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Development of a core outcome set for studies on Placenta Accreta Spectrum Disorder (COPAS): a study protocol

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Manuscripts

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3 **Development of a core outcome set for studies on Placenta Accreta Spectrum Disorder**
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5 **(COPAS): a study protocol**
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Abstract

Introduction: Placenta Accreta Spectrum (PAS) disorder is a life-threatening condition that may result in serious maternal complications, including mortality. The condition places individuals at high risk of major haemorrhage from attempts to remove the pathologically-adherent placenta from the uterine wall at delivery. Current research reports on PAS disorder outcomes have highly variable levels of information, which is therefore difficult for investigators to aggregate to inform practice. There is an urgent need to harmonize data collection in prospective studies to identify and implement best practices for management. One approach to standardize outcomes across any health area via the use of core outcome sets, which are consensus-derived standardised sets of outcomes that all studies for a particular condition should measure and report. This protocol outlines the steps for developing a core outcome set for PAS disorder (COPAS).

Methods and analysis This protocol outlines steps for the creation of COPAS. The first step, a systematic review, will identify all reported outcomes in the scientific literature. The second step will utilize qualitative one-on-one interviews to identify additional outcomes identified as important by patients and healthcare professionals that are not reported in the published literature. Outcomes from the first two steps will be combined to form an outcome inventory. This outcome inventory will inform the third step which is a Delphi survey that encourages agreement between patients and healthcare professionals on which outcomes are most important for inclusion in the core outcome set. The fourth step, a consensus group meeting of representative participants, will finalize outcomes for inclusion in the PAS disorder core outcome set.

Ethics and dissemination This study has obtained Research Ethics Board approval from Sunnybrook Health Sciences Centre (#2338, #1488). We will aim to publish the study findings in an international peer-reviewed OBGYN journal.

Registration details COMET Core Outcome Set Registration: <https://www.comet-initiative.org/Studies/Details/1127>.

Article Summary

Strengths and limitations of this study

- This study adheres to published guidelines on core outcome set development with adaptations to accommodate challenges arising from the COVID-19 pandemic.
- Through this study we ensure representation of pregnant persons that have experienced placenta accreta spectrum (PAS) disorder as well as a diverse group of healthcare professionals involved directly or indirectly in their care.
- The project has the support and participation of members of international bodies involved in PAS disorder and core outcome set development.
- The study will identify those outcomes that should be included as part of the core outcome set but will not address how these outcomes should be measured; this will be done as part of a separate study.

INTRODUCTION

Placenta accreta spectrum (PAS) disorder describes a continuum of conditions whereby the human placenta is pathologically anchored to the myometrium (placenta accreta), including its invasion of the myometrium (placenta increta), or its penetration invasion through to or beyond the uterine serosa (placenta percreta)¹. The inherent inability of the placenta, in whole or in part, to separate from the uterine wall following childbirth, may result in life-threatening hemorrhage, resulting in severe morbidity or even maternal death. Complications result either directly as a result of massive hemorrhage, or from surgical interventions to arrest blood loss, and include admission to an intensive care unit (ICU), prolonged hospital post-operative stay, increased risks of infection and thrombosis, and a substantially higher risk of maternal death compared with the general obstetric population²⁻⁶, with some research reporting maternal death rates in up to 7% of instances⁷.

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3 Estimates of the incidence of PAS disorder has risen dramatically in recent decades, from 1 in
4 4,027 pregnancies in the 1970s⁸ to 1 in 533 pregnancies in the 2000s⁹. This increase appears to
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6 parallel the increase in risk factors, primarily rising global rates of Caesarean births,^{6,10-12}
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8 placenta previa,^{6,9-12} advanced maternal age,¹³ all types of prior uterine surgeries,^{13,14} and
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10 conception via in-vitro fertilization (IVF)¹⁵.
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17 Though an increasing number of research studies on PAS disorder are now reporting larger
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19 numbers of both short- and long-term maternal and neonatal outcomes, there is little consistency
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21 in how these outcomes are defined or reported. For example, five recently-published papers on
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23 PAS disorder reported over 40 distinct maternal and neonatal outcomes, yet few outcomes were
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25 reported in more than one study and the majority of outcomes were reported in a single study¹⁶⁻
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27 ²⁰. Further, the reported outcomes were either defined differently from one study to another, or
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29 not defined at all. The lack of standardization in outcome selection, definitions, and reporting in
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31 research, and resulting publications, renders it difficult to compare results across studies,
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33 replicate research, or utilize findings to develop clinical practice guideline recommendations
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35 with strong recommendations. An international Delphi survey of PAS disorder experts (Susan E.
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37 O'Rinn et al., 2015) found that experts did not agree as a group with 70% of the published
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39 clinical guideline recommendations at that time for PAS management. Such divergent practice
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41 opinions and recommendations contribute to worldwide variations in clinical practice. In
42
43 addition, the outcomes reported in the literature that inform clinical guideline recommendations
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45 have thus far rarely included any preferences and priorities provided by affected patients and
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47 their families. Inclusion of preferences of pregnant individuals and families may be vital to
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3 guiding effective clinical care²¹ and this approach has been shown to increase patient satisfaction
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5 and improve overall outcomes²².
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10 In recent years, core outcome sets (COS) have been proposed as a way of standardizing outcome
11 reporting for any health condition. This approach formally incorporates the perspectives of
12 multiple stakeholders, including patients and healthcare providers involved in their care. A COS
13 is a consensus-derived, standardised set of outcomes that all studies on a particular health
14 condition should measure and report²³ and, when used in all research²³⁻²⁷, has the potential to
15 result in: a) higher-quality trials; b) results that are easier to compare, contrast, and combine for
16 meta-analyses; c) reduced heterogeneity between trials; d) research that is more likely to report
17 on relevant outcomes; e) reduced risk of outcome reporting bias; and f) all trials contributing
18 usable information²⁶. While there is no agreed upon gold standard method for the development
19 of Core Outcome Sets ²⁷, a handbook published by the Core Outcome Measures in Effectiveness
20 Trials (COMET) initiative provides the most comprehensive guidance for development of core
21 outcome sets²⁶.
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40 This protocol outlines the development of a core outcome set for placenta accreta spectrum
41 disorder (COPAS).
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47 **METHODS**

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49 The development of COPAS involves four distinct, but related, steps: systematic literature
50 review, interviews with relevant stakeholders, Delphi survey, and consensus meeting (see Figure
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54 1). COPAS has been registered on the COMET website (<https://www.comet->

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3 [initialiaive.org/Studies/Details/1127](https://www.bmj.com/initialiaive.org/Studies/Details/1127)) and its development will be guided by a steering committee
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6 comprised of this protocol's authors.
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10 **Step I: Systematic literature review**

