A protocol for developing, disseminating, and implementing a core outcome set for pre-eclampsia

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Running title: Developing a core outcome set for pre-eclampsia.

Abstract

Background

Pre-eclampsia is a serious complication of pregnancy and contributes to maternal and offspring mortality and morbidity. Randomised controlled trials evaluating therapeutic interventions for pre-eclampsia have reported many different outcomes and outcome measures. Such variation contributes to an inability to compare, contrast, and combine individual studies, limiting the usefulness of research to inform clinical practice. The development and use of a core outcome set would help to address these issues ensuring outcomes important to all stakeholders, including patients, will be collected and reported in a standardised fashion.

Methods

An international steering group including healthcare professionals, researchers, and patients, has been formed to guide the development of this core outcome set. Potential outcomes will be identified through a comprehensive literature review and semi-structured interviews with patients. Potential core outcomes will be entered into an international, multi-perspective online Delphi survey. All key stakeholders, including healthcare professionals, researchers, and patients will be invited to participate. The modified Delphi method encourages whole and stakeholder group convergence towards consensus 'core' outcomes. Once core outcomes have been agreed upon it is important to determine how they should be measured. The truth, discrimination, and feasibility assessment framework will assess the quality of potential outcome measures. High quality outcome measures will be associated with core outcomes. Mechanisms exist to disseminate and implement the resulting core outcome set within an international context.

Discussion

Embedding the core outcome set within future clinical trials, systematic reviews, and clinical practice guidelines could make a profound contribution to advancing the usefulness of research to inform clinical practice, enhance patient care, and improve maternal and offspring outcomes. The infrastructure created by developing a core outcome set for pre-eclampsia could be leveraged in other settings, for example selecting research priorities and clinical practice guideline development.

Prospective registration

[1] Core Outcome Measures in Effectiveness Trials (COMET) registration number: 588.

[2] International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42015015529.

Keywords

[1] Pre-eclampsia.

[2] Core outcome set.

[3] Systematic review.

[4] Semi-structured interviews.

[5] Modified Delphi method.

Background

Pre-eclampsia is an enigmatic pregnancy specific, multisystem syndrome characterised by reduced organ perfusion secondary to vasospasm and activation of the coagulation cascade. Despite extensive research, the cause of pre-eclampsia remains elusive. There is no international consensus regarding the diagnostic criteria for pre-eclampsia. The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) developing after 20 weeks gestation presenting with new-onset proteinuria, other maternal organ dysfunction, and / or uteroplacental dysfunction.[1] Pre-eclampsia is associated with maternal and offspring mortality and morbidity, especially in cases where severe features are present.[2] The development of therapeutic interventions to reduce this health burden is urgently required.

Selecting appropriate outcomes to reflect beneficial and harmful effects is a critical step in designing clinical studies. To ensure relevance to policy and practice the chosen outcomes need to be relevant to key stakeholders, including healthcare professionals, researchers, and patients. In the absence of a standardised approach important outcomes may not be routinely collected and reported. Even in the unlikely situation where outcomes have been consistently collected across studies, evidence synthesis can be limited by the use of different outcome measures (including definitions and instruments). For example, severe pre-eclampsia has been defined using different blood pressure thresholds, proteinuria thresholds, clinical symptoms, placental parameters, and fetal parameters.[3] The development and use of a collection of well-defined, discriminatory, and feasible outcomes, termed a core outcome set, would help to address these issues.[4]

Core outcome sets are agreed minimum sets of outcomes that can be measured in a standardised manner and reported consistently in the final publication.[4] They do not necessarily need to be extensive and represent a minimum data set. Researchers remain free to measure other outcomes in addition. We aim to replicate the success of the Outcome Measures in Rheumatology (OMERACT) initiative. This initiative has developed core outcome sets for many different conditions. Successful implementation of the rheumatoid arthritis core outcome set has resulted in a significant change in the quality and relevance of research and enriched clinical

practice by identifying consensus outcomes which are now routinely monitored by healthcare professionals and patients around the world.[5]

