Author’s response to reviews

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

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Author’s response to reviews:
Reviewer #1: Allotey JA et al herein present a protocol for prospective cohort aimed at developing and validating a predicting risk of adverse outcomes in early onset pre-eclampsia. The project is of importance in its field and the article is well written. The authors have developed a well thought out protocol for the project. I think the article is acceptable for publication with some clarifications.

1. in Table 2, in candidate predictor variables - have you considered including the following variables: pre-existing proteinuria (in history), those presenting with single seizure (under examination) and evidence of hemolysis (e.g. haptoglobin, LDH) under labs --> which also be combined with ALT and platelet into HEELP syndrome as single predictor.

We identified the predictors based on systematic reviews of literature. Pre-existing proteinuria is observed in chronic renal disease, which is included as a predictor. Presentation of single seizure is used as a definition of pre-eclampsia, and with seizures as an outcome (eclampsia), we have refrained from including it as a predictor. We avoided where possible combination of predictors, to minimise loss of information.

2. in Table 3, under outcomes, authors indicate hepatic dysfunction and provide definition of DIC. Are the authors planning to combine definition of DIC and hepatic dysfunction together. Should you have two categories, one for hepatic dysfunction, defined by hepatic enzymes and perhaps albumin levels and INR; and another for DIC defined by fibrinogen level, INR, PTT, etc?

We identified the individual components of the composite outcome, based on Delphi survey in the previously published PIERS study. Furthermore, the model predicts composite and not individual outcomes.

3. Sample size calculations - authors rightly indicate they need to 10 events per variable plan to recruit 500 women to assess 10 predictor variables. After adding pre-term delivery in their outcomes, the authors increase their putative variables to 22. Do you expect that pre-term delivery rate will increase your event by 40%? One consideration in model building if you do not have sufficient number of events to fit all variables in the same model, may be to use forward stepwise model building approach.

We thank the reviewer for this suggestion. With inclusion of preterm birth as an outcome, we were expecting the event rate to be higher than 40%. 
4. In statistical analyses, authors indicate they will plan to do backward selection procedure as well as fractional polynomial procedure for non linear trends. Is the plan to perform backward selection first and then assess for non linear trend those selected variables using polynomial models? Or are you planning to assess each variable for polynomial trend simultaneously while doing backward selection?

We performed the backwards selection procedure first and then assessed for non-linear trends.

Reviewer #2: 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.

We thank the reviewer for their comment. We have added information to the background section to clarify the expected management based on the model as follows
‘Early identification of mothers with early onset pre-eclampsia at risk of complications…’ (Page 4, para 4)

We have also provided example of how the management decision might work based on the risk status of the patient in the background section (Page 4, para 4, line 4).

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.

The 48 hours’ time interval is chosen because 48 hours is needed prior to delivery after administration of steroids to minimise respiratory distress syndrome in the newborn. Furthermore, decisions on the place of delivery and utero transfer to tertiary units are needed within this time frame. We have provided details in the methods section as follows ‘The 48 hours’ time interval was chosen to reflect the time recommended for delivery after administration of steroids to lower risks of respiratory distress in new-borns...’ (Page 5, para 2)

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.

Yes, this is a broader study plan. Once the model has been developed and is available for use, we will obtain future funding to set up a focus group with patient and public stakeholders to inform on what is perceived to be a high risk by patients.

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.

We agree with the reviewer on the need to identify clinical decision threshold. However, that work is outside the scope of our current proposal.