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12 The primary goal of the first step is to identify existing knowledge and generate a preliminary list
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14 of reported outcomes considered important by researchers. All reported outcomes and their
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16 definitions in studies on PAS disorder will be identified through a systematic review of the
17
18 literature. The systematic review will be conducted and reported in accordance with the Preferred
19
20 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²⁸ and the
21
22 protocol has been registered on PROSPERO, the internal prospective registry of systematic
23
24 reviews (CRD42020173426). The primary and secondary research questions are “What maternal
25
26 and fetal/neonatal outcomes have been reported in studies on PAS disorder?” and “How have
27
28 these reported outcomes been defined and measured?”
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35 The systematic literature review search strategy will be developed with input from a medical
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37 information specialist who has prior experience with COS development. A mix of MeSH,
38
39 Emtree, and keyword terms related to PAS disorder will be used to identify articles from several
40
41 bibliographic databases. All original research articles that report maternal and fetal/neonatal
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43 outcomes for pregnant persons with suspected or diagnosed PAS disorder will be included.
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49 All reported outcomes and their definitions or measurement instruments will be extracted
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51 verbatim from the source manuscript²⁹ to ensure transparency in the core outcome set
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53 development²⁶. Identified outcomes will be grouped under broader domains as per Dodd et al.'s
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3 taxonomy for outcomes in medical research³⁰. Study characteristics and data will be extracted
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5 and verified for accuracy and completeness. Given that the purpose of this systematic review is
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7 to determine what outcomes have been reported in the literature, regardless of the quality of the
8
9 study, no risk of bias (quality) assessment will be performed. This is consistent with other
10
11 systematic reviews conducted for the purposes of developing core outcome sets³¹.
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15 16 17 **Step II: Interviews with pregnant individuals and relevant stakeholders**

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19 Since outcomes reported in the literature may only represent a fraction of the outcomes
20
21 considered important to measure in clinical trials for pregnancy-related conditions^{32,33}, the goal
22
23 of the second step is to conduct interviews and independently identify outcomes considered
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25 important by those that have experienced PAS disorder (patients) and healthcare professionals
26
27 (e.g., maternal fetal medicine specialists, obstetricians, nurses, and midwives) who provide care
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29 for these individuals.
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35 We will interview participants who have either experienced PAS disorder themselves or those
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37 who have clinical experience with PAS disorder, in order to identify outcomes important to both
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39 groups. A purposive sampling³⁴ approach will be used to recruit a) persons who are experiencing
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41 or have experienced a pregnancy complicated by PAS disorder; and b) diverse healthcare
42
43 professionals involved in the care of individuals with PAS disorder. This approach to sampling
44
45 aims to elicit a range of perspectives and, given the heterogeneity of potential participants (for
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47 example, currently pregnant vs postpartum or professional type), it is expected that 15-20
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49 participants from each stakeholder group may be required.³⁵
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Data collection and analysis

We will conduct interactive, semi-structured interviews with participants to identify outcomes important to them. Separate interview guides will be developed for persons with lived experiences of PAS disorder and for those providing care to persons with PAS disorder. Interviews will be audio recorded, transcribed, and the (de-identified) transcripts analyzed qualitatively. Interviews will be conducted until thematic saturation is reached³⁶. Data collection and analysis will be an iterative process, with each informing the other³⁶. Data will be analyzed utilizing the thematic analysis approach outlined by Braun & Clark³⁷. This inductive process includes multiple readings of transcripts, and coding the textual data to identify emerging themes and patterns³⁷. Appropriate techniques for ensuring analytic rigor will be employed, including thick description, reflexivity, and comparison within and across groups^{37,38}.

Step III: Delphi survey

The primary goal of the third step is to condense the long list of outcomes generated in Steps I and II through employing Delphi survey methodology. The Delphi approach is an iterative and sequential process used to achieve consensus^{39,40} from relevant stakeholders on which outcomes are most important for inclusion in the core outcome set for PAS disorder.

Survey development

Prior to the Delphi survey, an outcome inventory, a comprehensive list of outcomes identified in the systematic literature review and the qualitative interviews, will be developed. The outcome inventory will be circulated to the steering committee to review for comprehension, assess the suitability of the domain groupings and ensure that each included statement represents an

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3 ‘outcome’, which for purposes of clinical trials and studies of modifiable exposures, is defined as
4 a measurement or observation used to capture and assess the effect of treatment (such as risk/
5 side-effect or benefit/ effectiveness) [COMET handbook], and which therefore, cannot exist
6 before the intervention or exposure. This will eliminate a large number of patient-reported
7 experience measures (PREMs), which will be presented separately in a thematic analysis, but not
8 used in further steps of COPAS development.
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19 In the context of COS, the Delphi technique is used to achieve convergence of opinion from
20 experts on the importance of different outcomes in sequential rounds. The Delphi survey will be
21 developed and distributed using DelphiManager⁴¹, an online survey tool. This will ensure
22 participant anonymity, feasibility, reproducibility, and minimize the effects of dominant
23 individuals while being cost-effective and facilitating international participation. The survey will
24 consist of all outcomes identified in the above inventory. Maternal outcomes will be presented
25 under the most relevant domains as described in the taxonomy of outcomes for medical
26 research³⁰, and fetal/neonatal outcomes will be presented under a separate domain. The survey
27 will be piloted to identify and resolve issues related to survey structure^{26,42}, survey length²⁶, lay
28 language summary, and survey logic glitches, prior to the start of the Delphi survey.
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45 *Survey panels*

46 The Delphi survey will consist of two panels, one comprised of persons that experienced PAS
47 disorder during a current or prior pregnancy, and the second of healthcare professionals that have
48 experience caring for those with PAS disorder in various capacities. Experts from both
49 participant groups will be recruited from the following sources: a) participants from the second
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3 step; b) PAS disorder patients from two University of Toronto-affiliated hospitals in Canada; c)
4 potential participants identified from patient and professional groups as described in Step II; d)
5 authors identified from studies included in Step I; e) authors and experts involved in generating
6 PAS disorder clinical guidelines; and f) recommendations from the project's steering committee,
7 in case of a lack of diversity among the recruited participants. This multi-faceted recruitment
8 approach should ensure a heterogeneous sample from both stakeholder groups. Individuals who
9 express interest in participating will be directed to the survey via a link. The survey's landing
10 page will serve as a traditional consent form and will describe the survey, risks and benefits, and
11 expectations. Participants will sign the consent form electronically, identify which stakeholder
12 group they belong to and then complete a brief demographic questionnaire.
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29 *Survey group size*

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31 While there should be adequate representation from both key stakeholder groups with qualified
32 experts who have a deep understanding of PAS disorder⁴², there is no standard recommendation
33 for a Delphi survey group size with group size expected to be determined based on several
34 factors, including the scope of the core outcome set, existing knowledge, and survey feasibility²⁶.
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36 Based on prior experience with COS development, we will aim to recruit approximately 20
37 persons with experience of PAS disorder in either a current or a prior pregnancy, with a focus on
38 diverse representation as per other obstetrical core outcome sets³¹. In addition, approximately 40
39 healthcare professionals that provide care on an ongoing basis for pregnant persons with PAS
40 disorder, representing various disciplines and geographical regions will be recruited.
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54 *Survey rounds*