A recent international initiative has developed a core outcome set for randomised trials evaluating interventions for asymptomatic preterm birth.[6] One hundred and seventy-four individuals, representing five stakeholder groups, including obstetricians, midwives, neonatologists, researchers, and patients, from twenty-five countries participated in a modified Delphi method. The method was able to reduce 227 outcomes identified by a systematic review of the literature and 33 outcomes suggested by participants to 13 consensus 'core' outcomes. Consensus was reached on four outcomes related to pregnant women: [1] maternal mortality; [2] maternal infection or inflammation; [3] preterm rupture of membranes; and [4] harm to mother from intervention. Consensus was reached on nine outcomes related to the offspring: [1] gestational age at delivery; [2] offspring mortality; [3] birthweight; [4] early neurodevelopmental morbidity; [5] late neurodevelopmental morbidity; [6] gastrointestinal morbidity; [7] infectious morbidity; [8] respiratory morbidity; and [9] harm to offspring from intervention.[6]

The objective of this study is to produce, disseminate, and implement a core outcome set for pre-eclampsia.

Methods

Prospective Registration

The Core Outcome Measures in Effectiveness Trials (COMET) initiative brings together researchers interested in the development, application, and promotion of core outcome sets. The study has been prospectively registered with the COMET initiative, the registration number is 588, and the International Prospective Register of Systematic Reviews (PROSPERO), the registration number is CRD42015015529. We will follow reporting guidelines for systematic reviews, as outlined by the referred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7]

Ethical Review

Approval for the qualitative patient interviews has been obtained from the National Research Ethics Service (NRES) Committee South Central ethics committee (reference number: 12/SC/0495) and all participants will be requested to provide informed written consent. The NRES has advised that the Delphi survey does not require ethical approval.

Study Funding

This study is funded by the National Institute for Health Research (reference: DRF-2014-07-051). The funder has no role in the design and conduct of the study, the collection, management, analysis, or interpretation of data, or manuscript preparation.

Steering Group and Study Management Group

An international steering group, including healthcare professionals, researchers, and patient representatives, has been formed to guide the development of this core outcome set. Members of the steering group have been selected to represent various disciplines, geographical areas, and expertise. Within the steering group a study management group has been established. The study management group consists of a study coordinator (JD) and three members of the steering group (KK, RM, and SZ) who will conduct the day-to-day management of the study.

Scope of this Core Outcome Set

The steering group recommended the core outcome set should apply to clinical studies evaluating therapeutic interventions for women with pre-eclampsia. All therapeutic interventions for pre-eclampsia will be considered regardless of type, setting, or mode of administration. In order to maximise generalisability, we will not differentiate between early and late onset or mild and severe pre-eclampsia. Pre-eclampsia will be defined as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) after 20 weeks gestation presenting with new-onset proteinuria, other maternal organ dysfunction, or uteroplacental dysfunction.[1]

We are not seeking to reach consensus regarding the definition of pre-eclampsia, the standardisation of other aspects of study design, or the development of a standardised database for perinatal research studies. We acknowledge the work of the Global Pregnancy Collaboration and the International Society for the Study of Hypertension in Pregnancy (ISSHP) in these areas.[1&8] We are actively collaborating with their efforts.

Endorsement

iHOPE is endorsed and supported by prominent national and international organisations including: [1] Action on Pre-eclampsia (APEC); [2] British Hypertension Society; [3] Core Outcomes in Women's Health (CROWN) initiative; [4] Global Obstetrics Network (GONet); [5] Global Pregnancy Collaboration (GONet); [6] International Society for the Study of Hypertension in Pregnancy (ISSHP); [7] Obstetric Anaesthetists Association; and [8] Pre-eclampsia-Eclampsia Monitoring, Prevention and Treatment (PRE-EMPT) initiative.

Study Overview

The study will be divided into three distinct stages: [1] identifying potential core outcomes; [2] determining core outcomes; and [3] determining how core outcomes should be measured (figure 1).

Stage One: Identifying Potential Core Outcomes

Systematic review: what outcomes have been reported before?

