Author's response to reviews

Title: Individual Patient Data meta-analysis of diagnostic and prognostic studies in obstetrics, gynaecology and reproductive medicine.

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Author's response to reviews: see over
Dear Editor,

Thank you for reviewing again our revised manuscript (manuscript number 1228890694225857) entitled Individual Patient Data meta-analysis of diagnostic and prognostic studies in obstetrics, gynaecology and reproductive medicine that we have submitted for publication to BMC Medical Research Methodology. We have read the comments of the reviewers with interest and we have tried to adjust the manuscript accordingly.

Included you find an adjusted version of the manuscript. We used “track-changes” to reflect the adjustments that have been made in the revised manuscript.

Below we reply to each comment of the referees, and indicate whether and which adjustments were made in the manuscript.

Reviewer 1

The reviewer mentions the heading ‘Identification and selection of studies’ should remain, as the search strategy is critical. The references cited here as having identified the primary studies were all published in 2002. These searches are therefore not up to date, and a strategy for updating them should be outlined here.

We putted the heading concerned back in the manuscript and added a few sentences in which we explain that we will update our literature search up to date, based on the previously performed reviews. We also added a description of the search strategy. See page 10, line 7 to 10 of the revised manuscript.

This protocol should also include a list of the studies identified to date for each of the topics. This would give an estimate of the number of studies for each topic, and the total number of women. This information would help giving an idea of whether there are likely to be sufficient data for the planned IPD analyses.

At present an updated list of included studies is not yet available. Figure 1 shows for each topic the number of studies included in the previously performed meta-analyses, related to the year of publication.

The reviewer mentioned that we could invite readers of the protocol to notify them of any missing studies.
This is a good suggestion that could reduce potential publication bias so we added an invitation to the readers on page 10, line 10 to 12.

There should be a section on inclusion and exclusion criteria. Whilst the detail could be cross referenced to their earlier work, it would help readers of this protocol if there was a summary of the criteria for each topic here.
As requested, we added a section on inclusion and exclusion criteria of the previous performed meta-analyses. See page 10, line 14 to page 11, line 3.

The reviewer asks for a description of the criteria for ‘inadequate data quality’ and ‘incomplete data’.
We added the description of ‘inadequate data quality’ in the revised manuscript on page 10, line 28 to page 11 line 3. The description of ‘incomplete data’ was added on page 12, line 17 to 22.

One of the potential advantages of IPD is that exclusions due to missing data from aggregate data analysis can sometimes be reduced. Hence studies excluded from the earlier reviews for missing data should not be automatically excluded from this analysis.
We will therefore also approach authors of studies that have potentially collected relevant data, but that have been excluded in previous analyses. This has been stated in the revised manuscript on page 11 line 6 to 7.

Asking for the full dataset for each study sounds like the analysis will be a huge task. The usual strategy for IPD within trials (and if this is likely to be different for diagnostic tests it would be useful to have the rationale in the protocol) is to agree which variables will be used for the meta-analysis, and then ask for these only. This has the advantage that the collaborators identify the appropriate variables within their own datasets, and that data are anonymous.
We ask authors to send the complete database as to minimise their efforts going through their dataset to select the appropriate variables. We added this explanation in the revised manuscript on page 11, line 12 to 13. We also added table 1 in which all minimal requested variables are shown.

The authors asks whether original hard copies will these be included when that is all that is available for some studies.
Yes, we will include these hard copies, because this would be one of the advantages of IPD MA.

It would clearly be useful to have the study protocols and CRFs, but in reality these are likely to be hard to come by. Hence ‘we will request’ would be more realistic than ‘we will obtain’.
We changed this sentence in the revised manuscript, see page 12 line 7.

For assessment of data quality it would be useful to have more detail. How will completeness and quality be assessed and judged? It is important the protocol is a-priori clear about the criteria for exclusion based on quality.
A description of both study and data quality assessment was introduced in the revised manuscript under the heading “Quality assessment” at page 11 and 12.

It might also be useful to plan a sensitivity analysis based on study quality.
We feel that these suggested analyses are already covered as part of assessing the association between study characteristics (including methodological/quality criteria) and test performance.

P12 line 3 refers to merging studies ‘to form one extensive database’. This implies data analysis will not be within study – which is not the case for IPD. Although later sections refer to analyses within each study it should be clear throughout the protocol that data always remain within study, with pooling across studies.

After checking the compatibility of variables of different studies and creation of a variable that identifies the study of origin, the databases are merged and patients will be pooled across studies. This explanation is also added in the revised manuscript on page 12, line 26 to 28.

This paragraph also refers to ‘subgroups on all relevant issues concerning the clinical problems’. All such subgroups should be clearly specified within this protocol, as should the methods for testing interaction effects. Much of the information on specific methods for the topics might be better presented in table format, or as lists. This would make it easier for readers to compare and contrast - patient characteristics and variables in the models, for example.

We added a table to provide an overview of the planned analyses, including analysis-specific in- and exclusion criteria, relevant subgroups, and variables to be used in the analysis, see table 2.

For prediction of preterm birth, multiple pregnancies should be included in patient characteristics.

We added multiple pregnancies as a patient characteristic, see table 1.

Prognostic studies are not covered in the protocol, and so should be dropped from the title and discussion. The title would be more accurate as ‘… prediction and diagnostic studies.’

Both terms are often used interchangeably. We prefer using ‘prognostic’ when referring to the probability of a target condition that may occur in the future and that may be altered by the appropriate diagnostic or therapeutic intervention.

The terms ‘preterm delivery’ and ‘preterm birth’ are used – it would be better to use just one of these, and preterm birth is preferable.

We changed ‘preterm delivery’ into ‘preterm birth’ throughout the manuscript.

Page 8 in the section on preterm birth it is unclear whether the main outcome is preterm labour or preterm birth – the final sentence implies preterm labour. Although this is clarified later, it would be helpful to clarify here too.

We changed preterm labour into preterm birth.

Page 8, last para, first sentence starts by discussing couples with subfertility, and then relates this to the woman’s age. Is the mans’ age not a factor too?!

Mans’ age is much less a factor for subfertility. The reference on which this part is based refers to women’s age.

Reviewer 2
The second reviewer suggests adding a table in which the outcome assessments, the published study predictor data and the IPD predictor data are summarized. This is in line with the comment of reviewer 1 on this issue, see our reply above, addressed by adding tables 1 and 2.

In the Discussion Section, the authors could elaborate on how a clinician would obtain and use results/routines generated from the large database. For a new patient; what information needs to be documented, how this is submitted for evaluation and what can be expected in the returned result(s).

With the data received from the original studies we will create prediction rules and diagnostic algorithms. These rules and algorithms will then be validated and implemented in clinical practice. At present we can not anticipate what information the clinician needs to predict the individual patient outcome.

We hope that these adjustments make the manuscript suitable for publication in your journal, and we look forward to your final decision on the manuscript.

On behalf of the other authors, yours sincerely,

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