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3 The Delphi survey will consist of two rounds^{31,43-45}. Each round will remain open for a minimum
4 of three weeks, with the option to extend if needed to improve low response rates and minimize
5 the potential for attrition bias. Following the closure of a Delphi round, an additional two weeks
6 will be required to analyze the data and prepare for the following round. Participants will score
7 each outcome according to their level of importance on a 9-point Likert scale, wherein a score of
8 1-3 indicates an outcome is of ‘limited importance’; 4-6 an outcome is ‘important but not
9 critical’; and 7-9 the outcome is ‘critical.’ The questionnaire will also include an ‘unable to
10 score’ category for respondents who feel they lack the expertise or experience to evaluate a
11 specific outcome. During the first Delphi round, participants will be asked to identify any
12 outcomes they feel are missing thus ensuring an exhaustive list of outcomes is included in the
13 Delphi survey. These outcomes will be added to the second round to be scored by all
14 participants, if they fulfil the criteria for outcomes in clinical trials as described above.
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33 *Survey feedback between rounds*

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35 Survey feedback between the two rounds will assess the extent of agreement (consensus
36 measurement) and increase the likelihood of convergence towards consensus of “core”
37 outcomes. Feedback for each outcome will be presented graphically and will include the mean
38 score for all participants, the mean score for each stakeholder group⁴⁶, as well as their own score
39 from the previous round. In the second survey round, participants will be encouraged to consider
40 these graphs and their original score before determining whether they would like to change or
41 maintain their score. This feedback provides a mechanism for reconciling different stakeholder
42 opinions and is critical in achieving consensus. Since this Delphi process involves two separate
43 stakeholder groups, feedback will be presented separately for each stakeholder group as well as
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3 together for both groups, as recommended⁴⁷. This approach allows for the preferences of both
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5 groups to be considered separately, as well as together²⁶. All outcomes from the first round,
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7 including newly suggested outcomes from participants, will be carried forward to the second
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9 round, regardless of how the outcome was scored in the first round⁴⁸⁻⁵⁰. All outcomes that have
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11 been scored in both rounds and that achieve consensus (see below), will be included in the next
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13 Step. Those that were introduced in the second round and therefore were only scored once, will
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15 be included in the next step, unless >70% of participants in both groups score the outcome <7.
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21 *Survey response rates and attrition*

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23 A survey response rate of 80% from each stakeholder group is deemed acceptable based on
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25 published recommendations²⁶. However, attrition rates for previous Delphi surveys vary from
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27 0%⁴⁸ to 17%⁵¹ and 21% to 48% for previous core outcome sets within Obstetrics & Gynaecology
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29 and Newborn Medicine respectively³⁹. In order to maximize the response rates and minimize
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31 attrition, we will implement strategies such as bi-weekly personalized email reminders and
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33 extend the survey window when needed, to make it convenient for participants. In the case of a
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35 continued inadequate response, the steering committee will evaluate the nature of attrition
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37 (selective groups vs. general attrition affecting all groups), cause and likelihood of improving
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39 uptake by extending the time period and the general consensus with regard to outcomes, when
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41 deciding whether to close data collection for the project.
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49 *Defining and assessing the degree of consensus*

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51 This survey will follow the consensus classification used by Williamson et al. (2012)⁴²:

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53 “consensus in” for inclusion in COPAS will be defined as >70% scoring 7-9 and <15% scoring
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3 1-3; “consensus out” for exclusion will be defined as >70% scoring 1-3 and <15% scoring 7-9;
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5 and “no consensus” will be defined as those that do not meet either threshold for critical or
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7 limited importance outcomes. Outcomes that meet the inclusion for “consensus in”, by all
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9 experts or by one group of experts, as well as “no consensus” outcomes will be considered in the
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11 next step of COPAS development.
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17 **Step IV: Consensus Group Meeting**

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19 At the end of the second round of the Delphi Survey, participants will be informed of the virtual
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21 consensus group meeting, and will be asked to indicate if they are interested in participating. The
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23 primary goal of the fourth step is to bring together key stakeholders to determine which
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25 outcomes should comprise COPAS.
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31 A minimum of five Delphi participants from each stakeholder group (pregnant persons with
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33 experience of PAS disorder and PAS disorder healthcare professionals) who have expressed
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35 interest as well as those that have not participated in prior rounds, will be invited to participate.
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37 Participants will be randomly selected while balancing the desire for equal representation
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39 amongst participants. Although some research suggests that face-to-face meetings are critical as
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41 they foster interactive debate between participants on key issues^{52,53} and allow participants to
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43 clarify their position and justify their viewpoint⁵⁴, given the uncertainties of the COVID-19
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45 pandemic and the logistics associated with bringing together international stakeholders, this
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47 consensus meeting will be virtual. In order to facilitate global participation and in recognition of
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49 differing time-zones and participant availabilities, the first stage of the consensus meeting may
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51 consist of several smaller meetings with representation from both stakeholder groups where
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possible while the second stage of the consensus meeting will include all available participants as well as the steering committee.

First stage

Each meeting will start with a presentation of the results from each step of the COPAS development: the systematic review; the qualitative interviews; and, the Delphi survey. The moderator will then facilitate a guided discussion starting with the “no consensus” outcomes from the Delphi survey, followed by an electronic vote for each of these items that will include three options: “IN”, “OUT” or “unable to score”. If all participants score an outcome as “IN” or “unable to score”, the outcome will be included in the next stage and if all participants score an outcome as “OUT” or “unable to score”, the outcome will be removed from the next stage. All non-consensus outcomes will be debated by the group until a consensus is reached. If consensus cannot be reached for an outcome, the outcome will be included in the next stage.

Second stage

Given the virtual format and the possibility of multiple meetings in the first stage, the second stage of the consensus meeting will consist of the steering committee along with available representatives from each stakeholder group and the final vote for inclusion of outcomes in COPAS will rest with these individuals. This meeting will start with a synthesis of the results from the meetings in the first stage. Obstetrical and gynecological core outcome sets have included a wide range of outcomes, from 11-48³⁹, however this core outcome set will endeavor to keep the number low in an effort to increase uptake by researchers and maintain the focus on the bare minimum number of critical outcomes for inclusion in future research.

ETHICS AND DISSEMINATION

Research Ethics Board (REB) approval for the steps involved in this study have been granted: step two has received REB approval from Sunnybrook Health Sciences Centre (#2338, #1488), The University of Toronto (#38312, #39503), and Sinai Health System (#20-0292-E); and, steps three and four have received REB approval from Sunnybrook Health Sciences Centre (#5087). We will aim to present these findings at appropriate international OBGYN conferences and publish the findings of the various steps in the OBGYN literature. COPAS will be archived in the Core Outcome Measures in Effectiveness Trials (COMET) database and we will aim to publish it in the OBGYN literature.

