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Outcome reporting across randomised controlled trials evaluating therapeutic interventions for pre-eclampsia: a systematic review.

James M N Duffy[1], Martin Hirsch[2,3], Anusuya Kawsar[3], Chris Gale[4], Louise Pealing[1], Maria N Plana[5], Marian Showell[6], Paula R Williamson[7], Khalid S Khan[2], Sue Ziebland[1], Richard J McManus[1]

On behalf of iHOPE: International Collaboration to Harmonise Outcomes in Pre-Eclampsia (*steering committee listed at the end of manuscript).

[1] Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom.

[2] Women's Health Research Unit, The Blizard Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom.

[3] Royal Free London NHS Trust, London, United Kingdom.

[4] Faculty of Medicine, Department of Medicine, Imperial College London, London, United Kingdom.

[5] Clinical Biostatistics Unit, Ramon y Cajal Institute of Research and Centro de Investigación Biomédica en Red Epidemiology and Public Health, Madrid, Spain.

[6] Cochrane Gynaecology and Fertility Group, University of Auckland, Auckland, New Zealand.

[7] MRC North West Hub for Trials Methodology Research, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom.

Correspondence to:

Dr James M N Duffy MBChB MRes BSc (Hons) PG HCL

Balliol College, University of Oxford, Oxford OX1 3BJ, United Kingdom

+44 (0)1865 289298

www.phc.ox.ac.uk/jamesduffy

james.duffy@balliol.ox.ac.uk

@jamesmnduffy

Running title: Outcome reporting in pre-eclampsia trials.

Abstract

Background: Standardising outcome collection and reporting in pre-eclampsia trials requires an appraisal of current outcome reporting.

Objectives: To map maternal and offspring outcome reporting across randomised trials evaluating therapeutic interventions for pre-eclampsia.

Search strategy: Randomised trials were identified by searching bibliographical databases from inception to January 2016.

Selection criteria: Randomised controlled trials.

Data collection and analysis: We systematically extracted and categorised outcomes reporting.

Main results: Seventy-nine randomised trials, reporting data from 31,615 maternal participants and 28,172 of their offspring, were included. Fifty-five different interventions were evaluated. Included trials reported 119 different outcomes, including 72 maternal outcomes and 47 offspring outcomes. Maternal outcomes were inconsistently reported across included trials, for example, 11 (14%) trials reported maternal mortality, reporting data from 12,422 participants (39%), and 16 (20%) trials reported cardiovascular morbidity, reporting data from 14,963 maternal participants (43%). Forty-three (54%) trials reported fetal outcomes and 23 (29%) trials reported neonatal outcomes. Twenty-eight trials (35%) reported offspring mortality. There was poor reporting of childhood outcomes: six trials (8%) reported neurodevelopmental outcomes. Less than half of included trials reported any relevant information regarding harms for maternal participants and their offspring.

Conclusions: Most randomised trials evaluating interventions for pre-eclampsia are missing information on clinically important outcomes and in particular have neglected to evaluate efficacy and safety in the offspring of participants. Developing and implementing a minimum core data set, known as a core outcome set, in future pre-eclampsia trials could help to address these issues.

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Key words: (1) Core outcome set; (2) Outcome reporting bias; (3) Pre-eclampsia; and (4) Systematic review.

Tweetable abstract: Future #preeclampsia research requires a core outcome set to reduce #research waste. @coreoutcomes

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Introduction

Pre-eclampsia is associated with significant maternal and offspring mortality and morbidity, especially in cases where severe features are present.[1] Therapeutic interventions which reduce this health burden require robust evaluation.

