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Standardizing definitions for the pre-eclampsia core outcome set: A consensus development study

Please carefully check your name, qualification, and affiliation.

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Please update your declarations of interest

Prof Mol is a consultant for ObsEva. Prof Karumanchi reports serving as a consultant to Roche, Siemens, and Thermofisher Scientific and has financial interest in Aggamin Pharmaceuticals. Prof McManus has received blood pressure monitors for research from Omron. The remaining authors declare no competing interests.

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Condensation
Using formal consensus methods, this study has developed standardized definitions for the pre-eclampsia core outcome set, implementation within future pre-eclampsia trials should standardize core outcome collection across future research.

Short title
Standardizing definitions for pre-eclampsia research

AJOG at a glance

A. Standardizing definitions for individual core outcomes presents an opportunity to develop additional harmony in future pre-eclampsia research and ensure secondary research can be undertaken prospectively, efficiently, and harmoniously.
B. Using formal consensus development methods healthcare professionals and researchers have developed standardized definitions for the pre-eclampsia core outcome set for use within future randomized controlled trials and systematic reviews.
C. Consensus on measurements for the pre-eclampsia core outcome set will help to ensure consistency across future randomized controlled trials and systematic reviews, making research evidence more accessible and facilitate the translation of research into clinical practice.

Keywords

Consensus development study, core outcome set, hypertension in pregnancy, outcome measure, pre-eclampsia, and randomized controlled trials.

Abstract

Background

While a core outcome set for pre-eclampsia has been established, this is necessary but not sufficient. Different definitions exist for individual core outcomes. Such variation makes it difficult to synthesize the results of individual randomized controlled trials within secondary research. Standardizing definitions for individual core outcomes presents an opportunity to develop additional harmony across future pre-eclampsia research

Objectives

To develop consensus definitions for the core outcome set for pre-eclampsia.

Study design

Potential definitions for outcomes previously chosen in the core outcome set development process were identified across four formal definition development initiatives, nine national and international guidelines, 12 Cochrane systematic reviews, and 79 randomized controlled trials, and entered into a consensus development conference. These definitions were entered into a consensus development conference, including ten healthcare professionals and three researchers, plus six participants with experience of conducting research in low- and middle-income countries. A definition hierarchy structured the discussion for each core outcome. A prior consensus definition was unanimous agreement.

Results

Eighty-six definitions were entered into the consensus development conference. Consensus was reached for all core outcomes including 14 maternal, four fetal, and four neonatal. When considering stroke, pulmonary edema, and neonatal seizures, separate consensus definitions were developed for high-income countries and low- and middle-income countries.

Conclusion(s)

Consensus on measurements for the pre-eclampsia core outcome set will help to ensure consistency across future randomized controlled trials, systematic reviews, and clinical practice guidelines. Such standardization should make research evidence more accessible and facilitate the translation of research into clinical practice.

Clinical trial registration

Core Outcome Measures in Effectiveness Trials Initiative, www.comet-initiative.org/studies/details/588, and registration number 588.

Introduction

Randomized controlled trials evaluating potential treatments for pre-eclampsia have reported many different outcomes.[1-3] Such variation contributes to challenges in comparing, contrasting, and combining individual pre-eclampsia trials, limiting the usefulness of research to inform clinical practice. The development, dissemination, and implementation of a core outcome set for pre-eclampsia should address the variation in outcome selection, collection, and reporting in randomized trials and ensure the future evidence base is meaningful to diverse stakeholders, including women with pre-eclampsia.[4]

While a core outcome set for pre-eclampsia has been established, this is necessary but not sufficient. Different definitions exist for individual core outcomes. For example, stillbirth has been defined using six different combinations of gestational ages, birth weights, and crown-heel heights (Table 1).[5] Such variation makes it difficult to synthesize the results of individual randomized controlled trials within secondary research, including individual pair-wise meta-analysis, patient data meta-analysis, and network meta-analysis.[6] Standardizing definitions for individual core outcomes presents an opportunity to develop additional harmony in future pre-eclampsia research and ensure secondary research can be undertaking prospectively, efficiently, and harmoniously.