PATIENT AND PUBLIC INVOLVEMENT

PAS disorder is a rare and specific pregnancy-related condition that most members of the public do not have the experience of or expertise on. Since prior experience and/or expertise is vital to the development of COPAS, public involvement will not be solicited. The involvement of pregnant individuals (patient involvement) and healthcare professionals involved in their care, is central to the development of COPAS. Since the methodology for COS development has been established²⁶, and the systematic review (Step I) needs to be conducted by experts, pregnant persons will be involved in this study from Step II onwards. Herein, pregnant persons, independently or as part of online groups, will assist with participant recruitment, study participation, and interpretation of study findings.

DISCUSSION

This protocol outlines the core outcome set development comprising the minimum number of outcomes to be included in future studies involving individuals with PAS disorder. The methods described reflect the steering committee's experience with developing COS for pregnancy-related conditions, as part of the Outcome Reporting in Obstetric Studies (OROS) initiative⁵⁵. In addition, it considers the need for modifications to protocols previously described, such as the need for including smaller numbers, the inclusion of virtual meetings and smaller group sessions, on account of challenges posed by the COVID-19 pandemic. When published, researchers will have an evidence-based rationale to include outcomes that have been prioritized by multiple stakeholders, including persons who have experienced the condition. This COS will contribute to the standardization of outcome collection and measurement for PAS disorder and will add to the growing literature and methodological approaches to the development of COS.

AUTHORS' CONTRIBUTIONS

SOR and RDS conceived the idea. SOR drafted the protocol manuscript based on relevant publications. RDS was the content expert for the systematic literature review, the Delphi survey, and the consensus meeting and JAP was the content expert for the qualitative methodology. JK and JB are clinical content experts. All authors have read and edited the manuscript at least once and have approved the final version.

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COMPETING INTERESTS

None declared.

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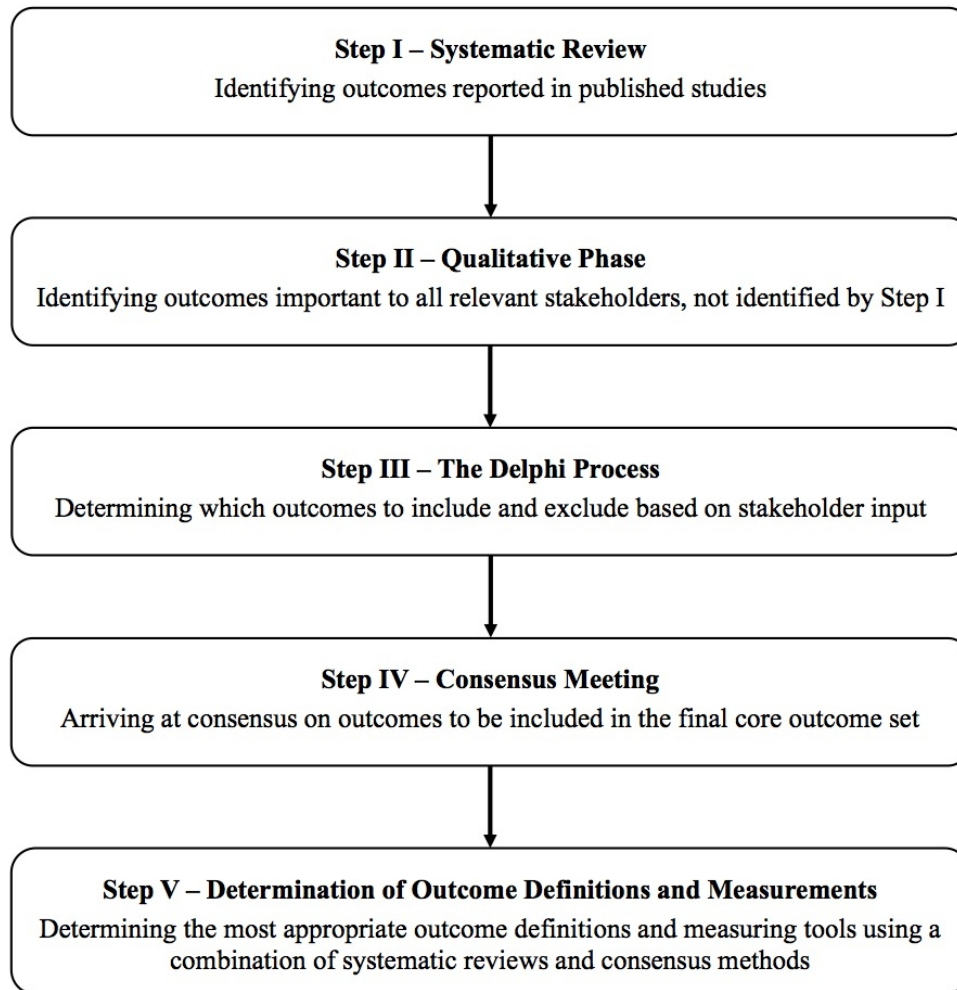
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18 Figure Legend

19
20 Figure 1. Framework for development of a Core Outcome Set³¹

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Framework for development of a Core Outcome Set

156x160mm (150 x 150 DPI)

 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

Scope 3a Describe the health condition(s) and population(s) that will be covered by the COS

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

BMJ Open

Engaging pregnant individuals and healthcare professionals in an international mixed methods study to develop a core outcome set for studies on Placenta Accreta Spectrum Disorder (COPAS): a study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-060699.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Apr-2022
Complete List of Authors:	O'Rinn, Susan E.; University of Toronto, Outcomes & Evaluation, Institute of Health, Policy, Management and Evaluation; University of Toronto, DAN Women & Babies Program, Evaluative Clinical Sciences, Sunnybrook Research Institute Barrett, Jon F.R.; McMaster University, Department of Obstetrics and Gynecology Parsons, Janet A.; University of Toronto, Department of Physical Therapy; Unity Health Toronto Kingdom, John C.; University of Toronto, Department of Obstetrics & Gynaecology D'Souza, Rohan; McMaster University, Obstetrics & Gynaecology and Health Research Methods, Evidence and Impact; University of Toronto
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Haematology (incl blood transfusion), Patient-centred medicine, Qualitative research
Keywords:	Maternal medicine < OBSTETRICS, QUALITATIVE RESEARCH, Blood bank & transfusion medicine < HAEMATOLOGY

SCHOLARONE™
Manuscripts

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5 2 **methods study to develop a core outcome set for studies on Placenta Accreta Spectrum**
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7 3 **Disorder (COPAS): a study protocol**
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3 **49 Abstract**

