideline in relation to vasa previa that are above the age of 18 and able to give informed consent and participate in an interview in English language. Women and their partners will be excluded if they (or their partners) had been diagnosed with vasa previa that was not confirmed at a later stage during pregnancy or birth.

Sampling: Women and their partners will be recruited through an established partnership with the International Vasa Previa Foundation - IVPF (http://vasaprevia.com). The IVPF is an all-volunteer charity created to promote awareness and provide support and advocacy to the general public and professionals regarding vasa previa. In the year 2018, the IVPF sent out an 'Expression of Interest' email to their members which was also shared on social media in relevant peer support groups as a means of recruitment. To ensure that the views of women with different experiences and backgrounds are represented, specific criteria (age, type of conception, time of diagnosis, and country where care was received) will be selected to provide maximum variation sampling as outlined in Table 1.(13) In addition to the categories outlined in the table, it is hoped that recruiting patients through the IVPF, known contacts, and other channels, will enable us to access representatives of the following groups (a) those currently pregnancy with a confirmed diagnosis of vasa previa, (b) those that have had pregnancies that resulted in live births, and those that resulted in fetal or neonatal death, (c) pregnancies with a complicated and relatively uncomplicated antenatal course, (d) those whose babies suffered serious consequences of prematurity, and (e) those that required unplanned/emergency caesarean deliveries vs. those whose caesarean deliveries occurred as scheduled. Healthcare providers and researchers will be recruited through email using a study flyer, via contact lists assembled by the study investigators. As is the norm with qualitative research, the exact sample size will be determined once data collection and analysis are commenced.(17) 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.

Consent: Information regarding the aims of the study and the process of interview will be provided to interested individuals in writing by means of a participant information sheet, highlighting that participation is voluntary. Individuals will be given an opportunity to contact the researchers to receive more information before they make an informed consent to participate in an interview. Only individuals who provide written and/or verbal consent will be interviewed.

Data collection: All interviews will be conducted online or over the phone. Upon commencement of the interview, the interviewer will confirm that the participant has read the participant information sheet and consent form and obtain verbal consent. The interviewer will then request certain demographic details, which the participants may or may not choose to answer. Demographic details will vary slightly depending on stakeholder group but include: age, occupation, education, ethnicity and descriptions of their experiences with vasa previa or number of years working with this population, as appropriate. After a brief introduction, and providing a description of the project and explanation of what constitutes health outcomes the interview will commence. The interviews are designed to be semi-structured and conversational using a topic guide (Appendix A). The goal is to ensure that the participant feels comfortable sharing their views and experience while ultimately eliciting health outcomes important to the participants that can then further inform our core outcome set development. During the reflective and iterative process of data collection and analysis, the topic guide may be refined and/or expanded to include the issues raised by earlier participants. One experienced qualitative researcher will

conduct all the interviews by telephone or online. The interviews will be audio-recorded and transcribed verbatim.

Data analysis: Thematic data analysis(18) taking a descriptive interpretive approach(19) will start after the first interview. The data will be imported into NVivo V.12 software, which will assist with data management and analysis. Transcripts will be read and coded by a qualitative researcher (NJ) who conducted the interviews. The codes, emerging categories and the related quotes will be discussed with the research team, that includes at least one physician that cares for pregnant women with vasa previa, to reach agreement. Information and outcomes obtained through this qualitative data analysis will be used to develop a list of outcomes deemed important by the participants, which will inform the subsequent Delphi study.

