Reviewer’s report

Title: Development and validation of prediction models for risk of adverse outcomes in women with early onset pre-eclampsia: protocol of the prospective cohort PREP study

Version: 0 Date: 12 Aug 2016

Reviewer: Sally Lord

Reviewer's report:

This is a very well written protocol describing the PREP study rationale and methods for the development and validation of prediction models for risk of adverse maternal and fetal/neonatal outcomes in women with early onset pre-eclampsia.

I did not identify any major omissions or items for correction. I note the background and methods sections comply with the TRIPOD statement checklist items for study reporting on Introduction and Methods sections. The discussion provides a useful summary of points relevant for consideration of the study design.

As an epidemiologist who is involved in (and challenged by) the design of studies for the development and validation of tests and prediction models to guide clinical decisions, I found this paper to be valuable reading as an example of the application of current recommended methods for the development and validation of prediction models; and strategies for dealing with challenges such as treatment paradox as a source of bias, and missing data.

Some minor comments for the authors' consideration:

1. Background: The clinical need for improving pre-eclampsia outcomes is clearly stated in the background section. In describing the study rationale, I would also find it helpful to read a brief statement on the critical clinical management decision/s for pre-eclampsia that the risk model is proposed to inform. Paragraphs 2-3 and the discussion section suggest to me the need for a risk tool to inform the decision for delivery versus expectant care. Paragraph 4 implies the risk tool is proposed to inform the decision "for transfer from secondary to tertiary unit for more specialised care."

I note the discussion re-iterates that "accurate prediction and early management can significantly improve these outcomes." An explicit example in the background (or discussion section) of the type of management decision the risk model could inform, and potential benefits, to support this statement would be helpful for the reader who is not familiar with this clinical area.
2. Methods: Was there a clinical reason for selecting 48 hours as the initial time point for risk prediction? eg. to inform immediate management decision for transfer/steroids/delivery? If so - suggest include this information.

3. Discussion: The discussion section mentions the study will "obtain input from patient focus groups". I did not find information about the focus group in the methods section. I assume this is a separate component of a broader study plan - needs clarification.

4. General comment

If the critical clinical management decision/s the risk model is proposed to inform can be identified (= the clinical need for the model), then I would suggest it is also useful at the protocol stage to propose the risk (/treatment) threshold or risk range that may be considered acceptable to guide this decision, and plan to assess the clinical performance of the model to correctly classify patients ≤/≥ this risk threshold. However, I can appreciate it may be premature to discuss acceptable clinical decision thresholds with clinicians if relevant data on current clinical practice and adverse event rates have not been previously available to inform this discussion.

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