Author's response to reviews

Title: Individual patient data systematic review and meta-analysis of ultrasonography of optic nerve sheath diameter for detecting raised intracranial pressure: protocol of the ONSD Research Group

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Author's response to reviews: see over
RESPONSES TO REVIEWER

Reviewer's report:

⇒ First, we want to thank the reviewer for these comments that allowed us to significantly improve our manuscript.

Please find above a point-by-point response to reviewer’s comments. We hope you will find the manuscript adequately revised.

Reviewer 1

This is a very well written protocol to support what is clearly a well thought out IPD review. I have suggested a number of minor amendments for consideration.

1) The title does not clearly reflect that this is a protocol for a systematic review and IPD meta-analysis. I accept that protocols are less likely to exist for non-systematic review ipd meta-analyses but would prefer the following title.

“INDIVIDUAL PATIENT DATA SYSTEMATIC REVIEW AND META-ANALYSIS OF ULTRASONOGRAPHY OF OPTIC NERVE SHEATH DIAMETER FOR DETECTING RAISED INTRACRANIAL PRESSURE: PROTOCOL OF THE ONSD RESEARCH GROUP”

⇒ We have made the modification and also add this information in the abstract

2) The authors state the rationale for the use of IPD as generic use of a gold standard, increased statistical power and definition of a cut off value for ONSD ultrasonography. I would welcome further details of all three.

⇒ We have tried to further explain all three.

⇒ So, we add this paragraph in the manuscript

“Indeed authors of each individual study have tried to determine the ONSD threshold in mm above which ICP is superior or equal to 20 mmHg, i.e. defining raised ICP, by constructing a ROC curve. This threshold varies from 4.8 mm to 5.9 mm according to studies. REF An IPD-MA is required to define an accurate cut-off. The other main advantages of IPD MA compared to meta-analysis of aggregated data are the possibility to carry out data checking and ensure appropriateness of analysis. Besides the statistical power is increased thanks to the incorporation of individual patient covariates and differences between studies. The interaction of these covariates accounts for a greater proportion of explained data than does analysis of mean values for patient’s characteristic and study difference performing with aggregated data."
a. Are there known specific reporting, quality or definition issues encountered in the aggregate review undertaken by the authors that would be addressed by use of IPD?

⇒ Yes. The main problem was the definition of a pinpoint cutoff value (see below). Besides IPD has major advantages that does not allow to simply aggregate data. Indeed IPD allows carrying out data checking and ensuring appropriateness of analysis. It also allows making subgroup analysis and initiating further research by creating a collaboration group.

b. Was statistical power limited and how will use of IPD increase power (Are extra studies available in IPD form or does the increased power rely on combining within study and across study information, where exchangeability assumptions may limit any power increases?)

⇒ IPD will increase power because:

- Two studies will be added compared to aggregated data that will allow increasing the number of subjects

- The increased power rely also on the possibility to combine information within study and across studies. Statistical significance is determined by the ratio of explained to unexplained variation. Incorporation of parameters as individual patient covariates or treatment differences and the interaction between these factors accounts for a larger proportion of explained variation than does analysis of mean values for patients characteristics.

- The problem of exchangeability is managed by weighting differently studies in a mixed model.

c. How were attempts to define cut-off values hampered in the aggregate review and why is the definition of the cut off value so important?

⇒ Owing to the fact that each paper has defined a cut-off (i.e. an ONSD measure in mm from which the intracranial pressure is considered high) from their own data by constructing a ROC curve, it was impossible to define an accurate cut-off value. Meta-analysis on aggregated allows pooling data thanks to the mixed effect model that account for different threshold between studies. IPD will help to estimate a pinpoint cut-off.

3) The rationale underlying secondary objectives needs greater definition. Is this purely exploratory or are there particular reasons for believing that specific groups of patients would result in different diagnostic accuracy? Are there any interactions anticipated between patient characteristics or patient and study characteristics? If this is exploratory, then I would explicitly state that this is the case. Similarly, the study characteristics require greater definition and rationale particularly in the case of quality. I would strongly encourage a priori definition of any quality cut-off threshold and consider any stratification within this as a form of sensitivity analysis.

⇒ We do not predict any different diagnostic accuracy between subgroups of patient’s characteristics. However we will explore all possibilities in order to make strong conclusions.

⇒ Concerning quality, in the section “quality assessment”, we describe the criteria used to define high and low quality studies. We will use the validated tool QUADAS 2. In cases of low quality study, we will perform sensitivity analysis.
⇒ We have added details on this point in the manuscript.

4) Is there any important variation in the way that ultrasonography is delivered that could impinge on the diagnostic accuracy and do you have any plans for exploring any resultant heterogeneity arising from that?

⇒ A priori, no heterogeneity may arise from the methodology of ultrasonography because the technique is widely described and each author seems to have used the same methodology.

5) Greater clarity about how knowledge of cut-off values will inform future research would also be valuable

⇒ The knowledge on a pinpoint cut-off will allow researchers to perform study using this threshold. They would start large trial with this reference threshold. Furthermore, we have formed the ONSD research group that will undoubtedly pursue its collaboration to deeply understand this interesting device in our field.

6) Typo in data collection “studies” level data should read “study level data”

⇒ We have made the modification

Finally, we also modified the date of end of search strategy to be sure to be up to date. We will run another search. The new date is “April 2013” instead of January 2012.