Step-3: **Delphi Methodology:**

Steps 1 and 2 generate a long list of outcomes considered important by researchers, women and other stakeholders involved in their care. The Delphi process that follows, is designed to achieve convergence of opinion on these outcomes, in an iterative and sequential manner.(20) For this step, we will identify four groups of participants: 1) women, family members and patient advocates or representatives, 2) healthcare providers, 3) researchers, epidemiologists/ methodologists and core outcome set developers, and 4) other stakeholders directly or indirectly involved in the care of pregnant women such as administrators, guideline developers and policy makers. These groups represent all stakeholders directly or indirectly involved in the care of pregnancies affected by vasa previa. The Delphi survey will be developed by grouping the long list of outcomes (obtained through steps 1 and 2) into five core outcome areas - mortality, morbidity (clinical/physiological), life-impact (functioning), resource-use, and adverse events -

based on a published taxonomy.(21) Lay-language summaries will appear alongside complex medical outcomes. The survey will be piloted with at least 10 people including one person from each stakeholder group. Since we will be using a familiar software, retaining all outcomes obtained through steps-1 and 2, and using pre-piloted lay-language summaries for common obstetric and neonatal outcomes developed by the OROS project(11, 12, 22), the only purpose of piloting the survey, is to ensure that representatives of all stakeholder groups have an opportunity to comment on content unique to COVasP. We believe that a sample of 10 people to be sufficient for this step. After piloting, the survey will be made available online (through links on social media) and widely distributed through identified listservers of relevant organizations, including but not restricted to the Cochrane Pregnancy and Childbirth Group (30 members), the Global Obstetric Network (237 members), Core Outcomes in Women's and Newborn Health (CrOWN) initiative (77 members), corresponding authors of publications on vasa previa included in a recent systematic review,(23) IVPF, United Kingdom Obstetric Surveillance System (UKOSS) https://www.npeu.ox.ac.uk/ukoss, UK Vasa Praevia Raising Awareness Trust (http://vasapraevia.co.uk), Australasian Maternity Outcomes Surveillance System (AMOSS) https://www.amoss.com.au, Perinatal Society of Australia and New Zealand (PSANZ) https://www.psanz.com.au and Vasa Praevia Support and Awareness Ireland (https://www.facebook.com/vasapraeviasupportandawarenessIreland). We will aim to recruit at least 25 individuals from each stakeholder group to ensure an appropriate degree of representation. An online approach using DelphiManager™ software will be employed, to ensure privacy, feasibility, cost effectiveness and reliability, while facilitating global representation.(9) Upon signing an online consent form and completing a brief demographic questionnaire, participants will be required to score each outcome on a 9-point Likert Scale based on its

perceived degree of importance. Scores of 1 to 3 will be considered as 'not essential'; 4 to 6, 'important but not critical'; and 7 to 9, 'critically important for inclusion'.(9) Participants will also be presented with a text box for them to enter any outcomes they deem important, which might not have been included in the list provided.

Analysis: For each outcome, scores will be plotted as histograms, stratified by the each participant's self-reported group, as follows: (a) patients and patient advocates, (b) clinicians and (c) researchers. All new outcomes emerging from round 1, if deemed by COVasP investigators as distinct from those presented, will be included into the second round. Upon completion of first-round analysis, an invitation will be sent out to all members requesting participation in the **second round.** Each member scoring outcomes in the second round will have access to the histograms presenting first-round scores stratified by the participant group, to enable participants to decide on whether they would like to retain their original score, or modify it. Email reminders will be sent out to ensure that at least 85% of respondents complete both surveys, to prevent attrition bias. Each participant will be asked whether they would like to and be able to attend a face-to-face consensus meeting, details of which will be determined, by this juncture.

Missing Data and Attrition: Participants will be given clear outlined expectations of timelines and a six-week window to complete each round of the survey. Should the response rate not achieve 80%, a level deemed acceptable by published recommendations(9), additional interventions will be implemented, guided by measures adopted by other COS developers. Telephone calls, emails, personal reminders and extension of the survey deadlines may be used to improve the response rate. Any feedback after the first round regarding obstacles when completing the survey in its entirety will be noted and addressed before the second round.

