Responses to Reviewer Comments, Manuscript ID BMJ.2016.036543

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 12.01.2017

Elizabeth Loder (chair), Angela Wade (stats), Wim Weber, Jose Merino, Georg Roggla, Tiago Villanueva, Daoxin Yin, Amy Price, Rubin Minhas

Decision: Ask for revision.

The committee was interested in the topic of your research. The following concerns were mentioned:

- This provides some data to inform the discussion about data sharing and access.
- The committee shared the reviewers concerns.
- Is the main finding novel?

Response: Thank you for your feedback. Our objectives within this work were twofold, firstly to examine characteristics associated with IPD retrieval rates (including changes over time) and to also provide a more detailed report of our experiences of the IPD requesting process, before, during and after the introduction of recent initiatives for improving access to IPD.

We are not aware of any work that has conducted a review of an IPDMA cohort as large as this one or to examine characteristics associated with IPD retrieval. We are also not aware of any previous work to document the data collection processes involved in IPDMA in this level of detail. We believe both of these objectives and the related findings to be novel and valuable to researchers, particularly as the approach of IPDMA is becoming more and more popular.

We have made further comments on the objectives of our work in our responses to reviewer 2.

- The search strategy needs clarification. You used search strategies used in a paper by Richard Riley. But you should describe them in this paper. Without this information, a reader would have to look for Richard’s papers before fully understanding what papers were included. What were the dates of considered IPDMAs? If all dates, that should be clarified.

Response: A complete list of search strategies has now been added as an Appendix with all relevant dates. Appendices have been renumbered accordingly.

- We are surprised at the very low proportion of IP data that most of these IPD meta-analyses contain. To the extent that they are supposed to be the pinnacle of the research hierarchy, that is disturbing.

Response: Yes, we agree that the finding is concerning. However, Reviewer 2 makes a good point that IPDMA has become more popular with increased numbers being conducted in areas where IPD may be hard to retrieve anyway. We have added this point to our discussion.

Of greater concern to us is the substantial proportion of IPDMA that do not acknowledge or account for missing IPD with their analyses. Exactly how much IPD is required in different settings to produce...
a reliable result (or conversely how much bias is introduced by varying amounts of missing IPD) is a whole other research question, but we hope that the uptake of the PRISMA-IPD statement will encourage review authors’ to consider and explore biases that may be introduced into their analyses due to unavailability of IPD.

One thing we wonder about is whether the lack of improvement over time reflects the availability of the data or the extent to which the MA team tries to get it, i.e. effort. Response: Yes, the approach taken to attempt to retrieve data is likely to influence how much data is provided (i.e. those who make the most effort get the most data). We had hoped, earlier on in the project, to investigate this but it became clear while piloting the data extraction form that we would not be able to quantify data collection methods in any systematic way as the vast majority of papers provided minimal or no details of their data collection methods. We have noted that this is a limitation in the relevant section of the discussion.

We hope that the update of the PRISMA-IPD statement will also result in clearer reporting of data collection methods. We have added this point to the paragraph in the discussion referring to PRISMA-IPD.

Odds ratios (table 2) are interpreted as relative risks in the text. Response: We have reworded the text of the manuscript and Statistical Appendix to reflect the use of odds rather than risk.

Table 1 shows that 48% of those with an authorship policy compared to 40% (208/517) of those without authorship policy retrieve 80% or more IPD. These are odds of 0.923 and 0.67, yielding an unadjusted OR of 1.38 which is substantially different to that from the multivariable model (3.4, table 2). Is the change due to the increase in authorship policy over time coupled with the decrease of percentages retrieved? It would perhaps be helpful to understanding to present all unadjusted OR for all characteristics and discuss why adjustment is making any large differences observed. Response: We believe there has been a misunderstanding here – in multivariable analysis, we have compared IPDMAs with any authorship policy (individual or collaborative group combined) compared to no authorship policy. This would correspond to 235/507 (46%) vs 89/253 (35%) in Table 1 and an unadjusted odds ratio of 3.1.

It is stated in our methods section that we are comparing any authorship policy to no authorship policy but in case of any confusion, we have added an additional couple of footnotes to Table 2 to clarify our definitions of the characteristics.