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5 **50 Introduction:** Placenta Accreta Spectrum (PAS) disorder is a life-threatening condition that may
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8 **51** result in serious maternal complications, including mortality. The placenta which is
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10 **52** pathologically-adherent to the uterine wall, places individuals at high risk of major haemorrhage
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12 **53** during the third stage of labour. Current research reports on PAS disorder outcomes have highly
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14 **54** variable levels of information, which is therefore difficult for investigators to aggregate to inform
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16 **55** practice. There is an urgent need to harmonize data collection in prospective studies to identify
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18 **56** and implement best practices for management. One approach to standardize outcomes across any
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20 **57** health area via the use of core outcome sets, which are consensus-derived standardised sets of
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22 **58** outcomes that all studies for a particular condition should measure and report. This protocol
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24 **59** outlines the steps for developing a core outcome set for PAS disorder (COPAS).
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31 **61 Methods and analysis** This protocol outlines steps for the creation of COPAS. The first step, a
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33 **62** systematic review, will identify all reported outcomes in the scientific literature. The second step
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35 **63** will utilize qualitative one-on-one interviews to identify additional outcomes identified as
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37 **64** important by patients and healthcare professionals that are not reported in the published
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39 **65** literature. Outcomes from the first two steps will be combined to form an outcome inventory.
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41 **66** This outcome inventory will inform the third step which is a Delphi survey that encourages
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43 **67** agreement between patients and healthcare professionals on which outcomes are most important
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45 **68** for inclusion in the core outcome set. The fourth step, a consensus group meeting of
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47 **69** representative participants, will finalize outcomes for inclusion in the PAS disorder core
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49 **70** outcome set.
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3 72 **Ethics and dissemination** This study has obtained Research Ethics Board approval from
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5 73 Sunnybrook Health Sciences Centre (#2338, #1488). We will aim to publish the study findings
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7 74 in an international peer-reviewed OBGYN journal.
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12 76 **Registration details** COMET Core Outcome Set Registration: [https://www.comet-
14 initiative.org/Studies/Details/1127](https://www.comet-
13 initiative.org/Studies/Details/1127).
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24 81 **Article Summary**

25 26 82 **Strengths and limitations of this study**

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28 83 • This study adheres to published guidelines on core outcome set development with
29 adaptations to accommodate challenges arising from the COVID-19 pandemic.
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31 84 • Through this study we ensure representation of pregnant persons that have experienced
32 placenta accreta spectrum (PAS) disorder as well as a diverse group of healthcare
33 85 professionals involved directly or indirectly in their care.
34
35 86 • The project has the support and participation of members of international bodies involved in
36 PAS disorder and core outcome set development.
37 87
38 88 • The study will identify those outcomes that should be included as part of the core outcome
39 set but will not address how these outcomes should be measured; this will be done as part of
40 a separate study.
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INTRODUCTION

Placenta accreta spectrum (PAS) disorder describes a continuum of conditions whereby the human placenta is pathologically anchored to the myometrium (placenta accreta), including its invasion of the myometrium (placenta increta), or its penetration invasion through to or beyond the uterine serosa (placenta percreta)¹. The inherent inability of the placenta, in whole or in part, to separate from the uterine wall following childbirth, may result in life-threatening hemorrhage, resulting in severe morbidity or even maternal death. Complications result either directly as a result of massive hemorrhage, or from surgical interventions to arrest blood loss, and include admission to an intensive care unit (ICU), prolonged hospital post-operative stay, increased risks of infection and thrombosis, and a substantially higher risk of maternal death compared with the general obstetric population²⁻⁶, with some research reporting maternal death rates in up to 7% of instances⁷.

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3 117 Estimates of the incidence of PAS disorder has risen dramatically in recent decades, from 1 in
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5 118 4,027 pregnancies in the 1970s⁸ to 1 in 533 pregnancies in the 2000s⁹. This increase appears to
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8 119 parallel the increase in risk factors, primarily rising global rates of Caesarean births,^{6,10-12}
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10 120 placenta previa,^{6,9-12} advanced maternal age,¹³ all types of prior uterine surgeries,^{13,14} and
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12 121 conception via in-vitro fertilization (IVF)¹⁵.
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17 123 Though an increasing number of research studies on PAS disorder are now reporting larger
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19 124 numbers of both short- and long-term maternal and neonatal outcomes, there is little consistency
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21 125 in how these outcomes are defined or reported. For example, five recently-published papers on
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23 126 PAS disorder reported over 40 distinct maternal and neonatal outcomes, yet few outcomes were
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25 127 reported in more than one study and the majority of outcomes were reported in a single study¹⁶⁻
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27 128 ²⁰. Further, the reported outcomes were either defined differently from one study to another, or
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29 129 not defined at all. The lack of standardization in outcome selection, definitions, and reporting in
30
31 130 research, and resulting publications, renders it difficult to compare results across studies,
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33 131 replicate research, or utilize findings to develop clinical practice guideline recommendations
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35 132 with strong recommendations. An international Delphi survey of PAS disorder experts (Susan E.
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37 133 O'Rinn et al., 2015) found that experts did not agree as a group with 70% of the published
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39 134 clinical guideline recommendations at that time for PAS management. Such divergent practice
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41 135 opinions and recommendations contribute to worldwide variations in clinical practice. In
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43 136 addition, the outcomes reported in the literature that inform clinical guideline recommendations
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45 137 have thus far rarely included any preferences and priorities provided by affected patients and
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47 138 their families. Inclusion of preferences of pregnant individuals and families may be vital to
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139 guiding effective clinical care²¹ and this approach has been shown to increase patient satisfaction
140 and improve overall outcomes²².

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142 In recent years, core outcome sets (COS) have been proposed as a way of standardizing outcome
143 reporting for any health condition. This approach formally incorporates the perspectives of
144 multiple stakeholders, including patients and healthcare providers involved in their care. A COS
145 is a consensus-derived, standardised set of outcomes that all studies on a particular health
146 condition should measure and report²³ and, when used in all research²³⁻²⁷, has the potential to
147 result in: a) higher-quality trials; b) results that are easier to compare, contrast, and combine for
148 meta-analyses; c) reduced heterogeneity between trials; d) research that is more likely to report
149 on relevant outcomes; e) reduced risk of outcome reporting bias; and f) all trials contributing
150 usable information²⁶. While there is no agreed upon gold standard method for the development
151 of Core Outcome Sets ²⁷, a handbook published by the Core Outcome Measures in Effectiveness
152 Trials (COMET) initiative provides the most comprehensive guidance for development of core
153 outcome sets²⁶.

154
155 This protocol outlines the development of a core outcome set for placenta accreta spectrum
156 disorder (COPAS).