Step 4: Consensus meeting

All outcomes that are deemed 'critically important for inclusion' (score 7-9 on the second round of the Delphi survey) by 70% of all stakeholders will be included in the final core outcome set. This includes intermediary and surrogate outcomes. In addition, in order to ensure that the patient-perspective is reflected, we will also retain and include in the final core outcome set, outcomes that are scored 7-9 by 70% of patients alone. Outcomes assigned scores 1-3 by >70% of all participants, will be discarded. Outcomes assigned scores of 4-6 (important but not critical) by >70% of stakeholders will be further discussed at a face-to-face consensus meeting, which will use a structured variation of a small-group discussion called the **nominal group technique**.(24) At the consensus meeting, participants will be first asked to independently decide whether each of these outcomes in question should be included in the core outcome set or not. This will be followed by small-group discussions, wherein members express their understanding of the logic and the relative importance of each of these 'important but not critical' outcomes, and debate whether they should be included in the final core outcome set or not. The final list of outcomes deemed as critical to include in the final core outcome set, presented by each small group, will be reflective of the group's overall preferences, and through mutual consensus will constitute the final core outcome set. The advantages of using nominal group technique is that the process prevents the domination of the discussion by a single person, encourages all group members to participate, and results in a set of recommendations that represent the group's preferences.

This consensus meeting will occur over a half-day and will be conducted in keeping with the specifications laid out by the Evaluation Research Team at the Centre for Disease Control,(24) and the entire process will be audio-recorded. Groups developing core outcome sets fof obstetric conditions have included between 14 and 29 participants in this step. Without pre-specifying a number, we will aim to ensure equal representation of each stakeholder group, and schedule this face-to-face meeting to coincide with an international obstetrics conference, in order to ensure global participation of representatives of various stakeholder groups. However, we acknowledge that this might be difficult to organize, and therefore, in the interest of feasibility, might have to settle for organizing this at the time of a local meeting, with most stakeholder representatives from within Canada. Since international representation will already have been sought through the Delphi survey, and on account of the cautious approach to eliminating outcomes described above, we do not believe this will compromise study integrity.

The OROS project, under whose initiative, COVasP is being developed, endeavours to achieve a balance between standardization and comprehensiveness of outcome reporting. While the development of a core outcome set will address the former, the latter is important to ensure inclusion of maternal and fetal outcomes representing all core outcome areas(21), which include mortality/survival, clinical/physiological, life-impact/functioning, resource-use and adverse events. There will therefore, be no limit on the final number of outcomes constituting COVasP. As described in protocols for other core outcome sets being developed by the OROS group, all outcomes identified through the above process, will be presented in tabular form, separating maternal from fetal/neonatal outcomes, each stratified by the five main core outcome areas,

and a supplementary table highlighting all outcomes, their Delphi scores, and the stages at which they were excluded will also be presented, for greater transparency(12).

Step 5: Measuring/defining core outcomes

Upon selection of a final list of core outcomes, we will employ the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) to assess measurement tools/ definitions for included outcomes based on four criteria: validity, responsiveness, reliability and interpretability.(25) We will begin the process by listing measurement instruments and/or definitions for outcomes where universal agreement exists. For outcomes where there is a lack of agreement on measurement instruments or definitions, we will conduct systematic reviews to determine all currently used instruments and definitions. This will be followed by Delphi surveys involving relevant stakeholder groups as required, to determine the most appropriate definition or measurement instrument for each identified core outcome where systematic reviews are inconclusive.(26) Details of this process will depend on the final list of outcomes, and are beyond the scope of this protocol.

Patient and Public Involvement

Although the steps of developing a core outcome set are standardized, we will involve patients and other stakeholders to participate in steps 2-4, through interviews, the Delphi survey and a consensus meeting. The purpose of their involvement is to determine what outcomes related to vasa previa are most important to them. The design of the study encourages stakeholders to consider outcomes related to domains such as functioning, resource use, satisfaction,

compliance, healthcare delivery and mental health concerns in addition to the clinical and physiological outcomes most commonly reported in research studies. We have taken steps to ensure that these outcomes considered important by patients are represented in the final core outcome set. We aim to involve patients in ensuring that COVasP is disseminated widely through the IVPF webpage and also through social media, in addition to ensuring knowledge translation to clinicians and researchers. The findings of each step of COVasP development will be published on the OROS website (https://www.obgyn.utoronto.ca/oros-project), enabling ongoing feedback from patients and the public.

