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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034018
Article Type:	Protocol
Date Submitted by the Author:	02-Sep-2019
Complete List of Authors:	D'Souza, Rohan; University of Toronto, Villani, Linda; University of Utah School of Medicine Hall, Chelsea; University of Toronto Seyoum, Meron; University of Toronto Kingdom, John; University of Toronto Krznaric, Michael; International Vasa Previa Foundation Donnolley, Natasha; University of New South Wales - Randwick Campus, Centre for Big Data Research in Health and School of Women's and Children's Health Javid, Nasrin; University of Technology Sydney
Keywords:	vasa previa, core outcome set, velamentous cord insertion, stakeholder and patient-reported outcomes

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3 **1 Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study**

4
5 **2 Protocol**

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7
8 3 Rohan D'Souza^{1,2}, Linda Villani³, Chelsea Hall⁴, Meron Seyoum¹, John Kingdom^{1,2}, Michael
9
10 4 Krznic⁵, Natasha Donnelly^{5,6}, Nasrin Javid⁷

11
12 5 ¹ Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai
13
14 Hospital, University of Toronto, Toronto, ON, Canada

15
16 7 ² Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada

17
18 8 ³ University of Utah School of Medicine, Salt Lake City, Utah, USA

19
20 9 ⁴ Faculty of Medicine, University of Toronto, Toronto, ON, Canada

21
22 10 ⁵ International Vasa Previa Foundation, Chester, Illinois, United States of America

23
24 11 ⁶ The National Perinatal Epidemiology and Statistics Unit, Centre for Big Data Research and
25
26 12 Health, University of New South Wales, Sydney, New South Wales, Australia

27
28 13 ⁷ Faculty of Health, University of Technology Sydney, New South Wales, Australia

29
30
31
32
33
34
35 **15 Email Addresses:**

36
37 16 Dr. Rohan D'Souza – rohan.dsouza@sinaihealthsystem.ca

38
39 17 Linda Villani - lian.villani@gmail.com

40
41 18 Chelsea Hall – chelsea.hall@mail.utoronto.ca

42
43 19 Meron Seyoum - mina.seyoum@gmail.com

44
45 20 John Kingdom - John.Kingdom@sinaihealthsystem.ca

46
47 21 Michael Krznic – michaelkrznic@gmail.com

48
49 22 Natasha Donnelly - n.donnelly@unsw.edu.au

50
51 23 Nasrin Javid - Nasrin.ZamaniJavid@student.uts.edu.au

24 Corresponding author:

25 Rohan D'Souza

26 Mount Sinai Hospital, 3-908 – 700 University Avenue, Toronto, Ontario M5G 1Z5, Canada.

27 Email: rohan.dsouza@sinaihealthsystem.ca

28 Ph: +1 (416) 586-4800 ext. 5127; F: +1 (416) 586-8649

29

30 Abstract**31 Introduction:**

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

40 Methods and analysis:

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

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3 47 members and patient advocates/representatives, 2) healthcare providers, 3) researchers,
4
5 48 epidemiologists and methodologists and 4) other stakeholders directly or indirectly involved in
6
7 49 the management of these pregnancies such as administrators, guideline developers and policy
8
9 50 makers. The fourth step will involve a face-to-face consensus meeting using a nominal group
10
11 51 approach to establish a finalized core outcome set. The final step will involve measuring and
12
13 52 defining the identified outcomes using a combination of systematic reviews and Delphi surveys.
14
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19 54 **Ethics and Dissemination**

20
21 55 This study as well as consent forms for stakeholder participation have received approval from the
22
23 56 Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the
24
25 57 Human Research Ethics Committee at The University of Technology Sydney, Australia on 30
26
27 58 July 2019 (UTS HREC REF NO. ETH19-3718). All progress will be documented on the
28
29 59 international prospective register of systematic reviews (PROSPERO) and Core Outcome
30
31 60 Measures in Effectiveness Trials (COMET) databases.
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38 62 **Keywords**

39
40 63 Vasa Previa, Core outcome set, velamentous umbilical cord insertion, stakeholder and patient-
41
42 64 reported outcomes
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46

47 66 **Registration details**

48
49 67 <http://www.comet-initiative.org/studies/details/1117>
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3 **70 Article summary**
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5 **71** This protocol describes the development of a core outcome set for studies on vasa previa.
6
7

8 **72 Strengths and Limitations of this study**
9

10 **73** - This core outcome set will draw from outcomes reported in all experimental and
11
12 **74** observational studies, as well as case reports and trial registrations, and will not eliminate
13
14 **75** outcomes from studies that would otherwise be considered at increased risk-of-bias, in
15
16 **76** order to obtain the most comprehensive initial list of outcomes possible.
17
18

19 **77** - The multinational group of investigators are supported by the International Vasa Previa
20
21 **78** Foundation and will draw input from numerous international organizations to ensure
22
23 **79** global representation of all stakeholders.
24
25

26 **80** - Increased emphasis is being placed on the qualitative steps of core outcome set
27
28 **81** development, in order to ensure that patient-reported outcomes and outcomes related to
29
30 **82** quality of life, resource use and functioning are considered alongside clinical outcomes.
31
32

33 **83** - This core outcome is being developed as part of the Outcome Reporting in Obstetric
34
35 **84** Studies (OROS) project (<https://www.obgyn.utoronto.ca/oros-project>), whose
36
37 **85** investigators not only have expertise in the conduct of core outcome sets, but are
38
39 **86** currently setting standards for outcome reporting in obstetric studies.
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42 **87**
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44 **88 Word count: 3329**
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91 Introduction

92 In normal fetal development, the placenta implants near the top of the uterus and the umbilical
93 cord inserts into the center of the placenta to transport nutrients and oxygen from the mother to
94 the fetus. In some cases, umbilical blood vessels run unprotected outside the umbilical cord and
95 are present in the membranes surrounding the baby. These abnormal vessels can cross the internal
96 opening of the cervix and interfere with the baby's path during labour(1). When the membranes
97 rupture, these abnormal vessels can rupture as well and put the baby at serious risk of severe
98 blood loss and death if delivered vaginally. This condition is called vasa previa and is believed to
99 affect one in 2174 pregnancies.(2) The proximity of fetal vessels to the internal os of the cervix
100 increases the risk of hemorrhage upon spontaneous or artificial rupture of the membranes
101 resulting in serious complications to the fetus, including hypotension, irregular heart rate and fetal
102 death from exsanguination. If vasa previa is not diagnosed prior to labour and vaginal delivery,
103 approximately 40-60% of newborns do not survive.(3, 4) Early diagnosis and the introduction of
104 clear management plans are imperative for improving outcomes in this population. However,
105 there is no consensus on the optimal methods for diagnosis and various aspects of management.
106 Women who have been diagnosed with this condition have described feeling "like a ticking time
107 bomb" and expressed the reality of "coping with inconsistent information".(5) Preferences of
108 pregnant women with the condition, and outcomes that they consider important have not yet
109 been elucidated. Finally, the cost implications to healthcare systems from inpatient vs. outpatient
110 management and the use of various diagnostic modalities and management protocols have not
111 been determined.

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

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3 114 considered important by pregnant women and other stakeholder groups including healthcare
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5 115 providers, researchers and policy makers. Determining this core set of outcomes that should
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8 116 comprise the bare minimum for inclusion in all further studies is therefore vital.

9
10 117 A core outcome set is a set of outcomes that are considered important by those suffering from
11
12 118 the condition, their family members and those involved in their care. Once developed, this
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14
15 119 minimum set of outcomes should be reported in all clinical studies on the condition.

16
17 120 The goal of this study is to gather patient and other stakeholder input regarding the outcomes
18
19 121 important to them, and use this to create a set of outcomes for studies involving vasa previa and
20
21 122 pregnancy which provide researchers in future studies a list of outcomes that must be reported, in
22
23
24 123 order to improve the translational value and clinical usage of such research. This project will
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26 124 reduce bias in outcome reporting, enable meta-analysis of published data to inform decision-
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28 125 making, and provide an empiric basis for inclusion of stated outcomes based on input from
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30
31 126 relevant stakeholders.