No guidelines have established recommendations regarding the selection of definitions for individual core outcomes.[7] Outside the context of core outcome set development, the World Health Organization's Working Group on Maternal Mortality and Morbidity Classifications has standardized and validated a range of definitions.[8] An international working group of experts undertook a systematic review of maternal mortality/morbidity definitions and assessed their feasibility in high-, middle-, and low-income countries. The systematic review supported the

development of standardized definitions for mortality and specific morbidities, including eclampsia, renal failure, and mechanical ventilation.[9] Standardized definitions were demonstrated to be feasible in a high-income country (Canada) and a middle-income country (Brazil).[10,11] Other initiatives, including the World Health Organization's ICD-11, Brighton Collaboration, and International Network of Obstetric Surveillance Systems, have standardized, but not validated, several maternal, fetal, and neonatal definitions.[5,12-15]

In this study, we used robust consensus development methods to generate agreement on definitions for the core outcome set for pre-eclampsia.

Materials and methods

An international steering group, including healthcare professionals, researchers, and patient representatives, was formed to guide the development of this core outcome measurement set. Members of the steering group represented various disciplines, geographical areas, and expertise.

Sources of potential definitions for individual core outcomes

Potential definitions were sourced from formal definition development initiatives, national and international guidelines, Cochrane systematic reviews, and randomized controlled trials (Figure 1). Specific methods have been published elsewhere, briefly:

- A systematic review was undertaken searching the Core Outcome Measures in Effectiveness Trials (COMET) initiative register to identify definition development initiatives relevant to pregnancy and childbirth research from inception to January 2017.[16]
- A recently published systematic review of national and international pre-eclampsia guidelines was used to source definitions used within these guidelines.[17]

- Cochrane systematic reviews evaluating potential treatments for pre-eclampsia were identified by searching the Cochrane Database of Systematic Reviews (CDSR) from inception to August 2017, again aiming to identify standardized definitions.
- Randomized controlled trials evaluating potential treatments for pre-eclampsia where outcomes may have been defined were identified by searching bibliographical databases, including the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE, from inception to January 2016.

An inventory of potential definitions was developed. Using a pilot-tested and standardized data extraction form, definitions were extracted verbatim from all sources. When a definition was not explicitly stated in a published trial report, the corresponding researcher was contacted to seek further clarification. From these different sources, 86 potential definitions were identified for the 14 maternal, four fetal, and four neonatal core outcomes that had already been identified (Table 2).[18]

Consensus development conference.

Healthcare professionals and researchers, who lived in the United Kingdom, and had participated in the development of a core outcome set for pre-eclampsia, were invited to participate in a consensus definition development conference.[4] There is no robust method for calculating the required number of participants which needs to be broad enough to include relevant stakeholders but small enough for adequate discussion to ensure that consensus is possible.[19] Following consultation with the study's steering group, we aimed to recruit between ten and 15 participants, as this number has yielded sufficient results and face validity in other settings.[19]

The consensus development method was delivered through a half day consensus development conference. The meeting was chaired by one of us who was an experienced

facilitator (RJM). Before starting the meeting, participants provided demographic details, including age, gender, and ethnic group, and made an explicit commitment to participate actively.

The group discussion followed an informal format with the chairperson providing direction. Each core outcome was discussed in turn. Potential definitions were displayed within the definition hierarchy. Participants were encouraged to voice their opinions on previously used definitions, to suggest new definitions if necessary and to reformulate individual definitions to improve clarity or comprehension. The *a priori* definition of consensus used within this study was unanimous agreement. Although the group was encouraged to reach consensus, members were able to express minority or alternative views when consensus could not be achieved.

Results

Eighty-six potential outcome definitions were drawn from four definition development initiatives,[5,8,12,14,15,20,21] nine national and international clinical practice guidelines,[22-28] 12 Cochrane systematic reviews,[29-39] and 79 pre-eclampsia trials (Appendix S1).[40-120] Thirteen participants participated in the consensus development conference (Table S1) comprising ten healthcare professionals (77%) and three researchers (23%). Six (46%) had experience or working in or conducting research in low- and middle-income countries.

Maternal core outcomes

Maternal mortality: Participants noted consistency across definitions in terms of a limit of 42 days after delivery, pregnant termination or miscarriage, a historical limit based upon the approximate timing of first menstrual period in non-lactating women (Table 3).[121] Participants discussed the possibility to extend the definition by including deaths attributable to

complications of pre-eclampsia later than 42 days, however, concerns were expressed regarding the feasibility of longer follow-up in low- and middle- income countries.