The Cochrane Central Register of Controlled Trials (CENTRAL) is a highly concentrated source of randomised controlled trials reports (RCT) identified by searching other bibliographical databases, including EMBASE and Medline, and other sources. We will search CENTRAL to identify trials evaluating therapeutic interventions for pre-eclampsia. The screening of the records retrieved will be performed in duplicate and disagreements will be resolved by discussion. No date or language restrictions will be applied, and translations will be obtained for non-English language reports. Full text reports will be reviewed for eligible studies and data will be extracted in duplicate using a standardised and piloted data extraction proforma recording study and outcome reporting characteristics. Disagreements will be resolved by discussion. Individual outcomes will be entered into the outcome inventory.

Qualitative patient Interviews: what outcomes do patients want?

Patients often identify outcomes not considered by other stakeholders or within the literature.[4] Women with lived experience of pre-eclampsia will be recruited to participate in qualitative interviews through National Health Service (NHS) clinics, the patient support group Action on Pre-eclampsia, and through social media. Potential participants will be asked to complete a recruitment questionnaire recording demographic details and information pertaining to their lived experiences of pre-eclampsia. We do not intend to interview all those who volunteer, but will select participants to deliver a maximum diversity sample. After obtaining informed consent, participants will be interviewed in a setting of their choice, usually their home. Interview questions were developed in consultation with the steering group and guided by the literature review. The interview will start with an open-ended narrative section followed by a semi structured section with questions exploring their lived experience. The interviews will be audio or video recorded and transcribed verbatim.

Data collection and analysis will be guided by a modified grounded theory approach, allowing data analysis of early interviews to enrich data collection of latter

interviews.[9] These data will be analysed in consultation with a second experienced qualitative researcher using both a systematic approach of coding managed in NVivo 10 (QSR International, USA) and Framework to aid contextual understanding.[10] Data analysis will identify outcomes to be entered into the outcome inventory. The wording of outcomes will be grounded in the interview data and will be decided in collaboration with the patient representatives. Data saturation will be achieved when no new substantive themes are being identified through the analysis.

Outcome inventory

A comprehensive inventory of outcomes identified by the systematic review and analysis of the qualitative interviews will be produced. If there is uncertainty as to how to classify or present an outcome the advice of the steering group will be sought. Following the steering group's agreement, the outcome inventory will be entered into the modified Delphi method.

Stage Two: Determining Core Outcomes

Combining professional and patients' views.

The modified Delphi methods enables key stakeholders to participate in a process which assesses the extent of agreement (consensus measurement) and then resolves disagreement (consensus development).[11] All key stakeholders including healthcare professionals (anaesthetists, general practitioners, obstetricians, midwives, and neonatologists), researchers, and patients will be invited to participate. There is no robust method for calculating the required sample size but typically groups have included 13 to 222 participants.[11] We aim to recruit a minimum of 18 participants for each stakeholder group (anaesthetists, general practitioners, obstetricians, midwives, neonatologists, researchers, and patients) with balanced representation from high, middle, and low income countries. Before entering the exercise participants will be allocated a unique identifier to anonymise their response. The online Delphi survey will be developed to ensure the ease of completion utilising appropriate patient terminology. Lay definitions will be available for individual outcomes. The survey will be piloted by the steering group before its use.

Round one

Participants will be invited to score individual outcomes on a nine point Likert scale anchored between one (labelled ‘of limited importance for making a decision’) and nine (labelled ‘critical for making a decision’). This scale was devised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group to facilitate the ranking of outcomes according to their importance and has been adopted widely by core outcome set developers.[12] Participants will be presented with the opportunity to add additional outcomes before completing the survey. Additional outcomes listed by participants will be reviewed and coded by the outcome committee and incorporated into round two.

Round two

All outcomes will be carried forward from round one into round two. For each outcome, the percentage of participants scoring individual outcomes during round one at each possible response from one to nine will be calculated and tabulated for each individual stakeholder group (healthcare professional, researchers, and patients). Participants will be able to view the results of individual stakeholder groups. Participants will be invited to rescore individual outcomes. The modified Delphi method promotes repeated reflection and rescoring promoting whole and stakeholder group convergence upon consensus “core” outcomes.[10]

A standardised definition will be applied to this round’s results enabling core outcomes to be identified:

[1] Consensus in (classify as a core outcome): Over 70% of participants in each stakeholder group score outcome 'critical for decision making' (score seven to nine) and less than 15% of participants in each stakeholder group score outcome 'of limited importance for decision making' (score one to three).