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33 127

34 35 128 **Methods and analysis**

36
37 129 The protocol for this Core Outcome Set for studies on Vasa Previa (COVasP) is registered on the
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39 130 Core Outcome Measures in Effectiveness Trials (COMET) website. It is guided by the COMET
40
41
42 131 handbook(6) and complies with the Core Outcome Set – Standardized Protocol Items (COS-
43
44
45 132 STAP) statement.(7) As with other core outcome sets being developed as part of the University
46
47 133 of Toronto’s Outcome Reporting in Obstetric Studies (OROS) project
48
49 134 (<https://www.obgyn.utoronto.ca/oros-project>), COVasP will be developed in five distinct steps,
50
51 135 involving qualitative and quantitative research methods, as outlined in Figure 1.(8, 9)

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3 **137 Step-1: Systematic Review:**
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5 **138** A systematic literature review will be undertaken to explore all reported outcomes in published
6
7 **139** studies involving pregnant women with vasa previa, and will generate a preliminary list of
8
9
10 **140** outcomes that are deemed important and hence reported by researchers. The protocol for this
11
12 **141** systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-
13
14 **142** Analyses (PRISMA) guidelines, is available on the international prospective register of
15
16 **143** systematic reviews - PROSPERO (CRD42018087837).
17
18

19 **144 Study selection:** Five bibliographic databases - Medline, Embase, Cochrane, PubMed and
20
21 **145** Clinicaltrials.gov will be searched from inception. All interventions and exposures will be
22
23 **146** included. Randomized or non-randomized studies, prospective and retrospective cohort studies,
24
25 **147** case-control studies, case series, case reports, qualitative research, as well as economic
26
27 **148** evaluation studies and decision analyses will be included in the search. We will exclude letters to
28
29 **149** the editor, commentaries, editorials, conference abstracts that do not describe clinical outcomes
30
31 **150** and reviews that do not report on outcomes or contain original research.
32
33

34
35 **151 Data Extraction:** Extracted information will include details on study characteristics such as
36
37 **152** publication year, number of participants, study type, number of included pregnancies, as well as
38
39 **153** individual and composite outcomes and their definitions, components and measurement
40
41 **154** instruments when available.
42
43

44
45 **155 Quality Assessment:** As the purpose of this review is to identify reported outcomes and not to
46
47 **156** determine the effectiveness of management strategies, no assessment of the study's
48
49 **157** methodological quality will be performed. Similarly, as the aim of this systematic review is to
50
51 **158** identify all reported outcomes in order to generate a long-list of outcomes to inform the
52
53 **159** development of the core outcome set, and there is no validated tool to assess the quality of
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3 160 outcome reporting, it was decided a priori that the quality of outcome reporting of included
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5 161 studies would not be assessed.

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8 162 **Analysis and presentation of results:** The proportion of studies reporting each outcome and the
9
10 163 components will be documented. No subgroup or sensitivity analysis is proposed.

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13 14 15 165 **Step 2: Stakeholder Consultation**

16
17 166 In addition to identifying outcomes reported by researchers, we aim to understand what maternal
18
19 167 and perinatal outcomes are considered important by women with a diagnosis of vasa previa, their
20
21 168 family members, health care providers and researchers. Qualitative methodology provides a
22
23 169 scope for all relevant stakeholders to discuss their views on important outcomes, and contributes
24
25 170 to the robustness of core outcome set development by identifying the new outcomes that were
26
27 171 not reported in the literature, exploring why the outcomes are considered important, and
28
29 172 understanding the scope and priority of the outcomes.(10) Our systematic literature review found
30
31 173 only three qualitative studies on vasa previa; that were conducted with the women,(5)
32
33 174 midwives(11) and obstetricians.(12) However, none specifically focused on identifying the
34
35 175 outcomes that could inform the development of COVasP. Hence, we will conduct a descriptive-
36
37 176 interpretive qualitative research study(13) with the relevant stakeholders in high-income
38
39 177 countries.

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41
42 178 **Inclusion criteria:** We will include women who have had a diagnosis of vasa previa (current or
43
44 179 previous) and their partners, health care providers who have cared for women with a diagnosis of
45
46 180 vasa previa, and health care professionals who have been involved in conducting research or
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48 181 development of a policy/guideline in relation to vasa previa that are above the age of 18 and able
49
50 182 to give informed consent and participate in an interview in English language. Women and their
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3 183 partners will be excluded if they (or their partners) had been diagnosed with vasa previa that was
4
5 184 not confirmed at a later stage during pregnancy or birth.
6

7
8 185 **Sampling:** Women and their partners will be recruited through an established partnership with
9
10 186 the International Vasa Previa Foundation - IVPF (<http://vasaprevia.com>). The IVPF is an all-
11
12 187 volunteer charity created to promote awareness and provide support and advocacy to the general
13
14 188 public and professionals regarding vasa previa. Earlier this year the IVPF sent out an 'Expression
15
16 189 of Interest' email to their members which was also shared on social media in relevant peer
17
18 190 support groups as a means of recruitment. To ensure that the views of women with different
19
20 191 experiences and backgrounds are represented, specific criteria (age, type of conception, time of
21
22 192 diagnosis, and country where care was received) will be selected to provide maximum variation
23
24 193 sampling as outlined in Table 1.(10) Healthcare providers and researchers will be recruited
25
26 194 through email using a study flyer, via contact lists assembled by the study investigators. As is the
27
28 195 norm with qualitative research, the exact sample size will be determined once data collection and
29
30 196 analysis are commenced.(14) We will conduct up to 20 patient interviews and 10-12 interviews
31
32 197 with clinicians/researchers until data saturation is reached and no new outcomes are identified in
33
34 198 two successive interviews.
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39
40 199 **Consent:** Information regarding the aims of the study and the process of interview will be
41
42 200 provided to interested individuals in writing by means of a participant information sheet,
43
44 201 highlighting that participation is voluntary. Individuals will be given an opportunity to contact
45
46 202 the researchers to receive more information before they make an informed consent to participate
47
48 203 in an interview. Only individuals who provide written and/or verbal consent will be interviewed.
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51 204 **Data collection:** All interviews will be conducted online or over the phone. Upon
52
53 205 commencement of the interview, the interviewer will confirm that the participant has read the
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3 206 participant information sheet and consent form and obtain verbal consent. The interviewer will
4
5 207 then request certain demographic details, which the participants may or may not choose to
6
7 208 answer. Demographic details will vary slightly depending on stakeholder group but include: age,
8
9 209 occupation, education, ethnicity and descriptions of their experiences with vasa previa or number
10
11 210 of years working with this population, as appropriate. After a brief introduction, and providing a
12
13 211 description of the project and explanation of what constitutes health outcomes the interview will
14
15 212 commence. The interviews are designed to be semi-structured and conversational using a topic
16
17 213 guide (Appendix A). The goal is to ensure that the participant feels comfortable sharing their
18
19 214 views and experience while ultimately eliciting health outcomes important to the participants that
20
21 215 can then further inform our core outcome set development. During the reflective and iterative
22
23 216 process of data collection and analysis, the topic guide may be refined and/or expanded to
24
25 217 include the issues raised by earlier participants. One experienced qualitative researcher will
26
27 218 conduct all the interviews by telephone or online. The interviews will be audio-recorded and
28
29 219 transcribed verbatim.

30
31 220 **Data analysis:** Thematic data analysis(15) taking a descriptive interpretive approach(16) will
32
33 221 start after the first interview. The data will be imported into NVivo V.12 software, which will
34
35 222 assist with data management and analysis. Transcripts will be read and coded by a qualitative
36
37 223 researcher (NJ) who conducted the interviews. The codes, emerging categories and the related
38
39 224 quotes will be discussed with the research team, that includes at least one physician that cares for
40
41 225 pregnant women with vasa previa, to reach agreement. Information and outcomes obtained
42
43 226 through this qualitative data analysis will be used to develop a list of outcomes deemed
44
45 227 important by the participants, which will inform the subsequent Delphi study.