Eclampsia: Participants identified inconsistencies in terminology across different definitions of eclampsia. A unanimous decision was made to define eclampsia as "the onset of convulsions in a woman with pre-eclampsia, not attributable to other causes". Participants discussed the importance of acknowledging the various terminology used in different settings related to convulsions including fits, generalized convulsions, tonic-clonic seizure, and seizure.

Stroke: Participants recognized pre-eclampsia as an important risk factor for both ischemic and hemorrhagic stroke.[122] Discussion focused upon the challenges of obtaining computerized tomography or magnetic resonance imaging in low- and middle-income countries, and as such separate definitions were agreed for high-income countries and low- and middle-income countries.

Cortical blindness: In the single potential definition identified, participants noted the requirement to measure visual acuity and the challenges of doing so. Such measurement is not a core competency for healthcare professionals in maternity settings, and the necessary equipment to measure visual acuity is often not readily available. Participants concluded a patient-reported symptom of visual impairment would be comparable and negate the requirement to undertake visual acuity measurement.

Retinal detachment: Participants appreciated the simplicity of the World Health Organization's definition: *"a condition in which the retina peels away from its underlying layer of support tissue."*[14] However, the importance of undertaking an ophthalmological examination to confirm the diagnosis was discussed and considered essential in securing a robust diagnosis.

Pulmonary edema: Participants agreed the clinical signs of pulmonary edema are relatively straightforward to elicit during respiratory system auscultation. The discussion focused upon chest x-ray confirmation. Concerns were expressed regarding the availability of X-ray facilities in low- and middle-income countries. To address these concerns, participants agreed to include the requirement for directive treatment and an oxygen saturation below 95% when a chest x-ray is unavailable.

Acute kidney injury: Participants noted a diverse range of different definitions of acute kidney injury. A pragmatic decision was made to implement the National Institute for Health and Care Excellence standardized definition which shares a common definition with other recent national and international initiatives including Risk, Injury, Failure, Loss, End-stage (RIFLE) renal disease, Acute Kidney Injury Network, and Kidney Disease: Improving Global Outcomes.[123-126] The discussion focused upon the measurement of creatinine during routine antenatal care. A baseline creatinine is not routinely measured in lower risk women and may not have been measured before pregnancy.[127] Therefore, an additional criterion was added to the consensus definition: serum creatinine >150 micromol/liter in the absence of a baseline serum creatinine.

Liver capsule hematoma: Participants unanimously recommended the definition previously reported in randomized trials adopted from the prediction of adverse maternal outcomes in pre-eclampsia study.[128]

Placental abruption: Participants unanimously agreed the definition developed as part of the Brighton Collaboration case definition study.[20]

Postpartum hemorrhage: Participants discussed the challenges of defining postpartum hemorrhage when considering the contribution of the mode of delivery, estimating blood

loss, and differences in thresholds when further medical or surgical intervention to manage postpartum hemorrhage is deemed necessary. Participants agreed a common starting point is the recognition of heavy abnormal bleeding following childbirth. A specific volume threshold was considered unhelpful as there is marked inter-observer variability in estimating blood loss.[129] Participants discussed the importance of demonstrating hypotension and/or the use of pharmacologic or surgical interventions to manage postpartum hemorrhage as important components of the consensus definition.

Raised liver enzymes: Participants recognized that the reference ranges for liver transaminases vary both during the three trimesters of pregnancy and between different laboratories. Participants unanimously recommended the consensus definition should not state a specific threshold but that aspartate aminotransferase (AST) and alanine transaminase (ALT) should be elevated at least twice the upper limit of normal.

Low platelets: Participants discussed the different thresholds defining thrombocytopenia, in pregnancy thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L, however, counts below 100 x10^9/L are more typical in HELLP syndrome and in severe cases, the platelet count may fall below 30 x10^9/L.[62,130] Participants agreed platelet counts below 100 x10^9/L should be used as the threshold for the consensus definition.

Maternal admission to intensive care unit required: Participants unanimously agreed on a consensus definition. The definition highlights the importance of collecting and reporting the requirement for intensive care unit admission even if women are unable to be admitted to an intensive care unit because of logistics or availability of such services. The lack of capacity will be particularly relevant to research conducted in low- and middle-income countries.[131]

Tracheal Intubation and mechanical ventilation not for purposes of operative delivery: Participants unanimously agreed a consensus definition.