158 **METHODS**

159 The development of COPAS involves four distinct, but related, steps: systematic literature
160 review, interviews with relevant stakeholders, Delphi survey, and consensus meeting (see Figure
161 1). COPAS has been registered on the COMET website (<https://www.comet->

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2
3 162 [initiative.org/Studies/Details/1127](https://www.initiative.org/Studies/Details/1127)) and its development will be guided by a steering committee
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5 163 comprised of this protocol's authors.
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10 165 **Step I: Systematic literature review**

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12 166 The primary goal of the first step is to identify existing knowledge and generate a preliminary list
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14 167 of reported outcomes considered important by researchers. All reported outcomes and their
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16 168 definitions in studies on PAS disorder will be identified through a systematic review of the
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18 169 literature. The systematic review will be conducted and reported in accordance with the Preferred
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20 170 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²⁸ and the
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22 171 protocol has been registered on PROSPERO, the internal prospective registry of systematic
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24 172 reviews (CRD42020173426). The primary and secondary research questions are “What maternal
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26 173 and fetal/neonatal outcomes have been reported in studies on PAS disorder?” and “How have
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28 174 these reported outcomes been defined and measured?”
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35 176 The systematic literature review search strategy will be developed with input from a medical
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37 177 information specialist who has prior experience with COS development. A mix of MeSH,
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39 178 Emtree, and keyword terms related to PAS disorder will be used to identify articles from several
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41 179 bibliographic databases. All original research articles that report maternal and fetal/neonatal
42
43 180 outcomes for pregnant persons with suspected or diagnosed PAS disorder will be included.
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49 182 All reported outcomes and their definitions or measurement instruments will be extracted
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51 183 verbatim from the source manuscript²⁹ to ensure transparency in the core outcome set
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53 184 development²⁶. Identified outcomes will be grouped under broader domains as per Dodd et al.'s
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3 185 taxonomy for outcomes in medical research³⁰. Study characteristics and data will be extracted
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5 186 and verified for accuracy and completeness. Given that the purpose of this systematic review is
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7 187 to determine what outcomes have been reported in the literature, regardless of the quality of the
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9 188 study, no risk of bias (quality) assessment will be performed. This is consistent with other
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11 189 systematic reviews conducted for the purposes of developing core outcome sets³¹.
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17 191 **Step II: Interviews with pregnant individuals and relevant stakeholders**

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19 192 Since outcomes reported in the literature may only represent a fraction of the outcomes
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21 193 considered important to measure in clinical trials for pregnancy-related conditions^{32,33}, the goal
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23 194 of the second step is to conduct interviews and independently identify outcomes considered
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25 195 important by those that have experienced PAS disorder (patients) and healthcare professionals
26
27 196 (e.g., maternal fetal medicine specialists, obstetricians, nurses, and midwives) who provide care
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29 197 for these individuals.
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35 199 We will interview participants who have either experienced PAS disorder themselves or those
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37 200 who have clinical experience with PAS disorder, in order to identify outcomes important to both
38
39 201 groups. A purposive sampling³⁴ approach will be used to recruit a) persons who are experiencing
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41 202 or have experienced a pregnancy complicated by PAS disorder; and b) diverse healthcare
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43 203 professionals involved in the care of individuals with PAS disorder. This approach to sampling
44
45 204 aims to elicit a range of perspectives and, given the heterogeneity of potential participants (for
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47 205 example, currently pregnant vs postpartum or professional type), it is expected that 15-20
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49 206 participants from each stakeholder group may be required.³⁵
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3 208 *Data collection and analysis*
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5 209 We will conduct interactive, semi-structured interviews with participants to identify outcomes
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7 210 important to them. Separate interview guides will be developed for persons with lived
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9 211 experiences of PAS disorder and for those providing care to persons with PAS disorder.
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11 212 Interviews will be audio recorded, transcribed, and the (de-identified) transcripts analyzed
12
13 213 qualitatively. Interviews will be conducted until thematic saturation is reached³⁶. Data collection
14
15 214 and analysis will be an iterative process, with each informing the other³⁶. Data will be analyzed
16
17 215 utilizing the thematic analysis approach outlined by Braun & Clark³⁷. This inductive process
18
19 216 includes multiple readings of transcripts, and coding the textual data to identify emerging themes
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21 217 and patterns³⁷. Appropriate techniques for ensuring analytic rigor will employed, including thick
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23 218 description, reflexivity, and comparison within and across groups^{37,38}.
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31 220 **Step III: Delphi survey**
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33 221 The primary goal of the third step is to condense the long list of outcomes generated in Steps I
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35 222 and II through employing Delphi survey methodology. The Delphi approach is an iterative and
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37 223 sequential process used to achieve consensus^{39,40} from relevant stakeholders on which outcomes
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39 224 are most important for inclusion in the core outcome set for PAS disorder.
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44 226 *Survey development*
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47 227 Prior to the Delphi survey, an outcome inventory, a comprehensive list of outcomes identified in
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49 228 the systematic literature review and the qualitative interviews, will be developed. The outcome
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51 229 inventory will be circulated to the steering committee to review for comprehension, assess the
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53 230 suitability of the domain groupings and ensure that each included statement represents an
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3 231 'outcome', which for purposes of clinical trials and studies of modifiable exposures, is defined as
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5 232 a measurement or observation used to capture and assess the effect of treatment (such as risk/
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7 233 side-effect or benefit/ effectiveness) [COMET handbook], and which therefore, cannot exist
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10 234 before the intervention or exposure. This will eliminate a large number of patient-reported
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12 235 experience measures (PREMs), which will be presented separately in a thematic analysis, but not
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14 236 used in further steps of COPAS development.
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19 238 In the context of COS, the Delphi technique is used to achieve convergence of opinion from
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21 239 experts on the importance of different outcomes in sequential rounds. The Delphi survey will be
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23 240 developed and distributed using DelphiManager⁴¹, an online survey tool. This will ensure
24
25 241 participant anonymity, feasibility, reproducibility, and minimize the effects of dominant
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27 242 individuals while being cost-effective and facilitating international participation. The survey will
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29 243 consist of all outcomes identified in the above inventory. Maternal outcomes will be presented
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31 244 under the most relevant domains as described in the taxonomy of outcomes for medical
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33 245 research³⁰, and fetal/neonatal outcomes will be presented under a separate domain. The survey
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35 246 will be piloted to identify and resolve issues related to survey structure^{26,42}, survey length²⁶, lay
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37 247 language summary, and survey logic glitches, prior to the start of the Delphi survey.
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43 44 249 *Survey panels*

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47 250 The Delphi survey will consist of two panels, one comprised of persons that experienced PAS
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49 251 disorder during a current or prior pregnancy, and the second of healthcare professionals that have
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51 252 experience caring for those with PAS disorder in various capacities. Experts from both
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53 253 participant groups will be recruited from the following sources: a) participants from the second
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3 254 step; b) PAS disorder patients from two University of Toronto-affiliated hospitals in Canada; c)
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5 255 potential participants identified from patient and professional groups as described in Step II; d)
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7 256 authors identified from studies included in Step I; e) authors and experts involved in generating
8
9 257 PAS disorder clinical guidelines; and f) recommendations from the project's steering committee,
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11 258 in case of a lack of diversity among the recruited participants. This multi-faceted recruitment
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13 259 approach should ensure a heterogeneous sample from both stakeholder groups. Individuals who
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15 260 express interest in participating will be directed to the survey via a link. The survey's landing
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17 261 page will serve as a traditional consent form and will describe the survey, risks and benefits, and
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19 262 expectations. Participants will sign the consent form electronically, identify which stakeholder
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21 263 group they belong to and then complete a brief demographic questionnaire.
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29 265 *Survey group size*