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229 **Step-3: Delphi Methodology:**

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

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3 252 representation. An online approach using DelphiManager™ software will be employed, to ensure
4
5 253 privacy, feasibility, cost effectiveness and reliability, while facilitating global representation.(6)
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8 254 Upon signing an online consent form and completing a brief demographic questionnaire,
9
10 255 participants will be required to score each outcome on a 9-point Likert Scale based on its
11
12 256 perceived degree of importance. Scores of 1 to 3 will be considered as ‘not essential’; 4 to 6,
13
14 257 ‘important but not critical’; and 7 to 9, ‘critically important for inclusion’.(6) Participants will
15
16
17 258 also be presented with a text box for them to enter any outcomes they deem important, which
18
19 259 might not have been included in the list provided.
20
21

22 260 **Analysis:** In order to mitigate respondent fatigue in the second round, outcomes assigned scores
23
24 261 of 1-3 by >70% participants from all stakeholder groups and 7-9 by <30% will be removed from
25
26 262 the next round. In order for an outcome to be removed, it is essential that the above criteria are
27
28 263 met by all stakeholder groups individually. Should an outcome fulfil criteria for removal by three
29
30 264 stakeholder groups, but not by patients, that outcome would still be retained for the second
31
32 265 round. All outcomes entered into text boxes, if deemed (by the COVasP investigators) as distinct
33
34 266 from those presented, will be included into the second round. Upon completion of first-round
35
36 267 analysis, an invitation will be sent out to all members requesting participation in the **second**
37
38 268 **round.** Each member scoring outcomes in the second round will have access to mean scores for
39
40 269 the entire group as well as those for individual stakeholder groups, to enable them to decide on
41
42 270 whether they would like to retain their original score, or modify it based on the total- and
43
44 271 individual group scores from the first round. Email reminders will be sent out to ensure that at
45
46 272 least 85% of respondents complete both surveys, to prevent attrition bias. In the final analysis, all
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48 273 outcomes that were scored 7-9 by >70% of participants from each stakeholder group and 1-3 by
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50 274 <30% will automatically be included into the core outcome set. All other outcomes, stratified
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3 275 under ‘important but not critical’ or ‘critical’ will be considered at a consensus group meeting.
4

5 276 Each participant will be asked whether they would like to and be able to attend the face-to-face
6
7 277 consensus meeting in Toronto, Canada.
8
9

10 278
11
12 279 **Missing Data and Attrition:** Participants will be given clear outlined expectations of timelines
13
14 280 and a six-week window to complete each round of the survey. We will clearly stipulate in the
15
16 281 original invitation to participate that those that do not complete the first round will not be invited
17
18 282 to the second round. Should the response rate not achieve 80%, a level deemed acceptable by
19
20 283 published recommendations(6), additional interventions will be implemented, guided by
21
22 284 measures adopted by other COS developers. Telephone calls, emails, personal reminders and
23
24 285 extension of the survey deadlines may be used to improve the response rate. Any feedback after
25
26 286 the first round regarding obstacles when completing the survey in its entirety will be noted and
27
28 287 addressed before the second round.
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33 288

35 289 **Step 4: Consensus meeting**

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37 290 Two to five representatives from each stakeholder group that express interest in participating will
38
39 291 be selected at random to attend the face-to-face consensus meeting, aimed at reaching consensus
40
41 292 on the core outcome set. We will use a **nominal group technique** (NGT), a structured variation
42
43 293 of a small-group discussion, to reach consensus on the final core outcome set.(20) NGT gathers
44
45 294 information by asking individuals to respond to questions posed by a moderator, and then asking
46
47 295 participants to prioritize the ideas or suggestions of all group members. The process prevents the
48
49 296 domination of the discussion by a single person, encourages all group members to participate,
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51 297 and results in a set of prioritized solutions or recommendations that represent the group’s
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3 298 preferences. This consensus meeting will occur over a half-day and will be conducted in keeping
4
5 299 with the specifications laid out by the Evaluation Research Team at the Centre for Disease
6
7 300 Control.(20) The first step will involve the moderator presenting outcomes that need to be
8
9 301 discussed, and encouraging each participant to work independently and silently. This will be
10
11 302 followed by encouraging group members to engage in a round-robin feedback session to
12
13 303 concisely record each outcome (without debate at this point), followed again by a discussion on
14
15 304 each outcome to determine clarity and importance. Here, there will be an opportunity for
16
17 305 members to express their understanding of the logic and the relative importance of the outcome.
18
19 306 The final step will involve a vote wherein participants will vote privately to prioritize the
20
21 307 outcomes. Participants will vote using an electronic device to ensure anonymity. The votes will
22
23 308 be tallied to identify the outcomes that are rated highest by the group as a whole. The moderator
24
25 309 will establish what criteria are used to prioritize the ideas. To start, each group member will
26
27 310 select the five most important outcomes from the list and write one idea on each index card.
28
29 311 Next, each member ranks the five ideas selected, with the most important receiving a rank of 5,
30
31 312 and the least important receiving a rank of 1. After members rank their responses in order of
32
33 313 priority, the moderator will create a tally sheet on the flip chart with numbers down the left-hand
34
35 314 side of the chart, which correspond to the ideas from the round-robin. The moderator will collect
36
37 315 all the cards from the participants and ask one group member to read the outcome number and
38
39 316 number of points allocated to each one, while the moderator records and then adds the scores on
40
41 317 the tally sheet. The outcomes that are the most highly rated by the group are the most favoured
42
43 318 group outcomes in response to the question posed by the moderator. The entire process will be
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45 319 audio-recorded.
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321 **Step 5: Measuring/defining core outcomes**

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

333 **Patient and Public Involvement**

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

1
2
3 344 clinicians and researchers. The findings of each step of COVasP development will be published
4
5 345 on the Outcome Reporting in Obstetric Studies website (9

347

348 **Discussion**

349 COVasP aims to provide researchers and clinicians with a systematically-derived list of
350 outcomes, incorporating preferences of patients and other relevant stakeholders, which will form
351 the minimum standard required to be collected, measured and recorded as a baseline in all
352 clinical studies on vasa previa. Input from various stakeholder groups will enhance the quality
353 and relevance of future studies on vasa previa, and go a long way in improving outcomes that are
354 considered most important by those that are affected by this rare but morbid obstetric condition.
355

356 **List of Abbreviations**

357 COSVasP – Core Outcome Set for Studies on Vasa Previa

358 COMET – Core Outcome Measurement in Effectiveness Trials

359 CROWN – CoRe Outcomes in Women’s and Newborn Health

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

361 IVPF - International Vasa Previa Foundation

362 NGT – Nominal Group Technique

363 OROS – Outcome reporting in Obstetric Studies

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

365 PROSPERO - Prospective Register of systematic reviews

366

367 **Ethics and dissemination**

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

380 **Author Contributions**

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

390 Funding

391 This study is funded by the David Henderson-Smart 2019 Scholarship awarded to Nasrin Javid
392 by the Perinatal Society of Australia and New Zealand, and the International Vasa Previa
393 Foundation (IVPF).

395 Competing Interests

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

400 Acknowledgements

401 None

403 Data statement

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

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31 470 Table 1. Sampling matrix for purposive sampling of women with a history of vasa previa
32