While much attention has been paid to standardising randomised controlled trial methods, the selection, collection, and reporting of outcomes has been largely overlooked.[2] Selecting appropriate outcomes to reflect both beneficial and harmful effects is a critical step in designing randomised trials. Such outcomes need to be relevant to clinical practice and key stakeholders, including patients, healthcare professionals, and researchers. For example, significant maternal morbidity is likely to be important outcomes for all but may not be collected. Evidence synthesis can be limited by different methods of measurement or definition, even when outcomes have been consistently collected across trials. For example, severe pre-eclampsia has been defined using different combinations of blood pressure thresholds, proteinuria thresholds, clinical symptoms, placental parameters, and fetal parameters.[1]

No consensus regarding a minimum data set currently exists in pre-eclampsia, therefore, we mapped maternal and offspring outcome reporting across randomised trials evaluating therapeutic interventions for pre-eclampsia.

Methods

We developed a protocol with explicitly defined objectives, including criteria for study selection, approaches to assessing study quality, as well as primary and secondary outcomes, and statistical methods. We registered the protocol with PROSPERO: International Prospective Register of Systematic Reviews, registration number CRD42014010641. We followed the reporting guidelines for meta-analyses and systematic reviews of randomised controlled trials, as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[3]

Randomised controlled trials were identified by searching: (1) Cochrane Central Register of Controlled Trials, (2) MEDLINE, (3) EMBASE, (4) PsycINFO, and (5) Cumulative Index to Nursing and Allied Health Literature from the inception of the database to January 2016 (Appendix S1 and S2). Two authors independently performed the screening of each potentially relevant record based on title and abstract and independently reviewed the full text of each selected study to assess eligibility. Discrepancies between the authors were resolved through discussion.

We included randomised controlled trials that evaluated the efficacy of therapeutic intervention for pre-eclampsia. We did not exclude trials in mixed populations of antenatal or postnatal patients with chronic hypertension, gestational hypertension or pre-eclampsia. We applied no restrictions for languages or publication date and translated two trial reports.[4, 5]

Using a standardised data extraction form, two authors independently extracted study characteristics including participants, interventions, and outcomes. Discrepancies between authors were resolved through discussion. A comprehensive inventory of outcomes was developed. We initially organised outcomes into five broad categories: maternal, fetal, neonatal, childhood and other outcomes. We subsequently organised these data into individual domains, in consultation with healthcare professionals, researchers, and patients. The harm domain included adverse events as defined within the British National Formulary. [6] We used descriptive statistics to characterise our included trials, mapping the availability of maternal and offspring outcomes across included trials.

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Results

We discovered 10,720 records. After excluding 3,627 duplicate records, 7,093 titles and abstracts were screened. Two independent reviewers evaluated 162 potentially relevant studies. Seventy-nine randomised trials reporting data from 31,615 maternal and 28,172 of their offspring met our inclusion criteria (Figure 1). [4, 5, 7-90] Included trials evaluated 55 different interventions of which 29 (37%) evaluated antihypertensive medication and 21 (27%) anticonvulsant medication (Table S1). The remaining 29 (37%) trials, evaluated a range of interventions including immediate delivery (six trials), anti-oxidants (six trials), and curettage (two trials). Eleven trials (14%) evaluated post-natal interventions.

Included trials reported 119 different outcomes, of which 72 were maternal outcomes and 47 offspring outcomes. These outcomes were organised in consultation with health care professionals, researchers, and patients into 28 outcome domains, including 15 maternal domains and 13 offspring domains (Figure 2). Included trials inconsistently reported morbidity and mortality outcomes (Table 1). Of the 79 included trials, reporting data from 31,615 maternal participants, 11 trials reported maternal mortality (reporting data from 12,422 (39%) participants); 16 trials reported cardiovascular morbidity (reporting data from 14,963 (43%) participants); and nine trials reported infectious morbidity (reporting data from 11,749 (37%) participants). When considering the largest 25 included trials, rates of eclampsia were reported by 20 trials (80%), renal failure by eight trials (32%), and disseminated intravascular coagulopathy by eight trials (32%) (Table 2).

Twenty-eight trials (35%) reported offspring mortality, reporting data from 25,839 offspring of participants (92%). Forty-three trials (54%), reporting data from 23,848 offspring of participants, reported fetal outcomes, and 23 trials (29%), reporting data from 24,227 of offspring participants (86%), reported neonatal outcomes (Table 1).