Fetal core outcomes

Stillbirth: Participants reviewed the different definitions which incorporated different quantifiable parameters, including clinical estimates of gestational age, birth weight, and crown-heel height.[32] Participants highlighted the World Health Organization's definition for stillbirth is the most widely used.[132] The inclusion of height and weight thresholds secures its feasibility in low- and middle-income countries.[132] Consensus was reached to select the World Health Organization's definition.[14]

Gestational age at delivery: Participants considered gestational age at delivery as a well-characterized outcome with an internationally accepted definition.[21] There was unanimous agreement to adopt this definition.

Birth weight: Participants agreed birth weight should be collected within 24 hours of birth.[21] Participants noted best practice recommendations regarding the measurement of birth weight should be adhered to in future pre-eclampsia research including weight assessed using a calibrated electronic scale with 10-gram resolution.[21] Participants noted in low- and middle-income countries calibrated electronic scales may not be readily available, and the calibration and type of scale should be clearly reported.

Small for gestational age: Participants discussed the importance of assessing small for gestational age using validated growth charts. A variety of different international, regional, and local growth charts are available.[133] Participants unanimously agreed a 10th percentile threshold was appropriate to identify small for gestational age newborn infants and any validated international, regional, or local customized growth chart could be used. Participants agreed small for gestational age infants should be reported for all births, including stillbirths.

Neonatal core outcomes

Neonatal mortality: Participants noted the consistent use of the World Health Organization definition for neonatal mortality, "d*eaths among live births during the first 28 completed days of life"*, across definition development initiatives, international and national guidelines, Cochrane systematic reviews, and randomized controlled trials.[14] Participants unanimously recommended this definition.

Neonatal seizures: Participants noted World Health Organization guidelines described the most practical method of diagnosing neonatal seizures, based upon clinical recognition.[134] Neonatal seizures commonly present with focal clonic movements, however, they can present with more subtle signs which can be easily misinterpreted as either crying or cycling movements of the limbs.[134] Electroencephalogram (EEG) monitoring can support the diagnosis. However, its availability in low- and middle-income countries is limited. Participants agreed a common starting point is the recognition of neonatal seizures. Separate definitions were agreed for high-income countries and low- and middle-income countries.

Respiratory support: Participants agreed on a consensus definition which included continuous positive airway pressure, non-invasive positive pressure ventilation, or intubation and mechanical ventilation. Participants discussed the inclusion of supplemental oxygen; however concerns were expressed that this would represent an overly inclusive definition as supplemental oxygen is a commonly used non-specific intervention.[135]

Admission to special care baby unit or neonatal intensive care unit required: Participants discussed the lack of consensus regarding the local, regional, or national criteria used to assess the need for admission to a special care baby unit or neonatal intensive care unit.[136] Consensus was reached to recommend a broad definition to recognize this variation in

admission criteria. The definition highlights the importance of collecting and reporting the requirement for admission to a special care baby unit or neonatal intensive care unit even if the neonate cannot be admitted. The lack of capacity will be particularly relevant to research conducted in low- and middle-income countries.[137]

Comment

When pre-eclampsia trials, systematic reviews, and clinical practice guidelines have previously reported individual outcomes, they have been defined in many different ways. In developing a core outcome set it is therefore important to rigorously define the outcomes chosen. Using robust consensus science methods, ten healthcare professionals and three researchers systematically considered 86 definitions previously developed by formal definition development initiatives, randomized controlled trials, Cochrane systematic reviews, and/or clinical practice guidelines. Consensus was reached for all 14 maternal, four fetal, and four neonatal core outcomes. When considering stroke, pulmonary edema, birth weight, and neonatal seizures, separate consensus definitions were developed for high-income countries and low- and middle-income countries because of the key role of imaging in the high-quality diagnosis of these conditions that may not be available in lower income settings.

Interpretation

Differences in the definition of individual outcomes can be accommodated in a meta-analysis. However, there are limits to what can be combined in a meaningful way due to heterogeneity, making it preferable to have core outcomes and definitions.[6] Such standardized outcome definitions, should enable robust meta-analysis and facilitate more sophisticated secondary research, including individual patient data and network meta-analysis. Effective evidence synthesis supports in turn the translation of research into clinical practice.[139]

Having established consensus definitions, primary and secondary researchers should use them, and guideline developers should build their clinical practice guidelines around them. Standardized consensus definitions are not meant to stifle the development and use of other appropriate definitions. For example, researchers undertaking research in Australia may wish to define stillbirth as occurring after 20 weeks of gestation in line with local Epidemiology and Surveillance Branch recommendations.[5] Researchers wishing to collect data using other definitions in the context of their own randomized controlled trial would continue to be able to do so. However, selective reporting should be avoided by presenting findings for both the consensus definition and any other definition used. Researchers would need to carefully consider how these data would be collected to fulfill different definitions. In the example of stillbirth, the common components of all definitions, including gestational age, birth weight, and crown-heel height, should be recorded separately and combined to fulfill the consensus definition (gestational age, birth weight, and crown-heel height) and the local definition (gestational age and birth weight).