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

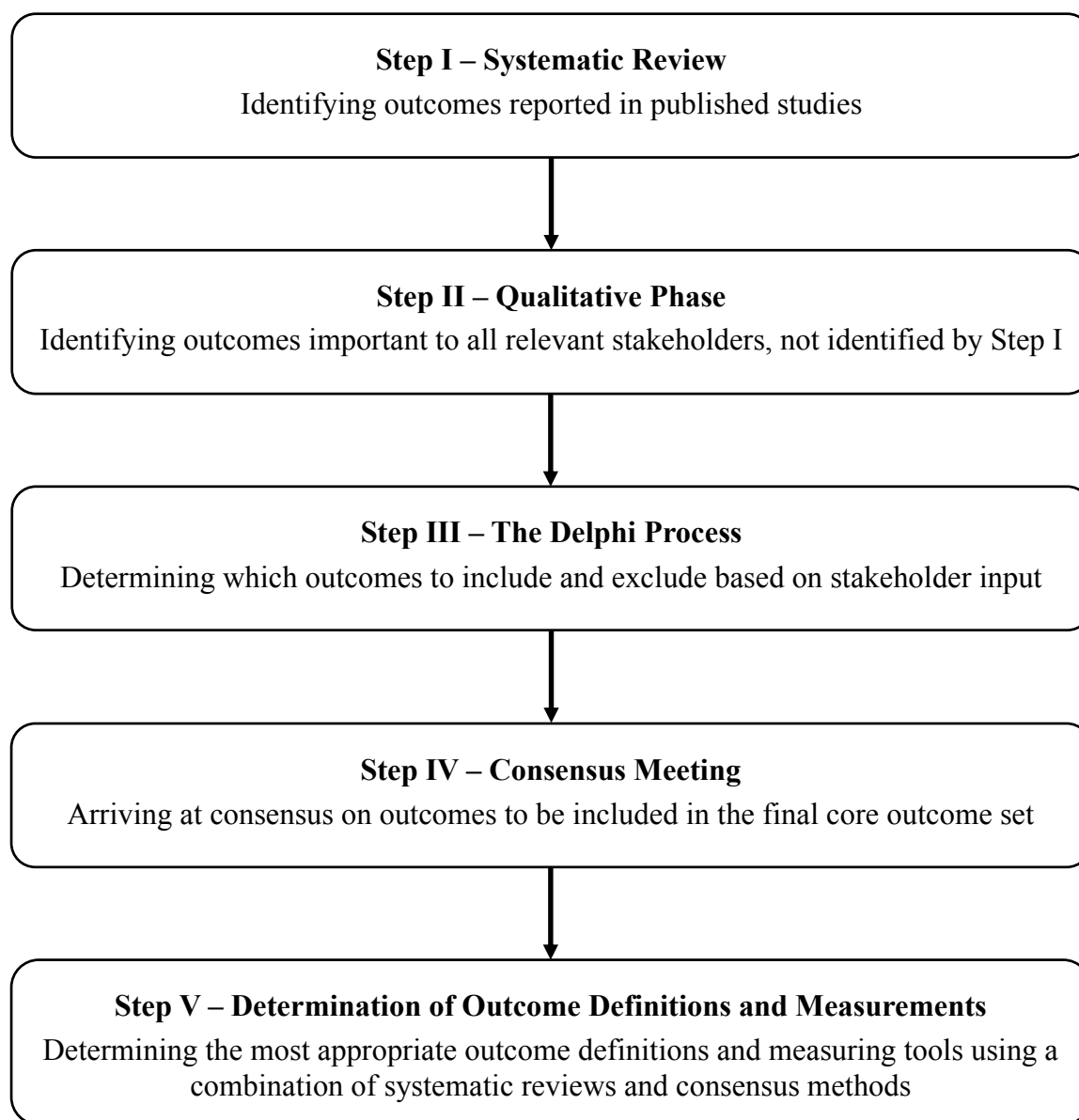
Continent	
North America	6-8
Europe	6-8
Australasia	6-8
Africa	1-3
South and Central America	2-3
Target total	20

471

472 Figure Legend

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

474



COVasP – Interview Guide

1	ID number	
2		
3	Interview date	
4		
5	Country	
6		
7	Date/ Year of diagnosis of vasa previa	
8		
9	Age	
10		
11	Sex and Gender	
12		
13	Education	
14		
15	Profession	
16		
17	Ethnicity	
18		
19	Marital status (of women with vasa previa)	
20		
21	Parity	
22		
23	Method of conception (In vitro fertilization /spontaneous)	
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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

- 1
- 2
- 3 12. What are the main pieces of advice you would share with a friend with vasa previa?
- 4
- 5 ○ Probe: we're interested in hearing about any aspect of your care, health or well-being.
- 6
- 7
- 8 13. In your opinion, what is an outcome?
- 9
- 10 14. What outcomes do you think are essential and should be measured?
- 11
- 12 ○ Probe: These outcomes may be related to you (your partner) and/or your baby
- 13
- 14
- 15 15. Can you tell me if your opinion on what is important has changed over time?
- 16
- 17 16. Is there anything else you would like to add?
- 18
- 19 17. Would you be interested in an online survey a few months from now?
- 20
- 21

Other Stakeholders

- 22
- 23
- 24 1. Based on experience, what are some considerations you typically have while caring for women
- 25 with vasa previa?
- 26
- 27
- 28 2. What aspects of mother's or baby's health matter most to you when caring for these women?
- 29
- 30
- 31 3. What outcomes influence your management of women with vasa previa?
- 32
- 33 4. What are some concerns and negative or positive experiences that these women typically share
- 34 with you?
- 35
- 36
- 37
- 38 5. What are the main pieces of advice you would share with a colleague who does not care for this
- 39 population as frequently as you do?
- 40
- 41
- 42 6. In your opinion, what is an outcome?
- 43
- 44
- 45 7. What outcomes do you think are essential and, therefore, need to be measured in research?
- 46 ○ Probe: These outcomes may be maternal and/or fetal/neonatal
- 47 ○ Do you discuss any of these with women? (If yes) Which one?
- 48
- 49
- 50
- 51 8. Is there anything else you would like to add?
- 52
- 53
- 54 9. Would you be interested in participating in an online survey a few months from now?
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Core Outcome Set-STANDARDISED Protocol Items: The COS-STAP Statement Checklist

TITLE/ABSTRACT		1a	P1
Title	1a Identify in the title that the paper describes the protocol for the planned development of a COS	1b	P2-3
Abstract	1b Provide a structured abstract	2a	P5-6
INTRODUCTION		2b	P6
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	3a	P5
	2b Describe the specific objectives with reference to developing a COS	3b	P6
Scope	3a Describe the health condition(s) and population(s) that will be covered by the COS	3c	P6
	3b Describe the intervention(s) that will be covered by the COS	4	P8,9,11
	3c Describe the context of use for which the COS is to be applied	5a	P6-10
METHODS		5b	P12-13
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	6	P13-14
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	7a	P12-13
	5b Describe how outcomes may be dropped/combined, with reasons	7b	P12-14
Consensus process	6 Describe the plans for how the consensus process will be undertaken	8	P12-13
Consensus definition	7a Describe the consensus definition	9	P13
	7b Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	10	P17
ANALYSIS		11	P17
Outcome scoring/feedback	8 Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	12	P18
Missing data	9 Describe how missing data will be handled during the consensus process	13	P18
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)		
Dissemination	11 Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination		
ADMINISTRATIVE INFORMATION			
Funders	12 Describe sources of funding, role of funders		
Conflicts of interest	13 Describe any potential conflicts of interest within the study team and how they will be managed		

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034018.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Mar-2020
Complete List of Authors:	D'Souza, Rohan; University of Toronto, Villani, Linda; University of Utah School of Medicine Hall, Chelsea; University of Toronto Seyoum, Meron; University of Toronto Kingdom, John; University of Toronto Krznaric, Michael; International Vasa Previa Foundation Donnelly, Natasha; University of New South Wales - Randwick Campus, Centre for Big Data Research in Health and School of Women's and Children's Health Javid, Nasrin; University of Technology Sydney
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	vasa previa, core outcome set, velamentous cord insertion, stakeholder and patient-reported outcomes

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3 **1 Core Outcome Set for Studies on Pregnant Women with Vasa Previa (COVasP): A Study**

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5 **2 Protocol**

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8 3 Rohan D'Souza^{1,2}, Linda Villani³, Chelsea Hall⁴, Meron Seyoum¹, John Kingdom^{1,2}, Michael
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10 4 Krznaric⁵, Natasha Donnelly^{5,6}, Nasrin Javid⁷

11
12 ¹ Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai
13
14 Hospital, University of Toronto, Toronto, ON, Canada

15
16
17 ² Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada

18
19 ³ University of Utah School of Medicine, Salt Lake City, Utah, USA

20
21 ⁴ Faculty of Medicine, University of Toronto, Toronto, ON, Canada

22
23
24 ⁵ International Vasa Previa Foundation, Chester, Illinois, United States of America

25
26
27 ⁶ The National Perinatal Epidemiology and Statistics Unit, Centre for Big Data Research and
28
29 Health, University of New South Wales, Sydney, New South Wales, Australia

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31 ⁷ Faculty of Health, University of Technology Sydney, New South Wales, Australia

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35 **15 Email Addresses:**

36
37
38 16 Dr. Rohan D'Souza – rohan.dsouza@sinaihealthsystem.ca

39
40 17 Linda Villani - lian.villani@gmail.com

41
42 18 Chelsea Hall – chelsea.hall@mail.utoronto.ca

43
44 19 Meron Seyoum - mina.seyoum@gmail.com

45
46 20 John Kingdom - john.kingdom@sinaihealthsystem.ca

47
48 21 Michael Krznaric – michaelkrznaric@gmail.com

49
50 22 Natasha Donnelly - n.donnelly@unsw.edu.au

51
52 23 Nasrin Javid - nasrin.javid@health.nsw.gov.au

1
2
3 24 **Corresponding author:**
4

5 25 Rohan D'Souza
6

7 26 Mount Sinai Hospital, 3-908 – 700 University Avenue, Toronto, Ontario M5G 1Z5, Canada.
8
9

