Development of a core set of outcomes and outcome measures for future randomised trials evaluating potential treatments for pre-eclampsia in lower resource settings.

A collaborative study with the Department of Reproductive Health and Research, World Health Organization, Geneva.

Dr James M. N. Duffy

Balliol College, University of Oxford

Randomised trials evaluating potential treatments for pre-eclampsia have reported many different outcomes and outcome measures. The is study has developed a core outcome set for randomized trials evaluating potential treatments for pre-eclampsia in lower resource settings. Rigorous implementation of a core outcome set should ensure outcomes important to all stakeholders, including women with pre-eclampsia, will be collected and reported in a standardised fashion, advancing the usefulness of research to inform clinical practice.

This is independent research arising from the EGA Hospital Charity Travelling Fellowship in Memory of Anne Boutwood who generously supported the study.

Pre-eclampsia is an enigmatic pregnancy specific, multisystem syndrome characterised by reduced organ perfusion secondary to vasospasm and activation of the coagulation cascade.(1) It is associated with maternal and offspring mortality and morbidity, especially in lower resource settings.(1) The development of new treatments to reduce this health burden is urgently required.

Potential new treatments require robust evaluation. Selecting appropriate outcomes to reflect beneficial and harmful effects is a critical step in designing future randomised trials. To ensure relevance to policy and practice the chosen outcomes need to be relevant to key stakeholders, including healthcare professionals, researchers, and women with pre-eclampsia. In the absence of a standardised approach, most pre-eclampsia trials have not reported information on clinically important outcomes.(2) For example, the majority of pre-eclampsia trials have neglected to evaluate their efficacy and safety of potential treatments in the participants' offspring, particularly over the longer term.(2)

Two hundred and eight one healthcare professionals, 41 researchers, and 110 patients, representing 55 different countries, have contributed to the development of a core outcome set for pre-eclampsia (Figure 1). Implementing a core outcome set ensures outcomes important to individual stakeholder groups, including women with pre-eclampsia, are consistently collected and reported in future pre-eclampsia trials.(3)

Core outcomes require standardised definitions.(4) Without a standardised approach, researchers would be able to choose from a variety of different definitions for individual core outcomes. For example, stillbirth has been defined using different combinations of gestational ages, birth weights, and crown-heel heights (Table 1).(5) Such variation can make it difficult, often impossible, to synthesise the results of individual trials within secondary research methods including individual patient data meta-analysis, pair-wise meta-analysis, and network meta-analysis.(2)

Figure 1. A core outcome set for pre-eclampsia.

- Maternal mortality
- Eclampsia
- Stroke
- Cortical blindness
- Retinal detachment
- Pulmonary oedema
- Liver capsule haematoma
- Abruption
- Raised liver enzymes
- Low platelets
- Intubation and mechanical ventilation
- Stillbirth
- Neonatal mortality
- Small for gestational age

Table 1. International and national stillbirth definitions.(5)

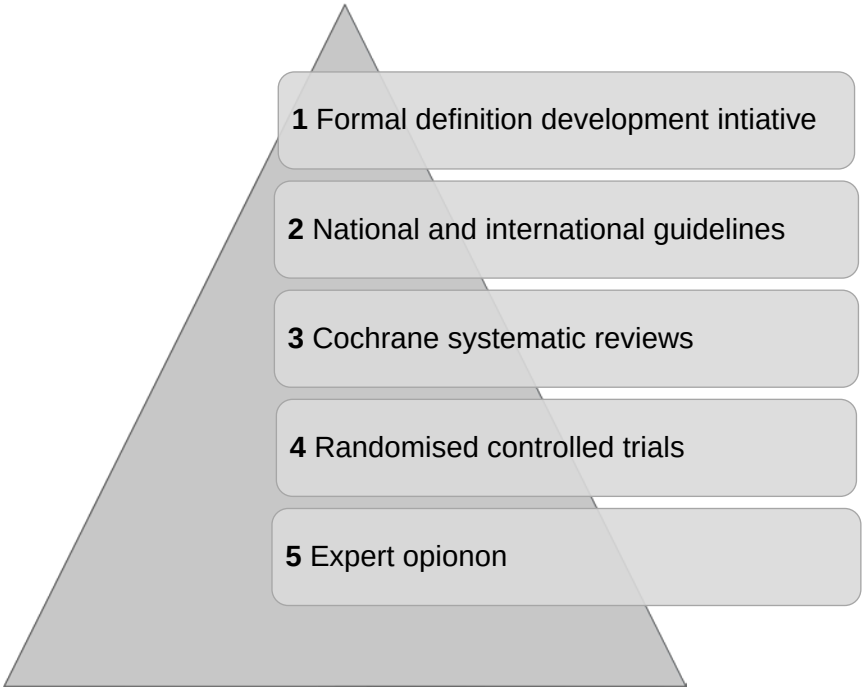
Stillbirth definition	Gestational age	Birth weight	Crown-heel height
International definitions			
World Health Organization	≥ 28 weeks + 0 / 7 days	≥ 1000 grams	≥ 35 cm
Europe	≥ 22 weeks + 0 / 7 days		
National definitions			
Australia	≥ 20 weeks + 0 / 7 days	≥ 350 grams	
United Kingdom	≥ 24 weeks + 0 / 7 days		
United States			
ACOG	≥ 20 weeks + 0 / 7 days	≥ 350 grams	
CDC	≥ 20 weeks + 0 / 7 days	≥ 350 grams	
SCRN	≥ 20 weeks + 0 / 7 days	≥ 400 grams	

Abbreviations. ACOG: American College of Obstetricians and Gynaecologists. CDC: Centre for Disease Control and Prevention. cm: centimetres. SCRN: Stillbirth Collaborative Research Network.