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31 266 While there should be adequate representation from both key stakeholder groups with qualified
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33 267 experts who have a deep understanding of PAS disorder⁴², there is no standard recommendation
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35 268 for a Delphi survey group size with group size expected to be determined based on several
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37 269 factors, including the scope of the core outcome set, existing knowledge, and survey feasibility²⁶.
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39 270 Based on prior experience with COS development, we will aim to recruit approximately 20
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41 271 persons with experience of PAS disorder in either a current or a prior pregnancy, with a focus on
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43 272 diverse representation as per other obstetrical core outcome sets³¹. In addition, approximately 40
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45 273 healthcare professionals that provide care on an ongoing basis for pregnant persons with PAS
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47 274 disorder, representing various disciplines and geographical regions will be recruited.
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54 276 *Survey rounds*

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3 277 The Delphi survey will consist of two rounds^{31,43-45}. Each round will remain open for a minimum
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5 278 of three weeks, with the option to extend if needed to improve low response rates and minimize
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7 279 the potential for attrition bias. Following the closure of a Delphi round, an additional two weeks
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10 280 will be required to analyze the data and prepare for the following round. Participants will score
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12 281 each outcome according to their level of importance on a 9-point Likert scale, wherein a score of
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14 282 1-3 indicates an outcome is of ‘limited importance’; 4-6 an outcome is ‘important but not
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16 283 critical’; and 7-9 the outcome is ‘critical.’ The questionnaire will also include an ‘unable to
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18 284 score’ category for respondents who feel they lack the expertise or experience to evaluate a
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20 285 specific outcome. During the first Delphi round, participants will be asked to identify any
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22 286 outcomes they feel are missing thus ensuring an exhaustive list of outcomes is included in the
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24 287 Delphi survey. These outcomes will be added to the second round to be scored by all
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26 288 participants, if they fulfil the criteria for outcomes in clinical trials as described above.
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32 33 290 *Survey feedback between rounds*

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35 291 Survey feedback between the two rounds will assess the extent of agreement (consensus
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37 292 measurement) and increase the likelihood of convergence towards consensus of “core”
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39 293 outcomes. Feedback for each outcome will be presented graphically and will include the mean
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41 294 score for all participants, the mean score for each stakeholder group⁴⁶, as well as their own score
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43 295 from the previous round. In the second survey round, participants will be encouraged to consider
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45 296 these graphs and their original score before determining whether they would like to change or
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47 297 maintain their score. This feedback provides a mechanism for reconciling different stakeholder
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49 298 opinions and is critical in achieving consensus. Since this Delphi process involves two separate
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51 299 stakeholder groups, feedback will be presented separately for each stakeholder group as well as
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3 300 together for both groups, as recommended⁴⁷. This approach allows for the preferences of both
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5 301 groups to be considered separately, as well as together²⁶. All outcomes from the first round,
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7 302 including newly suggested outcomes from participants, will be carried forward to the second
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9 303 round, regardless of how the outcome was scored in the first round⁴⁸⁻⁵⁰. All outcomes that have
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11 304 been scored in both rounds and that achieve consensus (see below), will be included in the next
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13 305 Step. Those that were introduced in the second round and therefore were only scored once, will
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15 306 be included in the next step, unless >70% of participants in both groups score the outcome <7.
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20 21 308 *Survey response rates and attrition*

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23 309 A survey response rate of 80% from each stakeholder group is deemed acceptable based on
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25 310 published recommendations²⁶. However, attrition rates for previous Delphi surveys vary from
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27 311 0%⁴⁸ to 17%⁵¹ and 21% to 48% for previous core outcome sets within Obstetrics & Gynaecology
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29 312 and Newborn Medicine respectively³⁹. In order to maximize the response rates and minimize
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31 313 attrition, we will implement strategies such as bi-weekly personalized email reminders and
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33 314 extend the survey window when needed, to make it convenient for participants. In the case of a
34
35 315 continued inadequate response, the steering committee will evaluate the nature of attrition
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37 316 (selective groups vs. general attrition affecting all groups), cause and likelihood of improving
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39 317 uptake by extending the time period and the general consensus with regard to outcomes, when
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41 318 deciding whether to close data collection for the project.
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48 49 320 *Defining and assessing the degree of consensus*

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51 321 This survey will follow the consensus classification used by Williamson et al. (2012)⁴²:
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53 322 “consensus in” for inclusion in COPAS will be defined as >70% scoring 7-9 and <15% scoring
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3 323 1-3; “consensus out” for exclusion will be defined as >70% scoring 1-3 and <15% scoring 7-9;
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5 324 and “no consensus” will be defined as those that do not meet either threshold for critical or
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7 325 limited importance outcomes. Outcomes that meet the inclusion for “consensus in”, by all
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9 326 experts or by one group of experts, as well as “no consensus” outcomes will be considered in the
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11 327 next step of COPAS development.
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17 329 **Step IV: Consensus Group Meeting**

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19 330 At the end of the second round of the Delphi Survey, participants will be informed of the virtual
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21 331 consensus group meeting, and will be asked to indicate if they are interested in participating. The
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23 332 primary goal of the fourth step is to bring together key stakeholders to determine which
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25 333 outcomes should comprise COPAS.
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31 335 A minimum of five Delphi participants from each stakeholder group (pregnant persons with
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33 336 experience of PAS disorder and PAS disorder healthcare professionals) who have expressed
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35 337 interest as well as those that have not participated in prior rounds, will be invited to participate.
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37 338 Participants will be randomly selected while balancing the desire for equal representation
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39 339 amongst participants. Although some research suggests that face-to-face meetings are critical as
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41 340 they foster interactive debate between participants on key issues^{52,53} and allow participants to
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43 341 clarify their position and justify their viewpoint⁵⁴, given the uncertainties of the COVID-19
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45 342 pandemic and the logistics associated with bringing together international stakeholders, this
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47 343 consensus meeting will be virtual. In order to facilitate global participation and in recognition of
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49 344 differing time-zones and participant availabilities, the first stage of the consensus meeting may
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51 345 consist of several smaller meetings with representation from both stakeholder groups where
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346 possible while the second stage of the consensus meeting will include all available participants as
347 well as the steering committee.

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349 *First stage*

350 Each meeting will start with a presentation of the results from each step of the COPAS
351 development: the systematic review; the qualitative interviews; and, the Delphi survey. The
352 moderator will then facilitate a guided discussion starting with the “no consensus” outcomes
353 from the Delphi survey, followed by an electronic vote for each of these items that will include
354 three options: “IN”, “OUT” or “unable to score”. If all participants score an outcome as “IN” or
355 “unable to score”, the outcome will be included in the next stage and if all participants score an
356 outcome as “OUT” or “unable to score”, the outcome will be removed from the next stage. All
357 non-consensus outcomes will be debated by the group until a consensus is reached. If consensus
358 cannot be reached for an outcome, the outcome will be included in the next stage.