[2] Consensus out (do not classify as a core outcome): Over 70% of participants in each stakeholder group score outcome domain 'of limited importance for decision making' (score one to three) and less than 15% of participants in each stakeholder group score outcome domain 'critical for decision making' (score seven to nine); or

[3] No Consensus (do not classify as a core outcome): Anything else.

The round two results will be reviewed by the steering group to consider the need for a further Delphi survey round.

Consensus meeting

The results from the modified Delphi method will be considered within a consensus meeting. The meeting will include a range of views from participants that will be purposefully sampled. The objective of the consensus meeting will be to discuss outcomes not reaching consensus and approve a final core outcome set for pre-eclampsia. To ensure unbiased consensus formation amongst a group of varied participants, the steering committee will ensure that the meeting is informal, inclusive, participatory and values all opinions.

Stage Three: Determining How Core Outcomes Should Be Measured

Ensuring outcome measures fit for purpose.

Once core outcomes are agreed upon it will be important to determine how the outcomes should be defined and measured. Currently no guidelines are available to support outcome measurement instrument selection. The Core Outcome Measurement Instrument Selection (COMIS) project is in the process of developing standard for assessing the methodological quality of studies exploring the measurement properties of instruments.[13] We will assess potential instruments using the developed framework. The assessment will be undertaken in duplicate using a standardised and piloted data extraction proforma. If there is disagreement or uncertainty as to how to classify an outcome measurement the advice of the steering group will be sought. High quality outcome measures will be associated with each core outcome. The study will not advocate the use of a single outcome measure if several high quality outcome measures are identified for a single outcome. If no high quality outcome measures exist for a core outcome this will be acknowledged.

Discussion

Implementing core outcome sets in future clinical studies, systematic reviews, and clinical guidelines could make a profound contribution to advancing the reach and relevance of research in informing clinical practice, enhancing patient care, and improving maternal and offspring outcomes.

Improving clinical trial outcome selection. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement, supported by funders of health research, recommend the use of core outcome sets where they exist.[14] A core outcome set would ensure consensus outcomes important to all stakeholders, including patients, are collected and reported. When clinical studies use consensus outcomes and outcome measures prospective meta-analysis using individual patient data is feasible.

Improving clinical trial reporting and evidence synthesis. The Core Outcomes in Women's Health (CROWN) initiative, supported by 74 speciality journals, including the Cochrane Pregnancy and Childbirth Group, has resolved to implement core outcome sets.[15] Participating journals will require authors to report the results for core outcomes within trial reports and systematic reviews and offer conclusions based on these outcomes rather than non-core or surrogate outcomes. Where core outcome sets have not been collected the authors will be asked to report this deficiency and its implications for their findings.[15]

Improving clinical practice guidelines. The National Institute for Health and Care Excellence (NICE) supports the use of core outcomes sets when selecting outcomes during evidence scoping and synthesis. As this activity forms the basis of updating guideline recommendations the core outcome set could have a direct impact in influencing clinical practice.

Developing infrastructure to support international collaboration. Developing a core outcome set will establish an international network of key stakeholders, including

healthcare professionals, researchers, and patients, with experience of contributing to a collaborative online study. This infrastructure could be leveraged in other settings, for example selecting research priorities and clinical practice guideline development.

Conclusion

Embedding the core outcome set within future clinical trials, systematic reviews, and clinical practice guidelines could make a profound contribution to advancing the usefulness of research to inform clinical practice, enhance patient care, and improve maternal and offspring outcomes. The infrastructure created by developing a core outcome set for pre-eclampsia could be leveraged in other settings, for example selecting research priorities and clinical practice guideline development.

Box 1: How do I contribute to improving pre-eclampsia research?

We acknowledge the expertise and commitment of this journals' readership to improving patient care. We warmly invite readers to participate in the modified Delphi survey by registering their interest to participate here: www.phc.ox.ac.uk/ihope

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Declaration of interest

Prof Ben Mol is a consultant for ObsEva. Dr Karumanchi reports serving as a consultant to Roche, Siemens and Thermofisher Scientific and has financial interest in Aggamin Phamaceuticals. The remaining authors declare no competing interests.

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