Standardized definitions should prevent misclassifications and reduce measurement error.[140] Such standardization ensures the consensus definitions can be applied symmetrically to the trial arms, avoiding bias in the measurements. Several consensus definitions, including abruption, postpartum hemorrhage, and neonatal seizures, require professional assessment. Any assessment should be determined by an observer with comprehensive training. Differential and biased misclassification of outcomes can occur in poorly designed randomized trials, for example, when outcome assessors are not blinded to the treatment allocation. Consider the diagnosis of postpartum hemorrhage: outcome assessors may perform laboratory investigations more regularly in participants allocated to the experimental treatment when compared to the control. Systematic evaluations of observer bias have demonstrated non-blinded outcome assessors consistently over diagnose clinical outcomes when compared with blinded outcome assessors.[141] Several strategies exist to increase the likelihood standardized definitions are applied to accurately classify clinical outcomes,

including standardized data collection tools, validation studies, and independent adjudication panels. This would increase the likelihood that core outcomes are classified accurately and without variation .[142]

A recent systematic review identified 33 core outcome sets relevant to pregnancy and childbirth currently under development.[16] Each set will contain a unique collection of core outcomes. Ideally, core outcomes which overlap several core outcome sets should utilize a consistent definition. The International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE) is establishing an inventory of outcome definitions relevant to pregnancy and childbirth research, which could facilitate the efficient development of definitions for different core outcome sets. The inventory catalogs available definitions within a regional, national, and international context and supporting validation studies. Maternal and newborn health is in a unique position to benefit from such an initiative as individual obstetric conditions, such as pre-eclampsia, gestational diabetes, and obstetric cholestasis, are likely to share common core outcomes, for example, maternal mortality, neonatal mortality, and neonatal seizures.

The Core Outcomes in Women's and Newborn Health (CROWN) initiative, supported by over 84 specialty journals, including the Cochrane Pregnancy and Childbirth Group, has resolved to implement the core outcome set for pre-eclampsia.[143] Participating journals will require researchers to report the definition for individual core outcomes within published trial reports. When the consensus definition has not been used, the researchers will be asked to report this deficiency and its implications for their findings.[143] With time researchers will anticipate this scrutiny, which should support the implementation of the core outcome set for pre-eclampsia.

Strengths and weaknesses

This study has completed our overall objective of standardizing future pre-eclampsia research by identifying what outcomes to measure, when they should be measured, and how they should be measured. A comprehensive inventory of potential definitions was developed by a diverse range of researchers and healthcare professionals resulting in clear and objective definitions which could be used across settings.

This study was not without limitations. Pre-eclampsia is a disease with a global impact, especially in low- and middle-income countries, where the societal burden of the disease is high.[138] Participants in the consensus conference currently live in the United Kingdom, although six participants (46%) had lived, worked, or conducted research in a low- and middle-income country. This could have impacted on the generalisability of the consensus definitions prioritized but was a pragmatic choice in the light of limited resources which precluded inclusion of international participants. Use of the core outcome set in a variety of countries will ascertain the extent to which this is an issue and definitions may need further adjustment.

The *a priori* definition of consensus used within this study was unanimous agreement. Once a consensus definition was formally agreed, participants had the opportunity to comment further. A contingency for participants who did not agree with a consensus definition was available but not used. The study could have been adjusted to undertake formal and anonymous voting to assess the level of agreement for individual consensus definitions. Individual participants could have rated their agreement with an individual consensus definition using a Likert scale anchored between strongly disagree and strongly agree. Further methodological research is required to develop an appropriate definition of consensus in exercises similar to ours.

Conclusion

519 Ensuring core outcomes are consistently defined across future randomized controlled trials,
520 systematic reviews, and clinical practice guidelines, will ensure evidence is more accessible
521 and facilitate the translation of research into clinical practice.
522
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