359

360 *Second stage*

361 Given the virtual format and the possibility of multiple meetings in the first stage, the second
362 stage of the consensus meeting will consist of the steering committee along with available
363 representatives from each stakeholder group and the final vote for inclusion of outcomes in
364 COPAS will rest with these individuals. This meeting will start with a synthesis of the results
365 from the meetings in the first stage. Obstetrical and gynecological core outcome sets have
366 included a wide range of outcomes, from 11-48³⁹, however this core outcome set will endeavor
367 to keep the number low in an effort to increase uptake by researchers and maintain the focus on
368 the bare minimum number of critical outcomes for inclusion in future research.

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8 371 **ETHICS AND DISSEMINATION**9
10 372 Research Ethics Board (REB) approval for the steps involved in this study have been granted:11
12 373 step two has received REB approval from Sunnybrook Health Sciences Centre (#2338, #1488),13
14 374 The University of Toronto (#38312, #39503), and Sinai Health System (#20-0292-E); and, steps15
16 375 three and four have received REB approval from Sunnybrook Health Sciences Centre (#5087).17
18 376 We will aim to present these findings at appropriate international OBGYN conferences and19
20 377 publish the findings of the various steps in the OBGYN literature. COPAS will be archived in21
22 378 the Core Outcome Measures in Effectiveness Trials (COMET) database and we will aim to23
24 379 publish it in the OBGYN literature.25
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31 381 **PATIENT AND PUBLIC INVOLVEMENT**32
33 382 PAS disorder is a rare and specific pregnancy-related condition that most members of the public34
35 383 do not have the experience of or expertise on. Since prior experience and/or expertise is vital to36
37 384 the development of COPAS, public involvement will not be solicited. The involvement of38
39 385 pregnant individuals (patient involvement) and healthcare professionals involved in their care, is40
41 386 central to the development of COPAS. Since the methodology for COS development has been42
43 387 established²⁶, and the systematic review (Step I) needs to be conducted by experts, pregnant44
45 388 persons will be involved in this study from Step II onwards. Herein, pregnant persons,46
47 389 independently or as part of online groups, will assist with participant recruitment, study48
49 390 participation, and interpretation of study findings.50
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392 **DISCUSSION**

393 This protocol outlines the core outcome set development comprising the minimum number of
394 outcomes to be included in future studies involving individuals with PAS disorder. The methods
395 described reflect the steering committee's experience with developing COS for pregnancy-
396 related conditions, as part of the Outcome Reporting in Obstetric Studies (OROS) initiative⁵⁵. In
397 addition, it considers the need for modifications to protocols previously described, such as the
398 need for including smaller numbers, the inclusion of virtual meetings and smaller group sessions,
399 on account of challenges posed by the COVID-19 pandemic. When published, researchers will
400 have an evidence-based rationale to include outcomes that have been prioritized by multiple
401 stakeholders, including persons who have experienced the condition. This COS will contribute to
402 the standardization of outcome collection and measurement for PAS disorder and will add to the
403 growing literature and methodological approaches to the development of COS.

405 **AUTHORS' CONTRIBUTIONS**

406 SOR and RDS conceived the idea. SOR drafted the protocol manuscript based on relevant
407 publications. RDS was the content expert for the systematic literature review, the Delphi survey,
408 and the consensus meeting and JAP was the content expert for the qualitative methodology. JK
409 and JB are clinical content experts. All authors have read and edited the manuscript at least once
410 and have approved the final version.

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2
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4
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10 417 **COMPETING INTERESTS**

11
12 418 None declared.
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18
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20
21 422 the manuscript.
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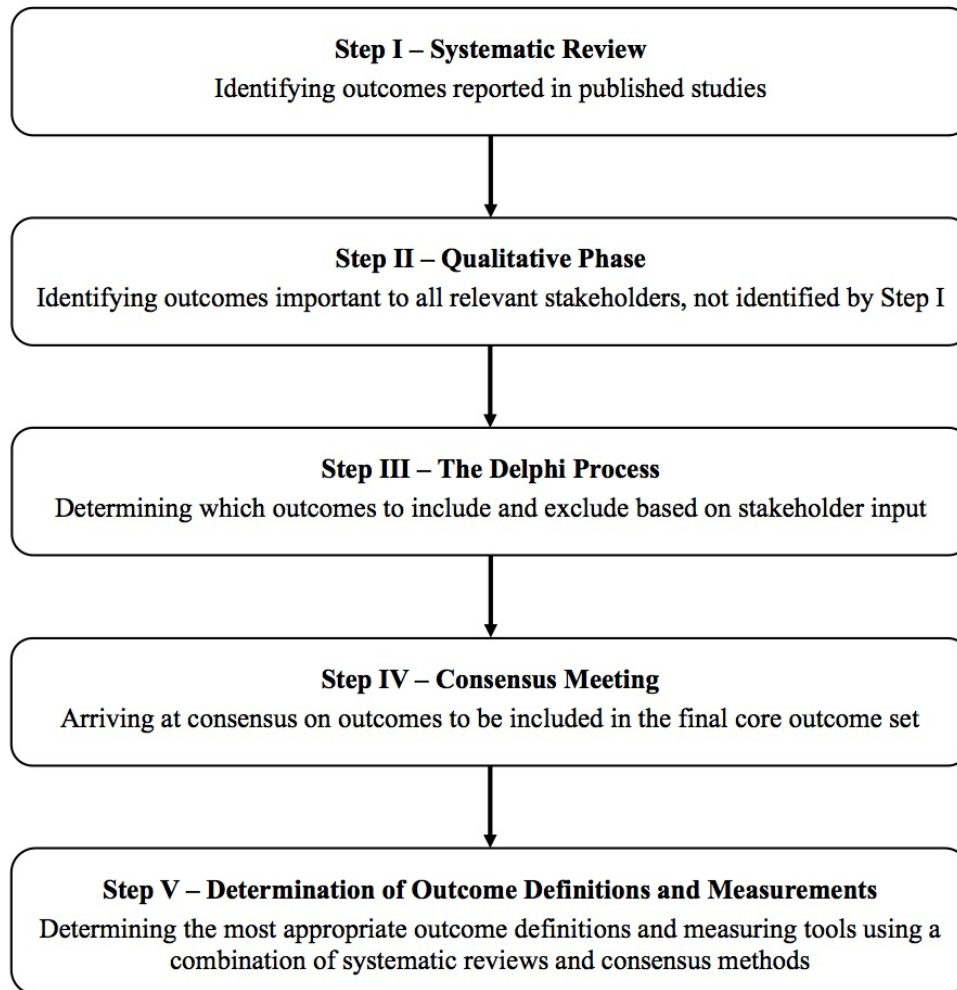
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18 555 Figure Legend
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20 557 Figure 1. Framework for development of a Core Outcome Set³¹
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Framework for development of a Core Outcome Set

156x160mm (150 x 150 DPI)

 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

Scope 3a Describe the health condition(s) and population(s) that will be covered by the COS

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