Supported by the EGA Hospital Charity Travelling Fellowship in Memory of Anne Boutwood, this study has developed standardised definitions relevant to lower resource settings in co-operation with the Department of Reproductive Health and Research, World Health Organization, Geneva.

To inform decision-making the potential definitions were inventoried across formal definition development initiatives, national and international guidelines, Cochrane systematic reviews, and randomised controlled trials (Figure 2).

Figure 2. Definition hierarchy: a framework for evaluating potential definitions for individual core outcomes.



Potential definitions were entered into a series of consensus development workshops. Each workshop included healthcare professionals, researchers, and women with lived experience of pre-eclampsia with experience of healthcare delivered in lower resource settings. At the start of each meeting the inventory of definitions were presented to the decision-making group. Participants were encouraged to ask questions and discuss the potential definitions during an informal group discussion. Although the group were encouraged to reach a consensus, participants were empowered to include minority or alternative views where consensus could not be achieved. Consensus definitions were developed for all core outcomes (Table 2).

Table 2. Consensus definitions for core outcomes.

Maternal core outcomes	**Hierarchy level**	**Outcome definition**
Maternal mortality	1	Death of a woman while pregnant or within 42 days after the end of pregnancy
Eclampsia	5	Onset of convulsions* in a woman with pre-eclampsia not attributable to other causes. (*Interchangeable terminology: fits, generalised convulsions, tonic-clonic seizure, and seizure.)
Stroke	4	Acute symptoms of focal brain injury that have lasted over 24 hours.
Cortical blindness	4	Visual impairment in the presence of intact papillary response to light.
Retinal detachment	5	A condition in which the retina peels away from its underlying layer of support tissue diagnosed by ophthalmological exam.
Pulmonary oedema	4	Clinical diagnosis of excess fluid in the lungs requiring directive treatment.
Liver capsule haematoma	4	Blood collection under the hepatic capsule as confirmed by diagnostic imaging or laparotomy.
Abruption	1	Vaginal bleeding in the second or third trimester with signs of hypovolemic shock or coagulopathy.
Raised liver enzymes	2	Elevated transaminases at least twice upper limit of normal.
Low platelets	1	An acute reduction in the number of platelets in the blood to below 100,000 platelets/ml.
Intubation and mechanical ventilation	4	Intubation by ventilation, endotracheal intubation tube, or continuous positive airway pressure.
Stillbirth	1	Gestational age over 22+0 and / or birth weight over 500g and / or crown-heel length over 25cm.
Neonatal mortality	1	Death of a live born infant before 28 completed days of life.
Small for gestational age	1	Weight below 10th percentile for gestational age as assessed against a validated global, regional, or local standard.

Embedding the core outcome set within future clinical trials, systematic reviews, and clinical practice guidelines should make a profound contribution to advancing the usefulness of research to inform clinical practice, enhancing patient care, and improving maternal and neonatal outcomes.(3)

The Core Outcomes in Women's and Newborn Health initiative, supported by over 80 speciality journals, including the Cochrane Pregnancy and Childbirth Group, has resolved to implement this core outcome set.(3) Participating journals will require authors to report core outcomes within trial reports and offer conclusions based on these outcomes. Where core outcome sets have not been collected the authors will be asked to report this deficiency and its implications for their findings.

International and national research funding bodies, including the National Institute for Health Research and European Union, have committed to implementing core outcome sets and ensuring researchers are funded to collect and report core outcomes. Researchers committing to creating harmony in outcome collection and reporting will be secure in the knowledge that journal editors will not penalise them. Over time research consumers, including healthcare professionals, researchers, and patients, should become accustomed to reviewing complete core outcome sets in trial reports. As a result, the temptation for selective reporting based on statistical significance could be substantially reduced.

References

1. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The Classification, Diagnosis, and Management of the Hypertensive Disorders of Pregnancy: A Revised Statement from the ISSHP. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2014;4(2):97-104.
2. Duffy JMN, Hirsch M, Kawsar A, Gale C, Pealing L, Plana MN, et al. Outcome Reporting Across Randomised Controlled Trials Evaluating Therapeutic Interventions for Pre-eclampsia. BJOG: An International Journal of Obstetrics and Gynaecology. 2017;124(12):1829-39.
3. Duffy JMN, Rolph R, Gale C, Hirsch M, Khan KS, Ziebland S, et al. Core Outcome Sets in Women's and Newborn Health: A Systematic Review. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(10):1481-9.
4. Duffy JMN, van 't Hooft J, Gale C, Brown M, Grobman W, Fitzpatrick R, et al. A protocol for developing, disseminating, and implementing a core outcome set for pre-

eclampsia. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2016;6(4):274-8.

5. Da Silva FT, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data(). Vaccine. 2016;34(49):6057-68.