Reviewer’s report

Title: External validation, update and development of prediction models for pre-eclampsia using an Individual Participant Data (IPD) meta-analysis: the International Prediction of Pregnancy Complication Network (IPPIC Pre-eclampsia) protocol

Version: 0 Date: 09 Jul 2017

Reviewer: Alfonso Iorio

Reviewer's report:

The manuscript describes the study protocol for a project aiming to identify an optimal approach to the management of risk of eclampsia. I can't honestly find a more "scientific" description of the scope, since the project includes a SR of existing models, their validation, eventual update, and, in case none is found to be "good enough", the derivation and validation of a new prognostic algorithm. The algorithm, furthermore, is expected to predict (as a single tool or as a group of tools) both any, early or late eclampsia.

As a result, the manuscript is very complex, with a lot of recursive parts (anticipation or posticipation of concepts), which prompt to non-linear and heavy reading.

Also, the manuscript, whereas clearly reflective the high methodological standard of the plan, is still very immature in the writing style, consistency, crispness. I understand this is not a final report, but a working protocol, however, I wonder whether it needs additional work to reach the level needed for publication. Many examples are provided below.

Specific comments:

The abstract need to be rewritten better focusing on decision rules; also, value of the network approach and related IPD can be better explained

Page 5, line 27: "and should be started on prophylactic aspirin to reduce adverse outcomes." Is this statement is based on ref 8? If so, please reference it here as well. If not provide a dedicated reference.

aggregate data (Review). Cochrane Database Syst. Rev. 2016;(9):MR000007), the first of which is an example on prognostics.

Page 7, line 41: "or the relevant preeclampsia outcomes are not studied" - please rephrase, not really clear.

Page 7, line 51: which models? The pre-existing, new or old?

Page 7, line 58: To study the added role of novel biomarkers on the accuracy of the developed models; what I think is meant is: To study the effect of adding novel biomarkers on the accuracy of the basic models newly developed on clinical predictors only.

Page 11, 39-44: using PROBAST is acceptable, but being it not yet published, suboptimal. Why not to use any of REMARK, TRIPOD, RIGOR (even if not formal RoB tools)

Page 18, line 5: "It is likely that the distribution of the C-statistic is not normally distributed as it is a proportion and therefore bounded by the value 1". Recommend rewording as: "It is likely that the distribution of the C-statistic is not normal as it is a proportion and therefore bounded by the value 1" or similar.

Page 18, line 55: A graph showing the observed (O) and expected E probabilities for groups of patient. Please add brackets around E.

Page 19, line 44: the C-statistic will be pooled on the logit scale, as the simulation study suggested these to be more appropriate scales for pooling in a meta-analysis. Why "these" plural? Is not the logit scale singular?

Page 20, line 59: measurement of predictor measurement - I understand what is meant, but it is really cacophonous. Can't you tell: characteristics (or modality and precision) of predictor measurements

Page 21, line 10: please define "reasonably well" - it is daunting that in paper with such high level of methodology, a quantity so relevant to the entire process is defined so lously. Maybe you assume you use the same criteria as described below, but then this needs to be specified.

Page 21, line 41; smaller studies performed in studies with different; maybe: smaller studies performed in populations/cohorts with different

Page 21, line 54: have good validation performance; is this "validation results"?

Page 22, line 1: If there are an adequate number of studies available; if there is?

Page 23, line 1: Updating (re-calibrating) existing prediction models; again, not quantitative set of decisions; please provide some stricter or better defined guidance.

Page 23, line 24: idem
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An article whose findings are important to those with closely related research interests

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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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