When considering the largest 25 included trials, intraventricular haemorrhage by six trials (24%), bronchopulmonary dysplasia was reported by two trials (8%), and necrotising enterocolitis by five trials (6%) (Table 2). There was poor reporting of childhood outcomes: six trials, reported neurodevelopmental outcomes reporting data from 18,783 offspring of participants. The longest duration of follow-up was two years.

Twenty-eight trials included no data related to harms from 15,838 maternal participants and 13,438 of their offspring. Three trials performed an economic evaluation.

Discussion

Main findings

This systematic evaluation of the literature in pre-eclampsia illustrates widespread variation in the reporting of maternal, fetal, neonatal, and childhood outcomes in randomised trials. Of 79 randomised trials reporting data from 31,615 maternal and 28,172 of their offspring, fewer than 20% reported information on maternal mortality and less than a third reported information on offspring mortality. For childhood outcomes, including long term neurodevelopmental outcomes, less than a tenth of included trials reported any relevant information. Less than half of included trials reported any relevant information related to harms.

Strengths and limitations

The strengths of this prospectively registered systematic review include its comprehensive search strategy, methodological design, and statistical analysis. To our knowledge, this is the first systematic review to describe outcome reporting in obstetric trials. In order to prevent bias in the review process, the search was guided and developed by an experienced Cochrane Collaboration information specialist with no limitations (such as language or date restrictions) applied. We translated two trial reports. Study selection, data extraction, and methodological and outcome quality assessment were conducted independently by two authors.

Our empirical evaluation has some limitations. We included only randomised trials and so may have missed infrequent outcomes often reported in observational studies. By undertaking a systematic review of randomised trials, it is challenging to draw any firm conclusions regarding patient preferred outcomes. Further research utilising qualitative research methods, including semi-structured patient interviews, is required. The majority of trials were performed within high-resource settings, if the outcomes were entered into a modified Delphi method to determine a core outcome set, it may be less applicable to middle and low resource settings.

Interpretation

Randomised trials can be difficult and expensive to conduct and so there is an ethical imperative to make the best use of them.[91] These results suggest a lost opportunity in trials of pre-eclampsia, with only a minority reporting outcomes concerning morbidity and mortality and even fewer considering long term effects for offspring. Such deficits may lead to misleading results if these outcomes differ systematically between trials that do or do not report them.[92-94]

Over the past three decades, the outlook of pre-eclampsia research has widened, with long term childhood follow up becoming increasingly prioritised by patients, healthcare professionals, and researchers. Few pre-eclampsia trials have followed up offspring participants for sufficiently long to understand the beneficial and harmful effects of experimental interventions. As the importance of assessing long-term outcomes gains increasing momentum, challenging decisions with regards to the selection of long term outcomes, follow-up durations, and methods need to be made. Conducting long term follow up is costly and time consuming for researchers and impacts patients and their families.[95] We must be confident that long term follow-up is useful and justified. There is currently no consensus as to which outcomes are most important to measure, which definition or instrument should be used, and whether outcome measures remain valid regardless of the time point of measurement.

Several systematic reviews have highlighted the inconsistency in outcome reporting across obstetrics and gynaecology.[96-98] The Core Outcomes in Women's and Newborn Health (CROWN) initiative (www.crown-intative.org), aims to facilitate

consistent recording and reporting of outcomes across 84 journals, working closely with funders, healthcare professionals, researchers, and patients.[99] This requires robust methods to identify appropriate outcomes.[100] The Core Outcome Measures for Efficacy Trials (COMET) initiative has performed a systematic review of methods for the derivation of core outcome sets across diverse disciplines and suggests three broad stages: (1) identifying potential core outcomes; (2) determining core outcomes using robust consensus methods engaging key stakeholders; and (3) determining how core outcomes should be measured.[101] Several consortiums have been established developing core outcome sets across a broad range of healthcare conditions relevant to women's health.[102, 103]