10 27 Email: rohan.dsouza@sinaihealthsystem.ca
11

12 28 Ph: +1 (416) 586-4800 ext. 5127; F: +1 (416) 586-8649
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16
17 30 **Abstract**
18

19 31 **Introduction:**
20

21 32 Vasa previa is a condition where fetal blood vessels run unprotected in the membranes, outside
22 33 the umbilical cord, and cross the internal opening of the cervix. During rupture of membranes,
23 34 these vessels can rupture and put the baby at serious risk of severe blood loss and death.
24 35
25 36

26 37 Numerous studies are being conducted to improve diagnostic modalities and establish clear
27 38 management plans to improve pregnancy outcomes. However, the lack of a standardized set of
28 39 outcomes for studies on vasa previa makes it difficult to compare study findings and draw
29 40 meaningful conclusions. Through this project, we will be developing a core outcome set for
30 41 studies on pregnant women with vasa previa (COVasP).
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40 41 **Methods and analysis:**
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43 41 The development of COVasP will involve five steps. The first will be a systematic review, in
44 42 which we will generate a long list of outcomes based on published studies in pregnancies
45 43 complicated with vasa previa. The second will involve in-depth interviews with current and
46 44 former patients, their family members and healthcare providers that care for these patients. This
47 45 will be followed by a two-round Delphi survey, which will aim to narrow down the long list of
48 46 outcomes into those considered important by four groups of 'stakeholders': 1) patients, family
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3 47 members and patient advocates/representatives, 2) healthcare providers, 3) researchers,
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5 48 epidemiologists and methodologists and 4) other stakeholders directly or indirectly involved in
6
7 49 the management of these pregnancies such as administrators, guideline developers and policy
8
9 50 makers. The fourth step will involve a face-to-face consensus meeting using a nominal group
10
11 51 approach to establish a finalized core outcome set. The final step will involve measuring and
12
13 52 defining the identified outcomes using a combination of systematic reviews and Delphi surveys.
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19 54 **Ethics and Dissemination**

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21 55 This study as well as consent forms for stakeholder participation have received approval from the
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23 56 Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the
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25 57 Human Research Ethics Committee at The University of Technology Sydney, Australia on 30
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27 58 July 2019 (UTS HREC REF NO. ETH19-3718). All progress will be documented on the
28
29 59 international prospective register of systematic reviews (PROSPERO) and Core Outcome
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31 60 Measures in Effectiveness Trials (COMET) databases.
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38 62 **Keywords**

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40 63 Vasa Previa, Core outcome set, velamentous umbilical cord insertion, stakeholder and patient-
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42 64 reported outcomes
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47 66 **Registration details**

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49 67 <http://www.comet-initiative.org/studies/details/1117>
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3 70 **Article summary**
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5 71 **Strengths and Limitations of this study**
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- 7
8 72 - This core outcome set, which is being developed by a multi-national group of
9
10 73 investigators that comprise the Outcome Reporting in Obstetric Studies (OROS) project
11
12 74 (<https://www.obgyn.utoronto.ca/oros-project>), are supported by the International Vasa
13
14 75 Previa Foundation, and will draw input from numerous international organizations to
15
16 76 ensure global representation of all stakeholders.
17
18 77 - COVasP will draw from outcomes reported in all published studies and trial registrations,
19
20 78 and will not exclude outcomes from studies that are at increased risk-of-bias, in order to
21
22 79 obtain the most comprehensive initial list of outcomes.
23
24 80 - Increased emphasis is being placed on the qualitative steps of core outcome set
25
26 81 development, in order to ensure that patient-reported outcomes and outcomes related to
27
28 82 quality of life, resource use and functioning are considered alongside routinely-reported
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30 83 clinical outcomes.
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35 84 **Word count: 3577**
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87 Introduction

88 In approximately 7% of all singleton pregnancies, the umbilical cord inserts close to the
89 edge of the placenta (marginal insertion), and in 1% of cases, a more extreme variation is
90 encountered, wherein the umbilical cord inserts at the apex of the membranous sac (velamentous
91 cord insertion).(1) In both these instances, fetal blood vessels could run unprotected outside the
92 umbilical cord, in the membranes surrounding the baby; and when these membranous vessels
93 cross the internal opening of the cervix, preceding the presenting fetal part, the condition is
94 referred to as vasa previa(1, 2). Spontaneous or artificial rupture of the membranes around the
95 time of childbirth, could result in a rupture of these vessels, putting the baby at risk of severe
96 blood loss, hypotension, anaemia, and death by exanguination. Vasa previa is believed to affect
97 one in 1,667 – 2,174 pregnancies [0.46 – 0.60 per 1000 pregnancies].(3, 4) If vasa previa is not
98 diagnosed antenatally, and prior to the onset of labour and vaginal delivery, approximately 40-
99 60% of newborns do not survive.(5, 6) Early diagnosis and the introduction of clear management
100 plans are imperative for improving outcomes. However, there is no consensus on the optimal
101 approach to antenatal diagnosis as well as various aspects of antenatal and peripartum
102 management(7). As a result, women who have been diagnosed with vasa previa have described
103 feeling “like a ticking time bomb”, and expressed the reality of “coping with inconsistent
104 information”.(8) Preferences of pregnant women with the condition, and outcomes that they
105 consider important have not yet been elucidated. Finally, the cost implications to healthcare
106 systems from inpatient vs. outpatient management and the use of various diagnostic modalities
107 and management protocols have not been determined.

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

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2
3 110 that are considered important by pregnant women and other stakeholder groups including
4
5 111 healthcare providers, researchers and policy makers. Determining this core set of outcomes that
6
7 112 should comprise the bare minimum for inclusion in all further studies, is therefore vital. A core
8
9 113 outcome set is a set of outcomes that are considered important by those suffering from the
10
11 114 condition, their family members and those involved in their care(9).

12
13
14 115 The goal of this study is to gather patient and other stakeholder input regarding the
15
16 116 outcomes important to them, and use this to create a core outcome set for studies on vasa previa
17
18 117 which provide researchers with a list of outcomes that must be reported in all future studies, in
19
20 118 order to improve its translational value and clinical relevance. This project will reduce bias in
21
22 119 outcome reporting, enable meta-analysis of published data to inform decision-making, and
23
24 120 provide an empiric basis for inclusion of stated outcomes based on input from relevant
25
26 121 stakeholders.

27 28 29 30 31 122 32 33 123 **Methods and analysis**

34
35 124 The protocol for this Core Outcome Set for studies on Vasa Previa (COVasP) is registered on the
36
37 125 Core Outcome Measures in Effectiveness Trials (COMET) website. It is guided by the COMET
38
39 126 handbook(9) and complies with the Core Outcome Set – Standardized Protocol Items (COS-
40
41 127 STAP) statement.(10) As with other core outcome sets being developed as part of the University
42
43 128 of Toronto’s Outcome Reporting in Obstetric Studies (OROS) project
44
45 129 (<https://www.obgyn.utoronto.ca/oros-project>), COVasP will be developed in five distinct steps,
46
47 130 involving qualitative and quantitative research methods, as outlined in Figure 1.(11, 12)

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52 53 54 132 **Step-1: Systematic Review:**

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2
3 133 A systematic literature review will be undertaken to explore all reported outcomes in published
4
5 134 studies involving pregnant women with vasa previa, and will generate a preliminary list of
6
7
8 135 outcomes that are deemed important and hence reported by researchers. The protocol for this
9
10 136 systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-
11
12 137 Analyses (PRISMA) guidelines, is available on the international prospective register of
13
14
15 138 systematic reviews - PROSPERO (CRD42018087837).

16
17 139 **Study selection:** Five bibliographic databases - Medline, Embase, Cochrane, PubMed (non
18
19 140 Medline and in-process) and Clinicaltrials.gov will be searched from inception. All interventions
20
21 141 and exposures will be included. Randomized or non-randomized studies, prospective and
22
23 142 retrospective cohort studies, case-control studies, case series, case reports, qualitative research,
24
25 143 as well as economic evaluation studies and decision analyses will be included in the search. We
26
27 144 will exclude letters to the editor, commentaries, editorials, conference abstracts that do not
28
29 145 describe clinical outcomes and reviews that do not report on outcomes or contain original
30
31 146 research.

32
33
34
35 147 **Data Extraction:** Extracted information will include details on study characteristics such as
36
37 148 publication year, number of participants, study type, number of included pregnancies, as well as
38
39 149 individual and composite outcomes and their definitions, components and measurement
40
41
42 150 instruments when available.

