

# **Inadequate safety reporting in pre-eclampsia trials. A systematic evaluation.**

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## **Running title:**

Safety reporting in pre-eclampsia trials.

## Abstract

**Background:** Randomised trials and their syntheses in meta-analyses offer a unique opportunity to assess the frequency and severity of adverse reactions.

**Objective:** To assess safety reporting in pre-eclampsia trials.

**Search strategy:** Systematic search using bibliographic databases, including Cochrane Central Register of Controlled Trials, Embase, and MEDLINE, from inception to August 2017.

**Selection criteria:** Randomised trials evaluating anticonvulsant or antihypertensive medication for pre-eclampsia.

**Data collection and analysis:** Descriptive statistics appraising the adequacy of adverse reaction and toxicity reporting.

**Main results:** We included 60 randomised trials. Six trials (10%) were registered with the International Clinical Trials Registry Platform, two registry records referred to adverse reactions, stating “*safety and toleration*” and “*possible side effects*” would be collected. Twenty-six trials (43%) stated the frequency of withdrawals within each study arm and five (8%) trials adequately reported these withdrawals. Adverse reactions were inconsistently reported across eligible trials: 24 (40%) reported no serious adverse reactions and 36 (60%) reported no mild adverse reactions. The methods of definition or measurement of adverse reactions were infrequently reported within published trial reports.

**Conclusions:** Pre-eclampsia trials regularly omit critical information related to safety. Despite the paucity of reporting, randomised trials collect an enormous amount of safety data. Developing and implementing a minimum data set could help to improve safety reporting, permitting a more balanced assessment of interventions considering the trade-off between the benefits and harms.

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**Keywords:** Adverse reactions, core outcome sets, outcome reporting bias, pre-eclampsia, and systematic review.

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## Introduction

One of the oldest medical principles is *above all, do no harm*.<sup>1</sup> Randomised controlled trials and their syntheses in meta-analyses offer a unique opportunity to assess the frequency and severity of adverse reactions.<sup>2, 3</sup> Almost invariably, these are considered as secondary outcomes. There is usually no predefined hypothesis concerning harms in trials, and in cases of rare adverse reactions their sample sizes are underpowered.<sup>3, 4</sup> Collection and reporting of adverse reactions has drawn limited attention in general: for example, the Consolidated Standards of Reporting Trials (CONSORT) statement published an extension for harm reporting, five years after the original statement.<sup>5</sup>

Consider the following scenario: A pharmaceutical company decides to develop a therapeutic intervention and applies for a license. A regulatory agency subsequently considers granting a license based on the benefit to harm balance. Following approval, a healthcare provider decides whether to offer it. Finally, a patient makes their decision as whether to receive the treatment or not.<sup>3</sup> Without high-quality data relating to the trade-off between benefits and harms in every stage of this process, suboptimal decisions may be made.

Pre-eclampsia causes significant morbidity with a substantial public health burden.<sup>6</sup> Evaluation of safety reporting in pre-eclampsia trials represents a unique opportunity to consider a common multisystem syndrome within the context of varied classes of pharmacologic interventions and laboratory defined toxicity.

## Objective

We assessed safety reporting in randomised controlled trials evaluating pharmacologic interventions for the treatment of pre-eclampsia.

## Methods

We developed a protocol, with explicitly defined objectives, criteria for study selection, and data extraction methods. 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.<sup>7</sup>

Randomised controlled trials were identified by searching: (1) Cochrane Central Register of Controlled Trials (CENTRAL), (2) Cumulative Index to Nursing and Allied Health Literature (CINAHL), (3) Embase, (4) MEDLINE, and (5) PsycINFO from the inception of the database to August 2017 (Appendix S1).

We included randomised trials evaluating anticonvulsant medication or antihypertensive medication for pre-eclampsia. We applied no language restrictions and translated trial reports. We excluded pseudorandomised trials and non-randomised studies.

Using a pilot-tested and standardised data extraction form, two researchers independently extracted study characteristics including participants, interventions, and safety reporting. Discrepancies between researchers were resolved through discussion.

We extracted information pertaining to the trial's prospectively registered trial registry record. The registry record was reviewed and adverse reactions were extracted.

We extracted the reporting of withdrawals and discontinuations of study treatment due to adverse reactions. We defined adequate reporting as reporting the number of patients withdrawn from the study because of adverse reactions per study arm and its definition or instrument of measurement.

We assessed the adequacy of safety reporting using a predefined criterion.

