

1 Letter to the Editor, BJOG Exchange

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3 **Authors' reply re: Inadequate safety reporting in pre-eclampsia trials: a**

4 **systematic evaluation**

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6 We would like to thank Jana and colleagues for their interest in our recent study evaluating
7 safety reporting in pre-eclampsia trials.^{1,2} Their response highlights the unique opportunity
8 offered by randomised controlled trials, and their syntheses into meta-analyses, to assess
9 the frequency and severity of adverse reactions, including mortality, significant disability, and
10 birth defects.³ When considering interventions with narrow therapeutic interventions, under
11 reporting of adverse reactions could potentially cause substantial harm when experimental
12 interventions are implemented into routine clinical practice and limit the stimulus to
13 undertake future research.

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15 For example, when considering magnesium sulphate, Smith and colleagues illustrated the
16 variation in the frequency of respiratory depression reported in published pre-eclampsia trials
17 (0.8 to 8.2%).¹ Within clinical practice, lower estimates of toxicity could encourage less
18 emphasis being placed upon harms when discussing treatment with patients, decreased
19 vigilance when monitoring the sequential appearance of toxicity signs, and limit the
20 perceived need to train healthcare professionals in managing toxicity. Under-reporting could
21 also frustrate the future research agenda when considering the need for low-dose
22 magnesium sulphate regimens and underestimating the potential risks of high-dose regimens
23 recently proposed for obese and morbidly obese patients.

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25 We believe coordinated action is required to improve safety reporting in future research
26 evaluating treatments with narrow therapeutic windows or interventions associated with
27 substantial maternal or offspring harm, including magnesium sulphate, low molecular weight

28 heparin, and oral hypoglycaemic drugs. Developing core outcome sets, for individual
29 interventions, regardless of indication, would standardise the selection, collection, and
30 reporting of safety outcomes in future research.⁴ This would require a shift in the focus of
31 core outcome set developers from individual diseases to individual classes of
32 pharmacological interventions.

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34 Improvements in safety reporting in future research are only part of the solution. The 2011
35 European Union Directive on good pharmacovigilance practices emphasised the important
36 role healthcare professionals and patients should play, stating '*pharmacovigilance should be*
37 *based on the crucial role of healthcare professionals in monitoring the safety of medicines,*
38 *and should take account of the fact that patients are also well placed to report suspected*
39 *adverse reactions to medical products.*'

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41 Developing, disseminating, and implementing core outcome sets in future research and
42 engaging in good pharmacovigilance practices during routine clinical practice could drive
43 improvements in safety reporting which could permit a more balanced assessment of
44 interventions and enhance informed decision making when considering the trade-offs
45 between the benefits and harms.⁵

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47 Duffy JMN, Peeling L, McManus RJ on behalf of the International Collaboration to
48 Harmonise Outcomes for Pre-eclampsia (iHOPE)

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50 Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United
51 Kingdom.

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53 **References**

54 ¹ *Reference to letter to be added during production.*

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61 ⁴ Duffy JMN, Rolph R, Gale C, Hirsch M, Khan KS, Ziebland S, et al. Core outcome sets in
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