An international steering group, including healthcare professionals, researchers, and patient representatives, has been formed to guide the development of a core outcome set for pre-eclampsia including maternal, offspring, and long term outcomes.[104] The inventory of outcomes identified by this systematic review and outcomes identified by analysing in-depth qualitative patient interviews have been entered into a modified Delphi method. Key stakeholders, including healthcare professionals, researchers, and patients have participated in a multi-perspective online Delphi survey.[105] The modified Delphi method has encouraged convergence towards consensus 'core' outcomes.[105, 106 107]

Conclusion

Randomised trials evaluating interventions for pre-eclampsia have reported many different outcomes. Most randomised trials evaluating interventions for pre-eclampsia miss information on clinically important outcomes and neglect to evaluate their efficacy and safety in the participants' offspring, particularly over the long term. Such variations contribute to an inability to compare, contrast, and combine individual studies and limit the usefulness of secondary research to inform shared decision making. Developing and implementing a clinically relevant core data set, in future pre-eclampsia trials could help to address these issues.

International Collaboration to Harmonise Outcomes in Pre-eclampsia (iHOPE) Steering Group

James M. N. Duffy (Balliol College, University of Oxford); Janneke van 't Hooft (Academical Medical Centre, Amsterdam, Netherlands); Chris Gale (Imperial College London, London, United Kingdom); Mark Brown (St George and Sutherland Hospitals, Kogarah, Australia); William Grobman (Northwestern University, Chicago, United States); Ray Fitzpatrick (University of Oxford, Oxford, United Kingdom); S. Ananth Karumanchi (Harvard Medical School, Boston, Untied States); Nuala Lucas (Obstetric Anaesthetists' Association, London, United Kingdom); Laura Magee (St George's, University of London, London, United Kingdom); Ben Mol (University of Adelaide, Adelaide, Australia); Michael Stark (University of Adelaide, Adelaide, Australia); Shakila Thangaratinam (Queen Mary, University of London, London, United Kingdom); Mathew Wilson (University of Sheffield, Sheffield, United Kingdom); Peter von Dadelszen (St George's, University of London, London, United Kingdom); Paula R. Williamson (University of Liverpool, Liverpool, United Kingdom); Khalid S. Khan (Queen Mary, University of London, London, United Kingdom); Sue Ziebland (University of Oxford, Oxford, United Kingdom); and Richard J. McManus (University of Oxford, Oxford, United Kingdom).

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Conflicts of interest

R.J.M has received blood pressure monitors for research from Omron and Lloyds Pharmacies and expenses and honoraria for speaking from the Japanese Society of Hypertension and the American Society of Nephrology. The remaining authors declare no competing interests. The ICMJE disclosure forms are available as online supporting information.

Author contributions

JMD and MNP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: JMD, PRW, KSK, SZ, RMcM. Acquisition of data: JMD, MH, AK, LP, MS. Analysis and interpretation of data: JMD, MH, CG, MNP, PRW, KSK, SZ, RMcM. Drafting of the manuscript: JMD, CG, KSK, SZ, RMcM. Critical revision of the manuscript for important intellectual content: MH, AK, CG, LP, MNP, MS, PRW. Statistical analysis: MNP. Obtained funding: JMD, PRW, KSK, SZ, RMcM. Administrative, technical, or material support: PRW, MS. Study supervision: JMD, PRW, KSK, SZ, RMcM.

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Table 1. Maternal and offspring outcome domains reported by randomised trials evaluating therapeutic interventions for pre-eclampsia.