Two researchers independently extracted adverse reactions listed in the British National Formulary 72 (September 2016 – March 2017) for individual pharmacologic interventions.<sup>8</sup> In consultation with healthcare professionals, researchers, and women with lived experience of pre-eclampsia we classified the severity of adverse reactions by applying established criterion.<sup>9</sup> A mild adverse reaction was defined as *any untoward and unintended response to an investigational medicinal product which is related (a reasonable causal relationship) to any dose administered.*<sup>9</sup> A serious adverse reaction was defined as *any adverse reaction which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity.*<sup>9</sup> We defined adequate reporting of adverse reactions as providing the number of specific adverse effects per study arm and its definition or instrument of measurement. Laboratory toxicity was defined as acute medication poisoning confirmed by laboratory investigations.<sup>10</sup> We defined adequate reporting of laboratory defined toxicity as providing the number

of participants affected per study arm and reporting the specific numerical value defining toxicity.

We used descriptive statistics to characterise eligible trials, evaluating the reporting of adverse reactions and laboratory defined toxicity, and the adequacy of definition or measurement.

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## Results

We identified 10,898 records. After excluding 4,417 duplicate records, 6,481 titles and abstracts were screened. Two researchers independently evaluated 174 potentially relevant studies. Sixty randomised trials met our inclusion criteria (Figure 1).<sup>11-70</sup> Thirty-six trials (60%) evaluated antihypertensive medication, 23 trials (38%) evaluated anticonvulsant medication, and a single trial<sup>18</sup> (2%) compared an antihypertensive medication, nimodipine, with an anticonvulsant medication, magnesium sulphate (Table S1).

Only six trials (10%) were prospectively registered with the International Clinical Trials Registry Platform.<sup>27, 37, 43, 51, 54, 58</sup> Two registry entries made reference to the collection of harms or adverse reactions stating “*safety and toleration*” and “possible side effects and intolerance” would be reported as secondary outcomes.

Of 60 eligible trials, 26 (43%) stated the frequency of withdrawals within each study arm. Five trials (8%) adequately reported these events. Adverse reactions were inconsistently reported across eligible trials: 24 (40%) reported no serious adverse reactions and 36 (60%) reported no mild adverse reactions.

When considering the 23 included trials evaluating magnesium sulphate for seizure prevention and treatment in women with pre-eclampsia, 20 trials reported severe adverse reactions (Table 1). Commonly reported serious adverse reactions included respiratory depression (15 trials), hypotension (12 trials), and loss of tendon reflexes (11 trials). A single trial adequately reported serious adverse reactions. Fifteen trials reported mild adverse reactions, including flushing of skin (eight trials) and nausea or vomiting (eight trials). No trials adequately reported their mild adverse reactions. Nine trials reported laboratory defined toxicity.

When considering the 15 included trials evaluating beta-adrenoceptor blockers for the treatment of hypertension in women with pre-eclampsia, eight reported serious adverse reactions and eight reported mild adverse reactions (Table 2). Hypotension was the only commonly reported serious adverse reaction (eight trials) and headache was the only commonly reported mild adverse reaction (eight trials). There was limited reporting of mild adverse reactions. The reporting of adverse reactions was consistently inadequate.

When considering the 13 included trials evaluating calcium channel blockers for the treatment of hypertension in women with pre-eclampsia, seven trials reported



hypotension (Table 3). Six trials reported mild adverse reactions. There was limited reporting of mild and serious adverse reactions. The reporting of adverse reactions was consistently inadequate.

## **Discussion**

### **Main findings**

Our systematic evaluation has demonstrated widespread variation in safety reporting across pre-eclampsia trials, with the extent of neglect varying considerably. A minority of trials reported the frequency of withdrawals within each study arm, with only three trials adequately reporting the reasons. A third of trials reported no serious adverse reactions and over half of trials reported no mild adverse reactions. No serious adverse reactions were consistently reported across trials evaluating pharmacologic interventions within the same class. When adverse reactions were reported, their methods of definition or measurement were infrequently reported.

### **Strengths and limitations**

To our knowledge, this is the first systematic review to evaluate safety reporting in obstetric trials. To prevent bias in the review process, study selection, and data extraction were conducted independently by at least two researchers. Our evaluation has some limitations. We investigated a single disease area and further studies would be needed to confirm that these results are generalisable across all obstetric trials. To further reduce bias, we could have considered blinding reviewers by removing the authors, journal, and year of publication from the trial reports before assessment. Examining adverse reaction reporting and its relationship with other factors including journal impact factor and commercial funding could provide

additional insight.<sup>71</sup> However, no validated outcome reporting quality assessment tool exists, limiting our ability to undertake this analysis. Three trials (5%) were published in the 1980s and 25 trials (42%) were published in the 1990s. Adverse reactions known in 2017 may have differed or may not have been evident when considering these trials.