43
44
45 151 **Quality Assessment:** As the purpose of this review is to identify reported outcomes and not to
46
47 152 determine the effectiveness of management strategies, no assessment of the study's
48
49 153 methodological quality will be performed. Similarly, as the aim of this systematic review is to
50
51 154 identify all reported outcomes in order to generate a long-list of outcomes to inform the
52
53
54 155 development of the core outcome set, and there is no validated tool to assess the quality of

1
2
3 156 outcome reporting, it was decided a priori that the quality of outcome reporting of included
4
5 157 studies would not be assessed.

7
8 158 **Analysis and presentation of results:** The proportion of studies reporting each outcome and the
9
10 159 components will be documented. No subgroup or sensitivity analysis is proposed.

11
12 160

14 15 161 **Step 2: Stakeholder Consultation**

16
17 162 In addition to identifying outcomes reported by researchers, we aim to understand what maternal
18
19 163 and perinatal outcomes are considered important by women with a diagnosis of vasa previa, their
20
21 164 family members, health care providers and researchers. Qualitative methodology provides a
22
23 165 scope for all relevant stakeholders to discuss their views on important outcomes, and contributes
24
25 166 to the robustness of core outcome set development by identifying the new outcomes that were
26
27 167 not reported in the literature, exploring why the outcomes are considered important, and
28
29 168 understanding the scope and priority of the outcomes.(13) Our systematic literature review found
30
31 169 only three qualitative studies on vasa previa; that were conducted with the women,(8)
32
33 170 midwives(14, 15) and obstetricians.(7) However, these studies were focussed on eliciting
34
35 171 experiences of patients and midwives, identifying barriers and challenges to care, and
36
37 172 determining variations in opinions and clinical practice. None specifically focused on identifying
38
39 173 the outcomes that could inform the development of COVasP. Hence, we will conduct a
40
41 174 descriptive-interpretive qualitative research study(16) with the relevant stakeholders in high-
42
43 175 income countries.

44
45 176 **Inclusion criteria:** We will include women who have had a diagnosis of vasa previa (current or
46
47 177 previous) and their partners, health care providers who have cared for women with a diagnosis of
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49 178 vasa previa, and health care professionals who have been involved in conducting research or
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3 179 development of a policy/guideline in relation to vasa previa that are above the age of 18 and able
4
5 180 to give informed consent and participate in an interview in English language. Women and their
6
7
8 181 partners will be excluded if they (or their partners) had been diagnosed with vasa previa that was
9
10 182 not confirmed at a later stage during pregnancy or birth.

11
12 183 **Sampling:** Women and their partners will be recruited through an established partnership with
13
14 184 the International Vasa Previa Foundation - IVPF (<http://vasaprevia.com>). The IVPF is an all-
15
16 185 volunteer charity created to promote awareness and provide support and advocacy to the general
17
18 186 public and professionals regarding vasa previa. In the year 2018, the IVPF sent out an
19
20 187 'Expression of Interest' email to their members which was also shared on social media in
21
22 188 relevant peer support groups as a means of recruitment. To ensure that the views of women with
23
24 189 different experiences and backgrounds are represented, specific criteria (age, type of conception,
25
26 190 time of diagnosis, and country where care was received) will be selected to provide maximum
27
28 191 variation sampling as outlined in Table 1.(13) In addition to the categories outlined in the table, it
29
30 192 is hoped that recruiting patients through the IVPF, known contacts, and other channels, will
31
32 193 enable us to access representatives of the following groups (a) those currently pregnancy with a
33
34 194 confirmed diagnosis of vasa previa, (b) those that have had pregnancies that resulted in live
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36 195 births, and those that resulted in fetal or neonatal death, (c) pregnancies with a complicated and
37
38 196 relatively uncomplicated antenatal course, (d) those whose babies suffered serious consequences
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40 197 of prematurity, and (e) those that required unplanned/emergency caesarean deliveries vs. those
41
42 198 whose caesarean deliveries occurred as scheduled. Healthcare providers and researchers will be
43
44 199 recruited through email using a study flyer, via contact lists assembled by the study investigators.
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46 200 As is the norm with qualitative research, the exact sample size will be determined once data
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48 201 collection and analysis are commenced.(17) Based on interviews we have conducted with
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3 202 patients and healthcare professionals in this area, wherein data saturation was attained after the
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5 203 conduct of 14-20 interviews, we anticipate that we will conduct approximately 20 patient
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7 204 interviews and 10-12 interviews with clinicians/researchers until data saturation is reached and
8
9 205 no new outcomes are identified in two successive interviews.

10
11
12 206 **Consent:** Information regarding the aims of the study and the process of interview will be
13
14 207 provided to interested individuals in writing by means of a participant information sheet,
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16 208 highlighting that participation is voluntary. Individuals will be given an opportunity to contact
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18 209 the researchers to receive more information before they make an informed consent to participate
19
20 210 in an interview. Only individuals who provide written and/or verbal consent will be interviewed.

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22
23 211 **Data collection:** All interviews will be conducted online or over the phone. Upon
24
25 212 commencement of the interview, the interviewer will confirm that the participant has read the
26
27 213 participant information sheet and consent form and obtain verbal consent. The interviewer will
28
29 214 then request certain demographic details, which the participants may or may not choose to
30
31 215 answer. Demographic details will vary slightly depending on stakeholder group but include: age,
32
33 216 occupation, education, ethnicity and descriptions of their experiences with vasa previa or number
34
35 217 of years working with this population, as appropriate. After a brief introduction, and providing a
36
37 218 description of the project and explanation of what constitutes health outcomes the interview will
38
39 219 commence. The interviews are designed to be semi-structured and conversational using a topic
40
41 220 guide (Appendix A). The goal is to ensure that the participant feels comfortable sharing their
42
43 221 views and experience while ultimately eliciting health outcomes important to the participants that
44
45 222 can then further inform our core outcome set development. During the reflective and iterative
46
47 223 process of data collection and analysis, the topic guide may be refined and/or expanded to
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49 224 include the issues raised by earlier participants. One experienced qualitative researcher will
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3 225 conduct all the interviews by telephone or online. The interviews will be audio-recorded and
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5 226 transcribed verbatim.

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8 227 **Data analysis:** Thematic data analysis(18) taking a descriptive interpretive approach(19) will
9
10 228 start after the first interview. The data will be imported into NVivo V.12 software, which will
11
12 229 assist with data management and analysis. Transcripts will be read and coded by a qualitative
13
14 230 researcher (NJ) who conducted the interviews. The codes, emerging categories and the related
15
16 231 quotes will be discussed with the research team, that includes at least one physician that cares for
17
18 232 pregnant women with vasa previa, to reach agreement. Information and outcomes obtained
19
20 233 through this qualitative data analysis will be used to develop a list of outcomes deemed
21
22 234 important by the participants, which will inform the subsequent Delphi study.
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29 236 **Step-3: Delphi Methodology:**