Domain	Outcomes	Randomised trials	Maternal participants	Offspring participants
	n	n	n	n
All domains	**119**	**79**	**31,615**	**28,172**
Maternal mortality	1	11	12,422	
Offspring mortality	1	28		25,839
Maternal outcomes	**71**	**79**	**31,615**	
Cardiovascular morbidity	8	16	14,963	
Coagulation / haematological morbidity	2	11	14,747	
Gastrointestinal morbidity	3	5	11,334	
Genitourinary morbidity	2	10	11,853	
Neurological morbidity	3	2	10,252	
Respiratory morbidity	3	15	13,405	
Psychological morbidity	2	1	164	
Infectious morbidity	1	9	11,749	

Pregnancy, childbirth, and the puerperium	10	40	28,651
Labour and delivery characteristics	6	40	26,254
Therapeutic interventions	9	25	24,490
Patient reported outcomes	5	4	370
Harm	13	43	15,777
Resource utilisation	4	29	26,467
Offspring outcomes			
Fetal outcomes	**6**	**43**	**23,848**
Neonatal outcomes	**22**	**23**	**24,227**
Cardiovascular morbidity	3	8	2,134
Coagulation / haematological morbidity	1	2	41
Gastrointestinal morbidity	4	11	2,388
Neurological morbidity	3	14	21,068
Respiratory morbidity	5	15	4,118
Infectious morbidity	1	8	1,954
Therapeutic interventions	5	11	22,307
Childhood outcomes	**6**	**6**	**18,783**

Neurological morbidity	5	6	18,783
Disorders of psychological development	1	2	18,655
Harm	8	43	14,734
Resource utilisation	4	29	25,042

Table 2. Maternal and offspring outcomes reported by the largest twenty-five randomised trials evaluating therapeutic interventions for pre-eclampsia.

				Maternal outcomes																Offspring outcomes: Fetal					Offspring outcomes: Neonatal												Offspring outcomes: Childhood						
Study	**Maternal participants**	Maternal mortality	Offspring mortality	Eclampsia	HELLP syndrome	Pulmonary oedema	DIC	Renal failure	Infectious morbidity	Premature separation of placenta	Postpartum haemorrhage	Onset of labour	Augment labour	Indication for delivery	Mode of delivery	Anticonvulsant medication	Antihypertensive medication	Thromboembolic disease	Other maternal outcomes	Fetal growth	Gestational age at delivery	Birthweight	Placental weight	Other fetal outcomes	Intraventricular haemorrhage	Respiratory distress syndrome	Bronchopulmonary dysplasia	Meconium aspiration	Necrotising enterocolitis	Hypotension	Infectious morbidity	Intubation	Hypoglycaemia	Persistent pulmonary hypertension	Periventricular leukomalacia	Other neonatal outcomes	Cognitive impairment	Hearing impairment	Motor impairment	Speech impairment	Visual impairment	Autism	Other childhood outcomes
Duley 2002	10141	•	•	•		•	•	•	•	•	•	•	•	•	•		•	•	•		•	•															•	•	•	•	•	•	•
CLASP 1994	9364	•	•	•						•	•	•	•	•		•	•	•	•	•	•	•			•											•	•	•	•	•	•	•	•
Lucas 1995	2138		•	•						•					•	•			•			•														•							
Belfort 2003	1650			•			•			•				•	•				•		•	•				•				•		•				•							
Duley 1995	910	•	•	•		•	•	•	•		•	•	•		•				•													•											
Koopmans 2009	756		•	•	•	•				•	•	•		•	•	•	•	•	•		•	•		•		•		•			•					•							
Broekhuijsen 2015	703	•	•	•	•	•				•		•	•	•	•			•							•	•		•	•		•	•	•		•	•							
Ragab 2013 *	420	•		•																																							
Vigil-De Gracia 2013	267	•	•	•	•	•	•	•		•				•	•		•		•	•	•	•			•	•			•				•			•							
Livingston 2003	222			•	•				•		•				•																												
Amorim 1999	218	•	•	•	•	•	•	•	•	•			•		•			•	•		•	•			•	•	•		•					•									
Ganzevoort 2005	211	•	•	•	•	•		•	•	•					•	•	•	•	•	•	•				•	•	•		•		•	•		•	•	•							
Ehrenberg 2006 *	200			•												•			•																								
Sibai 1992	200		•		•					•			•	•	•				•	•	•	•	•													•							
Vigil-De Gracia 2006	200		•	•	•	•	•	•		•			•	•	•		•			•	•	•			•				•	•						•							
Owens 2014	169			•	•																•															•							
Ascarelli 2005 *	164								•		•						•		•																								
Darngawn 2012 *	150			•												•	•		•																								
Hall 2000	150	•	•	•	•	•		•	•	•				•	•		•		•		•	•				•										•							
Maki 2000	146	•	•	•	•	•	•												•	•	•	•																					
Witlin 1997	135			•					•		•		•		•				•																								
Aali 2002	126																•		•		•																						
El-Qarmalawi 1995	120									•		•	•		•		•				•	•	•							•						•							
Wide-Swensson 1995	118		•									•	•	•							•	•	•													•							
Maia 2014 *	112	•		•		•	•	•			•							•	•																								