Discussion

COVasP aims to provide researchers and clinicians with a systematically-derived list of outcomes, incorporating preferences of patients and other relevant stakeholders, which will form the minimum standard required to be collected, measured and recorded as a baseline in all clinical studies on vasa previa. Input from various stakeholder groups will enhance the quality and relevance of future studies on vasa previa, and go a long way in improving outcomes that are considered most important by those that are affected by this rare but serious obstetric condition.

List of Abbreviations

COSVasP – Core Outcome Set for Studies on Vasa Previa

COMET – Core Outcome Measurement in Effectiveness Trials

CROWN – CoRe Outcomes in Women's and Newborn Health

COSMIN – COnsensus-based Standards for the selection of health Measurement INstruments

IVPF - International Vasa Previa Foundation

OROS – Outcome reporting in Obstetric Studies

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - Prospective Register of systematic reviews

Ethics and dissemination

This study as well as consent forms for stakeholder participation have received approval from the Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the Human Research Ethics Committee at The University of Technology Sydney, Australia on 30 July 2019 (UTS HREC REF NO. ETH19-3718). The findings of the systematic review, patient interviews and final COS will be published in open-access journals and presented at national and international obstetrics and maternal-fetal medicine conferences. All progress will be documented on the PROSPERO, COMET and CROWN databases and made freely available through the IVPF webpage. Corresponding authors of studies included in the systematic review and participants in the qualitative interviews, Delphi surveys and consensus group meetings will be provided with a copy of all publications related to COVasP, to encourage its dissemination and use in future studies on the topic.

Author Contributions

RD conceived the idea, has experience with mixed-methods study design and development of core outcome sets and is the principal investigator and the founder of the Outcome Reporting in Obstetric Studies (OROS) project. NJ designed the qualitative research components of the study. LV, CH and MS helped with drafting various aspects of the manuscript. JK is a Maternal-Fetal Medicine Physician with clinical expertise in the management of vasa previa. MK, ND and NJ

represent the International Vasa Previa Foundation. NJ, RD, JK, MK and ND secured funding for the study. All authors contributed to and approved the final version of the manuscript prior to submission.

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Competing Interests

MK and ND are directors and NJ is a member of the International Vasa Previa Foundation that has provided part funding for this project. RD has received speaking honoraria from Ferring, Canada for presentations unrelated to this project. Other authors have no conflict of interest.

Acknowledgements

None

Data statement

The data for all steps of this project will be published in a data repository which will be made available on the OROS webpage - https://www.obgyn.utoronto.ca/oros-project