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32 237 Steps 1 and 2 generate a long list of outcomes considered important by researchers, women and
33
34 238 other stakeholders involved in their care. The Delphi process that follows, is designed to achieve
35
36 239 convergence of opinion on these outcomes, in an iterative and sequential manner.(20) For this
37
38 240 step, we will identify four groups of participants: 1) women, family members and patient
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40 241 advocates or representatives, 2) healthcare providers, 3) researchers, epidemiologists/
41
42 242 methodologists and core outcome set developers, and 4) other stakeholders directly or indirectly
43
44 243 involved in the care of pregnant women such as administrators, guideline developers and policy
45
46 244 makers. These groups represent all stakeholders directly or indirectly involved in the care of
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48 245 pregnancies affected by vasa previa. The Delphi survey will be developed by grouping the long
49
50 246 list of outcomes (obtained through steps 1 and 2) into five core outcome areas - mortality,
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52 247 morbidity (clinical/physiological), life-impact (functioning), resource-use, and adverse events -
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3 248 based on a published taxonomy.(21) Lay-language summaries will appear alongside complex
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5 249 medical outcomes. The survey will be piloted with at least 10 people including one person from
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7
8 250 each stakeholder group. Since we will be using a familiar software, retaining all outcomes
9
10 251 obtained through steps-1 and 2, and using pre-piloted lay-language summaries for common
11
12 252 obstetric and neonatal outcomes developed by the OROS project(11, 12, 22), the only purpose of
13
14 253 piloting the survey, is to ensure that representatives of all stakeholder groups have an opportunity
15
16
17 254 to comment on content unique to COVasP. We believe that a sample of 10 people to be sufficient
18
19 255 for this step. After piloting, the survey will be made available online (through links on social
20
21 256 media) and widely distributed through identified listservers of relevant organizations, including
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23
24 257 but not restricted to the Cochrane Pregnancy and Childbirth Group (30 members), the Global
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26 258 Obstetric Network (237 members), Core Outcomes in Women's and Newborn Health (CrOWN)
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28 259 initiative (77 members), corresponding authors of publications on vasa previa included in a recent
29
30 260 systematic review,(23) IVPF, United Kingdom Obstetric Surveillance System (UKOSS)
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33 261 <https://www.npeu.ox.ac.uk/ukoss>, UK Vasa Praevia Raising Awareness Trust
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35 262 (<http://vasapraevia.co.uk>), Australasian Maternity Outcomes Surveillance System (AMOSS)
36
37 263 <https://www.amoss.com.au>, Perinatal Society of Australia and New Zealand (PSANZ)
38
39 264 <https://www.psanz.com.au> and Vasa Praevia Support and Awareness Ireland
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41 265 (<https://www.facebook.com/vasapraeviasupportandawarenessIreland>). We will aim to recruit at
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44 266 least 25 individuals from each stakeholder group to ensure an appropriate degree of
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47 267 representation. An online approach using DelphiManager™ software will be employed, to ensure
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49 268 privacy, feasibility, cost effectiveness and reliability, while facilitating global representation.(9)
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51 269 Upon signing an online consent form and completing a brief demographic questionnaire,
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54 270 participants will be required to score each outcome on a 9-point Likert Scale based on its
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3 271 perceived degree of importance. Scores of 1 to 3 will be considered as ‘not essential’; 4 to 6,
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5 272 ‘important but not critical’; and 7 to 9, ‘critically important for inclusion’.(9) Participants will
6
7
8 273 also be presented with a text box for them to enter any outcomes they deem important, which
9
10 274 might not have been included in the list provided.

11
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13 275 **Analysis:** For each outcome, scores will be plotted as histograms, stratified by the each
14
15 276 participant’s self-reported group, as follows: (a) patients and patient advocates, (b) clinicians and
16
17 277 (c) researchers. All new outcomes emerging from round 1, if deemed by COVasP investigators
18
19 278 as distinct from those presented, will be included into the second round. Upon completion of
20
21 279 first-round analysis, an invitation will be sent out to all members requesting participation in the
22
23 280 **second round.** Each member scoring outcomes in the second round will have access to the
24
25 281 histograms presenting first-round scores stratified by the participant group, to enable participants
26
27 282 to decide on whether they would like to retain their original score, or modify it. Email reminders
28
29 283 will be sent out to ensure that at least 85% of respondents complete both surveys, to prevent
30
31 284 attrition bias. Each participant will be asked whether they would like to and be able to attend a
32
33 285 face-to-face consensus meeting, details of which will be determined, by this juncture.
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41 287 **Missing Data and Attrition:** Participants will be given clear outlined expectations of timelines
42
43 288 and a six-week window to complete each round of the survey. Should the response rate not
44
45 289 achieve 80%, a level deemed acceptable by published recommendations(9), additional
46
47 290 interventions will be implemented, guided by measures adopted by other COS developers.
48
49 291 Telephone calls, emails, personal reminders and extension of the survey deadlines may be used
50
51 292 to improve the response rate. Any feedback after the first round regarding obstacles when
52
53 293 completing the survey in its entirety will be noted and addressed before the second round.
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Step 4: Consensus meeting

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

315

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3 316 This consensus meeting will occur over a half-day and will be conducted in keeping with the
4
5 317 specifications laid out by the Evaluation Research Team at the Centre for Disease Control,(24)
6
7 318 and the entire process will be audio-recorded. Groups developing core outcome sets for obstetric
8
9 319 conditions have included between 14 and 29 participants in this step. Without pre-specifying a
10
11 320 number, we will aim to ensure equal representation of each stakeholder group, and schedule this
12
13 321 face-to-face meeting to coincide with an international obstetrics conference, in order to ensure
14
15 322 global participation of representatives of various stakeholder groups. However, we acknowledge
16
17 323 that this might be difficult to organize, and therefore, in the interest of feasibility, might have to
18
19 324 settle for organizing this at the time of a local meeting, with most stakeholder representatives
20
21 325 from within Canada. Since international representation will already
22
23 326 have been sought through the Delphi survey, and on account of
24
25 327 the cautious approach to eliminating outcomes described above,
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27 328 we do not believe this will compromise study integrity.
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35 330 The OROS project, under whose initiative, COVasP is being developed, endeavours to achieve a
36
37 331 balance between standardization and comprehensiveness of outcome reporting. While the
38
39 332 development of a core outcome set will address the former, the latter is important to ensure
40
41 333 inclusion of maternal and fetal outcomes representing all core outcome areas(21), which include
42
43 334 mortality/survival, clinical/physiological, life-impact/functioning, resource-use and adverse
44
45 335 events. There will therefore, be no limit on the final number of outcomes constituting COVasP.
46
47 336 As described in protocols for other core outcome sets being developed by the OROS group, all
48
49 337 outcomes identified through the above process, will be presented in tabular form, separating
50
51 338 maternal from fetal/neonatal outcomes, each stratified by the five main core outcome areas,
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3 339 and a supplementary table highlighting all outcomes, their
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5 340 Delphi scores, and the stages at which they were excluded will
6
7 341 also be presented, for greater transparency(12) .
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13 343 **Step 5: Measuring/defining core outcomes**

16 344 Upon selection of a final list of core outcomes, we will employ the COnsensus-based Standards
17
18 345 for the selection of health Measurement INstruments (COSMIN) to assess measurement tools/
19
20 346 definitions for included outcomes based on four criteria: validity, responsiveness, reliability and
21
22 347 interpretability.(25) We will begin the process by listing measurement instruments and/or
23
24 348 definitions for outcomes where universal agreement exists. For outcomes where there is a lack of
25
26 349 agreement on measurement instruments or definitions, we will conduct systematic reviews to
27
28 350 determine all currently used instruments and definitions. This will be followed by Delphi surveys
29
30 351 involving relevant stakeholder groups as required, to determine the most appropriate definition
31
32 352 or measurement instrument for each identified core outcome where systematic reviews are
33
34 353 inconclusive.(26) Details of this process will depend on the final list of outcomes, and are
35
36 354 beyond the scope of this protocol.
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44 356 **Patient and Public Involvement**

46 357 Although the steps of developing a core outcome set are standardized, we will involve patients
47
48 358 and other stakeholders to participate in steps 2-4, through interviews, the Delphi survey and a
49
50 359 consensus meeting. The purpose of their involvement is to determine what outcomes related to
51
52 360 vasa previa are most important to them. The design of the study encourages stakeholders to
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54 361 consider outcomes related to domains such as functioning, resource use, satisfaction,
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3 362 compliance, healthcare delivery and mental health concerns in addition to the clinical and
4
5 363 physiological outcomes most commonly reported in research studies. We have taken steps to
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7
8 364 ensure that these outcomes considered important by patients are represented in the final core
9
10 365 outcome set. We aim to involve patients in ensuring that COVasP is disseminated widely
11
12 366 through the IVPF webpage and also through social media, in addition to ensuring knowledge
13
14 367 translation to clinicians and researchers. The findings of each step of COVasP development will
15
16 368 be published on the OROS website (<https://www.obgyn.utoronto.ca/oros-project>), enabling
17
18 369 ongoing feedback from patients and the public.
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23 24 371 **Discussion**

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26 372 COVasP aims to provide researchers and clinicians with a systematically-derived list of
27
28 373 outcomes, incorporating preferences of patients and other relevant stakeholders, which will form
29
30 374 the minimum standard required to be collected, measured and recorded as a baseline in all
31
32 375 clinical studies on vasa previa. Input from various stakeholder groups will enhance the quality
33
34 376 and relevance of future studies on vasa previa, and go a long way in improving outcomes that are
35
36 377 considered most important by those that are affected by this rare but serious obstetric condition.
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41 42 379 **List of Abbreviations**

43
44 380 COSVasP – Core Outcome Set for Studies on Vasa Previa

45
46 381 COMET – Core Outcome Measurement in Effectiveness Trials

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48 382 CROWN – CoRe Outcomes in Women’s and Newborn Health