Abbreviations: HELLP Syndrome: Haemolysis, elevated liver enzyme levels, and low platelets syndrome; DIC: Disseminated intravascular coagulation. * Postnatal participants only.

Figure 1. Flow of included studies.

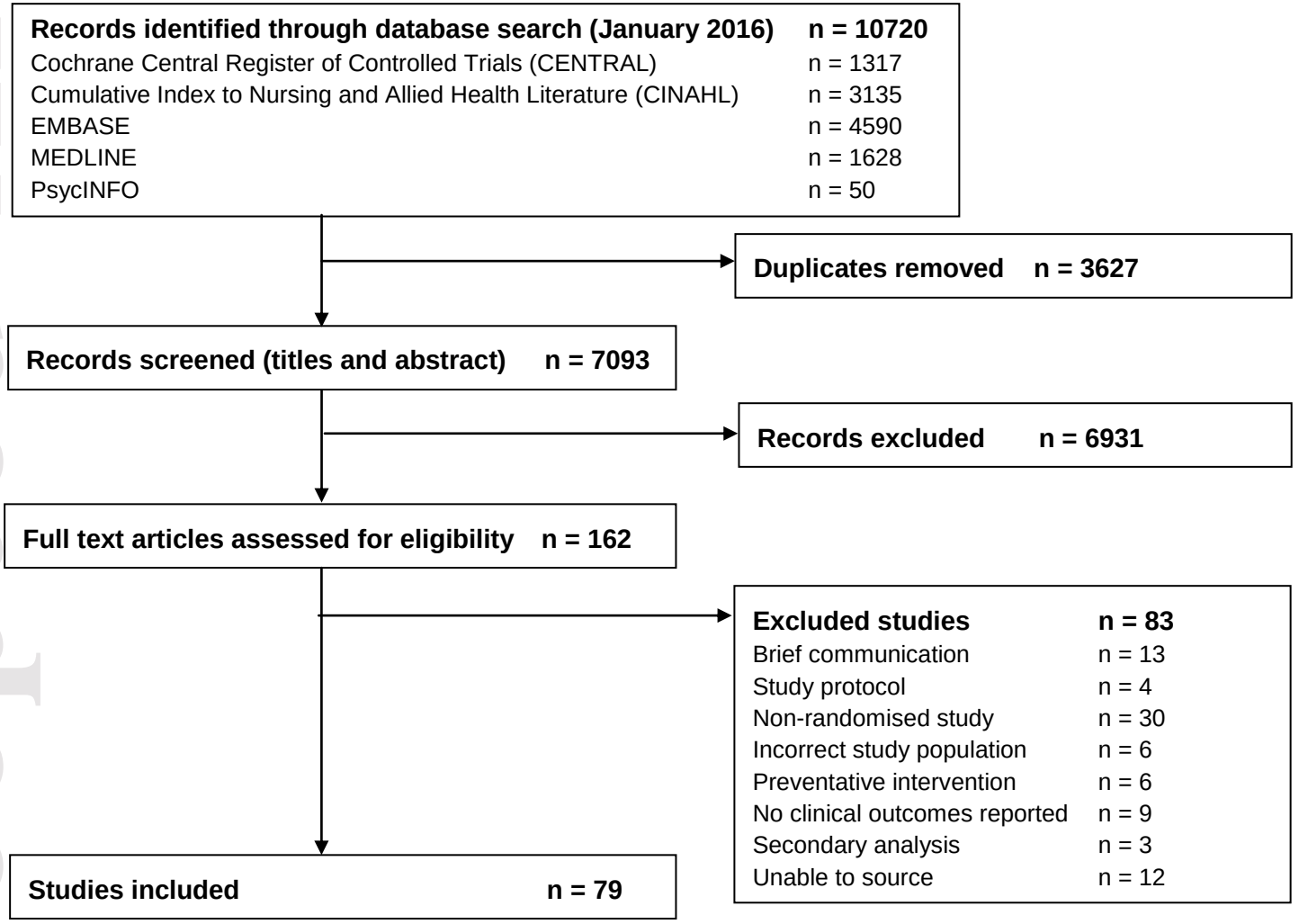

Figure 2. Maternal and offspring outcomes reported by randomised trials evaluating therapeutic interventions for pre-eclampsia.

Maternal outcomes

Maternal mortality

Cardiovascular morbidity
Acute myocardial infarction
Cardiac arrest
Cerebrovascular disease
Heart failure
Hypotension
Ischaemic heart disease
Pulmonary hypertension
Shock

Coagulation / haematological morbidity
Disseminated intravascular coagulation
Thromboembolic disease

Gastrointestinal morbidity
Liver haematoma
Hepatic failure
Hypoglycaemia

Genitourinary morbidity
Renal failure
Nephrotic syndrome

Neurological morbidity
Blindness
Coma
Encephalopathy

Respiratory morbidity
Pulmonary oedema
Respiratory arrest
Respiratory failure

Psychological morbidity
Anxiety disorder
Depressive episode

Infectious morbidity

Pregnancy, childbirth, and the puerperium
Antepartum haemorrhage
Eclampsia
HELLP syndrome [a]
Obstetric trauma
Postpartum haemorrhage
Premature rupture of membranes
Premature separation of placenta
Retained placenta
Ruptured uterus
Uterine atony

Labour and delivery characteristics
Onset of labour
Duration of labour
Augmented labour
Indication for delivery
Anaesthesia for delivery
Mode of delivery

Therapeutic interventions
Anticonvulsant medication
Antihypertensive medication