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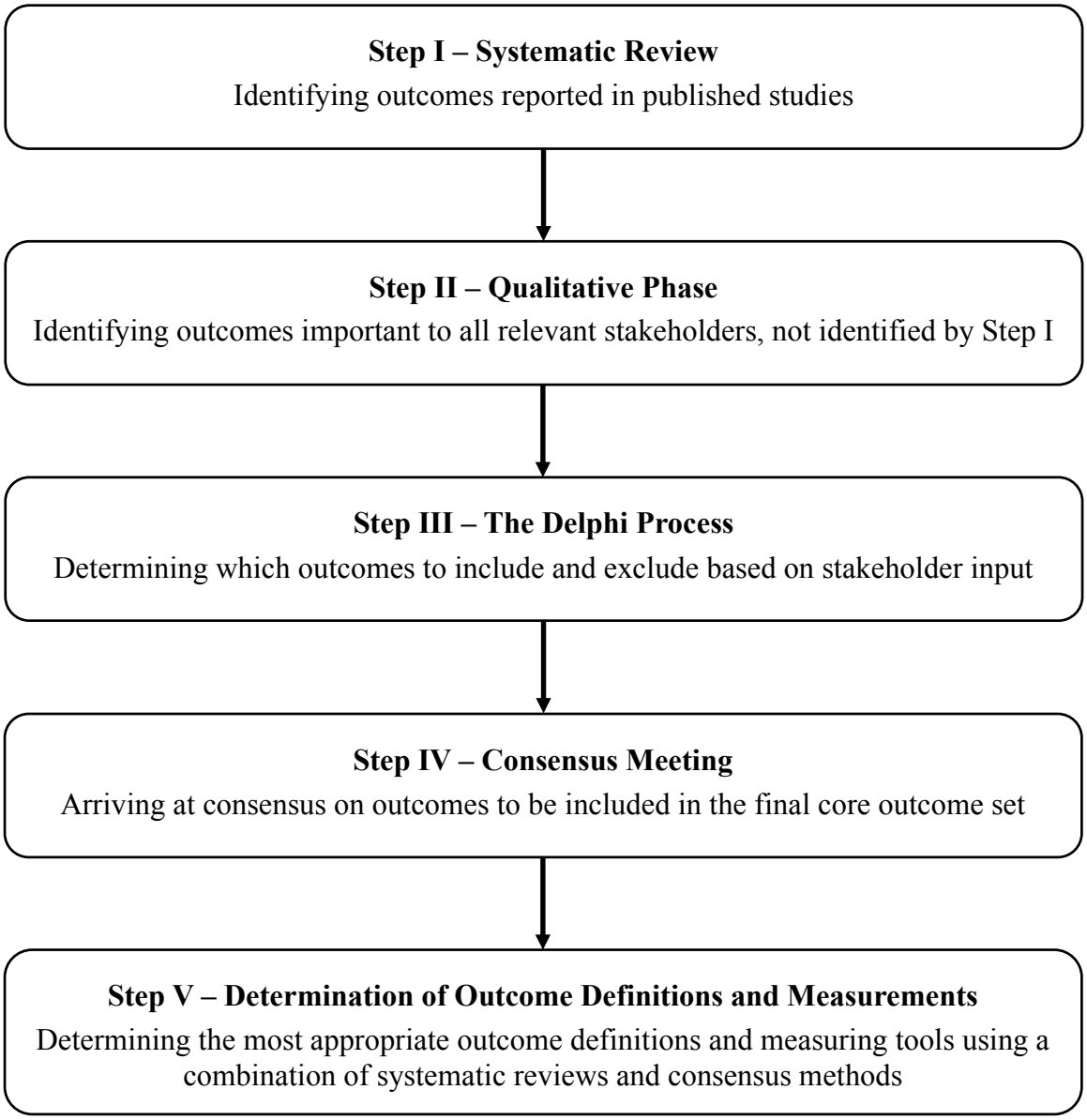
Table 1. Sampling matrix for purposive sampling of women with a history of vasa previa

Criteria	**Target number of participants**
Method of conception	
In vitro fertilization	3-5
Spontaneous conception	10-12
Pregnancy affected by vasa previa	
<5 years ago	6-8
>5 years ago	6-8
Time of diagnosis of vasa previa	
During pregnancy	10-12
During labor and childbirth	3-5
Continent	
North America	6-8
Europe	6-8
Australasia	6-8
Africa	1-3
South and Central America	2-3
Target total	20

Figure Legend

Figure 1 – Steps in the development of a core outcome set for studies on vasa previa


Step I – Systematic Review
Identifying outcomes reported in published studies
Step II – Qualitative Phase
Identifying outcomes important to all relevant stakeholders, not identified by Step I
Step III – The Delphi Process
Determining which outcomes to include and exclude based on stakeholder input
Step IV – Consensus Meeting
Arriving at consensus on outcomes to be included in the final core outcome set
Step V – Determination of Outcome Definitions and Measurements
Determining the most appropriate outcome definitions and measuring tools using a combination of systematic reviews and consensus methods

COVasP – Interview Guide

ID number	
Interview date	
Country	
Date/ Year of diagnosis of vasa previa	
Age	
Sex and Gender	
Education	
Profession	
Ethnicity	
Marital status (of women with vasa previa)	
Parity	
Method of conception (In vitro fertilization /spontaneous)	

Introduction

- Explain the objectives of the study to potential participants.
- Check whether they have any questions and answer their queries.
- Check if they are still happy to participate in research.