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50 383 COSMIN – COnsensus-based Standards for the selection of health Measurement INstruments

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52 384 IVPF - International Vasa Previa Foundation
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3 385 OROS – Outcome reporting in Obstetric Studies
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5 386 PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
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8 387 PROSPERO - Prospective Register of systematic reviews
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11
12 389 **Ethics and dissemination**
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14 390 This study as well as consent forms for stakeholder participation have received approval from the
15

16 391 Mount Sinai Hospital Research Ethics Board (REB# 18-0173-E) on 05/September/2018 and the
17

18 392 Human Research Ethics Committee at The University of Technology Sydney, Australia on 30
19

20 393 July 2019 (UTS HREC REF NO. ETH19-3718). The findings of the systematic review, patient
21

22 394 interviews and final COS will be published in open-access journals and presented at national and
23

24 395 international obstetrics and maternal-fetal medicine conferences. All progress will be
25

26 396 documented on the PROSPERO, COMET and CROWN databases and made freely available
27

28 397 through the IVPF webpage. Corresponding authors of studies included in the systematic review
29

30 398 and participants in the qualitative interviews, Delphi surveys and consensus group meetings will
31

32 399 be provided with a copy of all publications related to COVasP, to encourage its dissemination
33

34 400 and use in future studies on the topic.
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42 402 **Author Contributions**
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44 403 RD conceived the idea, has experience with mixed-methods study design and development of
45

46 404 core outcome sets and is the principal investigator and the founder of the Outcome Reporting in
47

48 405 Obstetric Studies (OROS) project. NJ designed the qualitative research components of the study.
49

50 406 LV, CH and MS helped with drafting various aspects of the manuscript. JK is a Maternal-Fetal
51

52 407 Medicine Physician with clinical expertise in the management of vasa previa. MK, ND and NJ
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2
3 408 represent the International Vasa Previa Foundation. NJ, RD, JK, MK and ND secured funding
4
5 409 for the study. All authors contributed to and approved the final version of the manuscript prior to
6
7
8 410 submission.

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10 411

11 412 **Funding**

12
13
14 413 This study is funded by the David Henderson-Smart 2019 Scholarship awarded to Nasrin Javid
15
16 414 by the Perinatal Society of Australia and New Zealand, and the International Vasa Previa
17
18 415 Foundation (IVPF).

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20 416

21 417 **Competing Interests**

22
23
24 418 MK and ND are directors and NJ is a member of the International Vasa Previa Foundation that
25
26 419 has provided part funding for this project. RD has received speaking honoraria from Ferring,
27
28 420 Canada for presentations unrelated to this project. Other authors have no conflict of interest.

29
30 421

31 422 **Acknowledgements**

32
33 423 None

34 424

35 425 **Data statement**

36
37 426 The data for all steps of this project will be published in a data repository which will be made
38
39 427 available on the OROS webpage - <https://www.obgyn.utoronto.ca/oros-project>

40 428

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

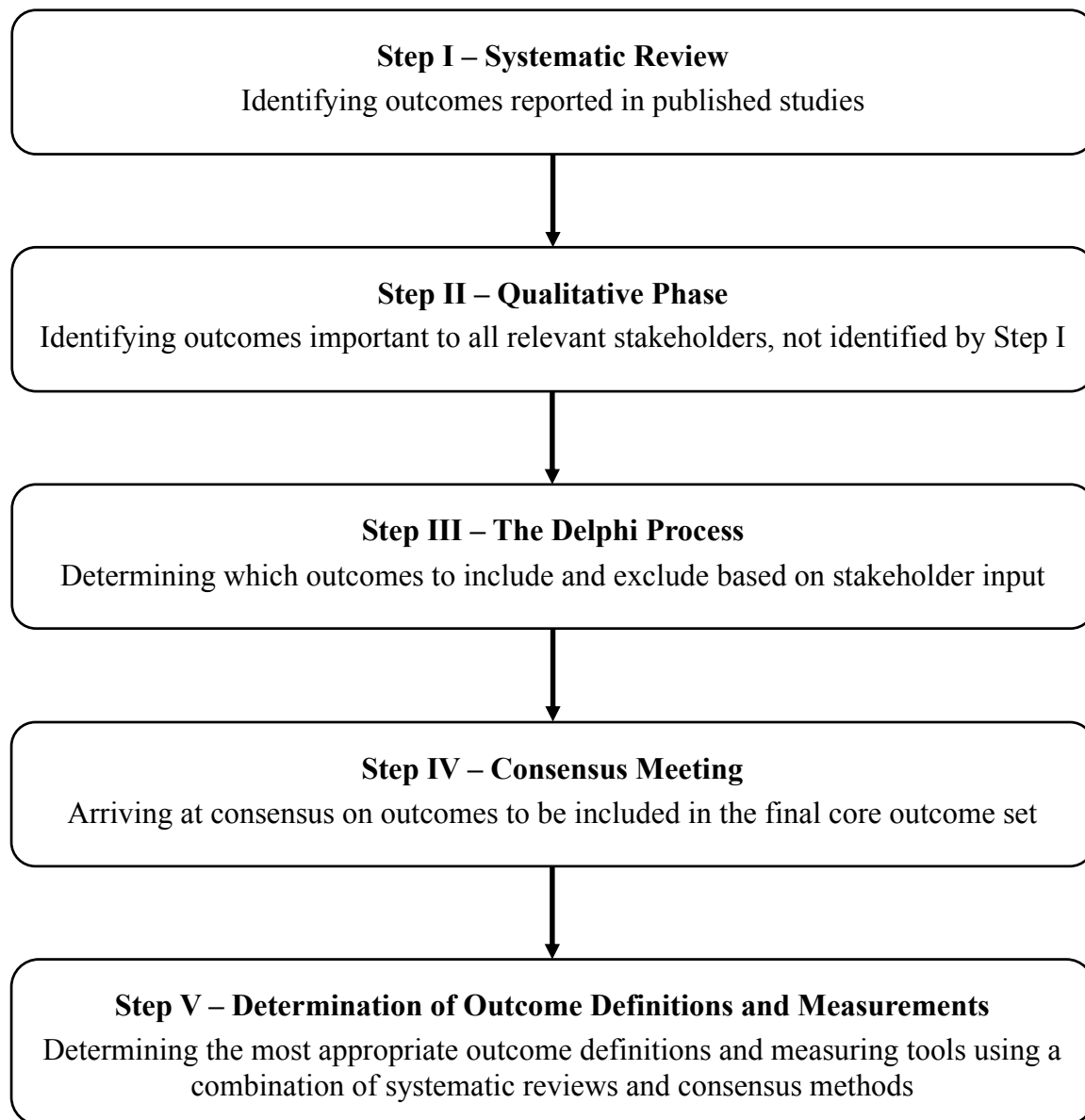
Criteria	Target number of participants
Method of conception	
In vitro fertilization	3-5
Spontaneous conception	10-12
Pregnancy affected by vasa previa	
<5 years ago	6-8
>5 years ago	6-8
Time of diagnosis of vasa previa	
During pregnancy	10-12
During labor and childbirth	3-5
Continent	
North America	6-8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

499

500 **Figure Legend**

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

502



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
Abstract	1b Provide a structured abstract
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
	2b Describe the specific objectives with reference to developing a COS
	3a Describe the health condition(s) and population(s) that will be covered by the COS
Scope	3b Describe the intervention(s) that will be covered by the COS
	3c Describe the context of use for which the COS is to be applied
	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
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
	5b Describe how outcomes may be dropped/combined, with reasons
Consensus process	6 Describe the plans for how the consensus process will be undertaken
Consensus definition	7a Describe the consensus definition
	7b Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process
ANALYSIS	
Outcome scoring/feedback	8 Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process
Missing data	9 Describe how missing data will be handled during the consensus process
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)
Dissemination	11 Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination
ADMINISTRATIVE INFORMATION	
Funders	12 Describe sources of funding, role of funders
Conflicts of interest	13 Describe any potential conflicts of interest within the study team and how they will be managed

1a	P1
1b	P2-3
2a	P5-6
2b	P6
3a	P5
3b	P6
3c	P6
4	P8,9,11
5a	P6-10
5b	P12-13
6	P13-14
7a	P12-13
7b	P12-14
8	P12-13
9	P13
10	P17
11	P17
12	P18
13	P18