Blood product transfusion
Cardiopulmonary resuscitation
Hysterectomy
Manual removal of placenta
Mechanical ventilation
Other pharmacologic intervention
Renal dialysis

Patient reported outcomes
Anxiety
Comfort
Functional status
Pain
Well being

Resource utilisation
Admission to level two or three care
Length of stay
Readmission
Cost

Harm

Offspring outcomes

Offspring mortality

Fetal Outcomes

Fetal growth
Intrapartum trauma
Birth asphyxia
Gestational age at delivery
Birth weight
Placental weight

Neonatal Outcomes

Cardiovascular morbidity
Anaemia
Cardiac failure
Hypotension

Coagulation / haematological morbidity
Coagulopathy

Gastrointestinal morbidity
Hypoglycaemia
Intestinal obstruction
Necrotising enterocolitis
Neonatal jaundice

Neurological morbidity
Convulsions
Intraventricular haemorrhage
Periventricular leukomalacia

Respiratory morbidity
Bronchopulmonary dysplasia
Meconium aspiration
Persistent pulmonary hypertension
Respiratory distress syndrome
Respiratory failure

Infectious morbidity

Therapeutic interventions
Enteral or parenteral nutrition
Breastfeeding
Non-invasive respiratory support
Intubation
Mechanical ventilation

Childhood Outcomes

Neurological morbidity
Cognitive impairment
Hearing impairment
Motor impairment
Speech impairment
Visual impairment

Disorders of psychological development
Autism

Resource utilisation
Admission to level two or three care
Length of stay
Readmission
Cost

Harm

Abbreviation: Haemolysis, elevated liver enzyme levels, and low platelets.