COVasP – Interview Guide

Women and family members

1. Could you describe your experience of vasa previa in your own words?
2. Do you recall being told about the diagnosis vasa previa? What was your reaction?
3. Can you tell me about any questions that you/ your partner sought answers to when you were diagnosed with vasa previa?
4. As you/ your partner progressed through the pregnancy, were there any specific considerations or concerns that arose?
    - Which of these have been the most important to you?
5. Can you tell me about the care that was offered to you/ your partner?
6. Can you tell me what extra monitoring you/ your partner received during pregnancy?
    - How did you feel about this extra monitoring?
    - How did you decide on undertaking this extra monitoring?
7. Tell me about the birth plan that was offered to you/ your partner?
    - How did you feel about this?
    - How did you decide on undertaking this?
8. Think about when you/ your partner had vasa previa during your pregnancy, and how you might decide if the care for vasa previa has worked?
9. When it comes to your baby specifically, what did you think most about? What aspects of their health did you take into consideration?
10. Overall in terms of your (partner's) health, or your baby's health, what matters most to you?
11. Is there anything that you have been thinking about in relation to pregnancy and having a child, that you feel did not get addressed?
    - (If yes), can you please tell me more about it?

COVasP – Interview Guide

12. What are the main pieces of advice you would share with a friend with vasa previa?
    - Probe: we're interested in hearing about any aspect of your care, health or well-being.
13. In your opinion, what is an outcome?
14. What outcomes do you think are essential and should be measured?
    - Probe: These outcomes may be related to you (your partner) and/or your baby
15. Can you tell me if your opinion on what is important has changed over time?
16. Is there anything else you would like to add?
17. Would you be interested in an online survey a few months from now?

Other Stakeholders

1. Based on experience, what are some considerations you typically have while caring for women with vasa previa?
2. What aspects of mother's or baby's health matter most to you when caring for these women?
3. What outcomes influence your management of women with vasa previa?
4. What are some concerns and negative or positive experiences that these women typically share with you?
5. What are the main pieces of advice you would share with a colleague who does not care for this population as frequently as you do?
6. In your opinion, what is an outcome?
7. What outcomes do you think are essential and, therefore, need to be measured in research?
    - Probe: These outcomes may be maternal and/or fetal/neonatal
    - Do you discuss any of these with women? (If yes) Which one?
8. Is there anything else you would like to add?
9. Would you be interested in participating in an online survey a few months from now?

Core Outcome Set-STAndardised Protocol Items: The COS-STAP Statement Checklist

TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	1a P1
Abstract	1b	Provide a structured abstract	1b P2-3
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	2a P5-6
	2b	Describe the specific objectives with reference to developing a COS	2b P6
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	3a P5
	3b	Describe the intervention(s) that will be covered by the COS	3b P6
	3c	Describe the context of use for which the COS is to be applied	3c P6
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	4 P8,9,11
Information sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	5a P6-10
	5b	Describe how outcomes may be dropped/ combined, with reasons	5b P12-13
Consensus process	6	Describe the plans for how the consensus process will be undertaken	6 P13-14
Consensus definition	7a	Describe the consensus definition	7a P12-13
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	7b P12-14
ANALYSIS			
Outcome scoring/ feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	8 P12-13
Missing data	9	Describe how missing data will be handled during the consensus process	9 P13
ETHICS and DISSEMINATION			
Ethics approval/ informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	10 P17
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	11 P17
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	12 P18
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	13 P18