## Interpretation

Despite the paucity of reporting, randomised trials collect an enormous amount of safety data including mortality, significant disability, and birth defect.<sup>3, 72</sup> Authors should be discouraged from not reporting adverse reactions.<sup>23</sup> Individual studies should collect and fully report adverse reactions, including zero events.<sup>73</sup> If the final published randomised trial report does not explicitly state a mild, moderate, or life-threatening adverse reaction did not occur, any future assumption that they were absent is likely to be correct but may not be secure. Combining individual trials, including zero events, within a meta-analysis would potentially allow adverse reactions to be well evaluated. The selective reporting of such data is a cause for concern.<sup>2</sup> Outcome reporting bias is defined as the selection for publication of a subset of the originally recorded outcome variables on the basis of the results. Over 75% of Cochrane reviews contain at least one trial at high risk of outcome reporting bias in relation to their primary harm outcome.

Robust reporting of adverse reactions, increasingly prioritised by healthcare professionals, researchers, and patients, should support shared decision making when considering the trade-off between the benefits and harms.<sup>53</sup> The responsibility to ensure comprehensive reporting of harms lies with authors of research and

publishing journals. The Consolidated Standards of Reporting Trials (CONSORT) group recommends that safety reporting is addressed in all sections of a journal article (albeit having originally ignored it).<sup>5, 73</sup> Emphasis is placed on the methods and results sections since adequate reporting in these areas is necessary for critical appraisal.<sup>3, 23</sup> We recognise that journals have limited space which can lead to selective outcome reporting and we would advocate the use of online supplementary information and automatic sharing of published data in public databases to facilitate comprehensive safety reporting.<sup>3, 74</sup>

When serious adverse reactions are rare it is particularly important that all sources of utilised. The 2011 European Union Directive on good pharmacovigilance practices emphasised the important role of healthcare professionals and patients should play, stating “*pharmacovigilance should be based on the crucial role of healthcare professionals in monitoring the safety of medicines, and should take account of the fact that patients are also well placed to report suspected adverse reactions to medical products*”.<sup>75</sup> Researchers should not lag behind this broader initiative to improve adverse reaction reporting.

Improving safety reporting in pre-eclampsia trials would ensure important information is available to guide regulators, healthcare funders, healthcare professionals, and women with pre-eclampsia in making decisions about treatments. One means to standardise the collection and reporting of adverse reactions in pre-eclampsia trials is to develop a core outcome set. The Core Outcomes in Women’s and Newborn Health (CROWN) initiative, a consortium of 84 specialty journals, including *BJOG: An International Journal of Obstetrics and Gynaecology*, has been formed to tackle

the challenge of addressing the unwarranted variation in outcome collection and reporting.<sup>76-78</sup> Core outcome sets are minimum sets of outcomes that can be measured and subsequently reported in a standardised manner.<sup>79</sup> Several consortiums, including the International Collaboration to Harmonise Outcomes in Pre-eclampsia (iHOPE), have been established to develop core outcome sets across our specialty.<sup>4, 80-86</sup>

The first step in developing a core outcome set is to generate a long list of potential core outcomes by mapping outcomes reported in published trial reports.<sup>87</sup> A systematic review has been undertaken mapping outcomes across pre-eclampsia trials, however, adverse reactions were pooled into a single domain, labelled harm.<sup>88</sup> Pooling adverse reactions within a domain is a common strategy deployed by core outcome set developers, as individual pharmacological classes are associated with different adverse reactions. Developing a core outcome set for adverse reaction collection and reporting, could be achieved by the selection and prioritisation of adverse reactions within individual pharmacological classes. With reference to established frameworks, possible pharmacologic interventions should be mapped to their corresponding pharmacological classes. A long list of possible adverse reactions would be generated for individual pharmacological classes. Each long list would be entered into a consensus process to identify consensus “core” adverse reactions. Future implementation would ensure researchers would be able to collect and report efficacy outcomes, common to all pre-eclampsia trials, and adverse reaction outcomes, specifically for the experimental intervention being evaluated.

## **Conclusion**

In conclusion, randomised trials evaluating pharmacologic interventions for pre-eclampsia regularly omit critical information related to safety. Despite the paucity of reporting, randomised trials collect an enormous amount of safety data. Developing and implementing a minimum data set in future pre-eclampsia trials could help to improve reporting. Improvements in safety reporting would permit a more balanced assessment of interventions and enhance informed decision making when considering the trade-off between the benefits and harms.

### **International Collaboration to Harmonise Outcomes in Pre-eclampsia (iHOPE)**

#### **Steering Group**

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### **Conflicts of interest**

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

### **Author contributions**

Study concept and design: JMD. Acquisition of data: JMD, MH, and MS. Analysis and interpretation of data: JMD, MH, KSK, SZ, and RMcM. Drafting of the manuscript: JMD, KSK, SZ, and RMcM. Critical revision of the manuscript for important intellectual content: MH and LP. Obtained funding: JMD, KK, SZ, and RMcM. Administrative, technical, or material support: MS. Study supervision: JMD, KSK, SZ, and RMcM.

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