We have also added a table of unadjusted odds ratios to Appendix 3 for complete information (although adjusted and unadjusted odds ratios are quite similar) and following comments from Reviewers 1 and 2, we have added an additional analysis to Appendix 3 separating out authorship policy further. We hope that these additional analyses and footnotes clarify our findings around authorship policy.

Figure 4 illustrates that the networks of epilepsy trials for those providing IPD or not are similar. No information is given re the content of the trials apart from that ‘on examination ... no clear differences ..’ and from this it is stated that the deduction was made that data not provided were likely to be MAR and ‘unlikely to systematically impact on the resulting NMA’. The statement should be better supported by evidence if it is to be made here. Response: Thank you for this comment. In hindsight we realise that this Figure and brief description is rather out of context of the main messages in this paper and that Figure 4 needs further detail to be fully understood. We have performed a more detailed comparison of characteristics of the studies with and without IPD which will be presented and discussed in more detail in the clinical paper of our
network meta-analysis results (to be published on the Cochrane Library) but have removed Figure 4 and the paragraph referring to Figure 4 from the current paper.

- Analyses in appendix 2 show that the publication rate of IPDMA over time was non-linear. However, all multivariable models appear to incorporate only a linear term. It does seem that adjustment for age of publication (table 2) may have a substantial impact on the OR for other factors. Hence the multivariable models should investigate more appropriate adjustment for age and how this impacts on the OR for other factors.
  
  Response: There may be a misunderstanding here. Table 2 refers to the proportion of IPD provided in published IPDMA while Appendix 2 refers to the number of IPDMA published per year. These are two separate analyses and we did not wish to investigate any factors associated with the number of IPDMA published per year. This analysis was intended to be exploratory rather than predictive. Again in hindsight, we realise that the non-linear modelling of IPDMA publication rate is out of context with the other objectives of the manuscript and we have removed this analysis from the Appendix.

- The paper aligns with The BMJ values of promoting data sharing and transparency. And, I did not see any fatal in reviewers' comments
  
  Response: Thank you for the feedback.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to the additional comments by the committee.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is a clear and very well written manuscript that uses appropriate methods to evaluate the success of past IPD-MAs in obtaining data. These findings are complemented and contextualised by a more qualitative and personal reflection of 20 years experience of conducting IPD-MA in epilepsy. I have no substantive comments and believe that, with current interest in IPD-MA and data sharing, that the paper will be of interest to BMJ readers.

Response: Thank you, we appreciate your feedback.

Although the paper is able to comment on the data yield (where it is possible to calculate this), what it has understandably not been able to do is to assess whether there are differences between the available and unavailable data. Thus whether the data obtained and analysed are representative or whether they are unrepresentative and consequently biased. The authors mention representativeness in the introduction, but it may be worth mentioning in the strength and weakness section.

Response: Thank you for the comment. We agree that discussion of the representativeness of data included in an IPDMA is of great importance. As the reviewer appreciates, it is difficult to explore
impacts on clinical conclusions in a systematic way as the impact of missing IPD will vary across the wide range of settings and clinical contexts included in this review. To consider exactly how much IPD is required in different settings to produce a reliable result (or conversely how much bias is introduced by varying amounts of missing IPD) would be a whole other research question. The implications of our findings which is concerning, is the substantial proportion (25% of IPDMA) that make no reference at all to the potential for bias introduced into results from missing IPD (via additional analyses, narrative summary of trials without IPD or discussion of potential ‘availability bias.’) We have added a couple of additional sentences into the Discussion (Relation to other studies and implications) to emphasise our concerns.

As we say in the following paragraph of that section, we hope that uptake of PRISMA-IPD will encourage review authors’ to consider and explore biases that may be introduced into their analyses due to unavailability of IPD.

The discussion would be enhanced by the authors briefly reflecting on the correlations between IPD-MA attributes and percentage of data retrieved (table 2). The reasons for yield being greater in IPD-MA with an authorship policy may warrant further consideration - because it is something that those carrying out IPD-MA can change. It would be interesting to know what proportions of those IPD-MAs with such policies had group authorship. I suspect that having an up-front policy that grants some form of group authorship may serve as an incentive to participate. The presence of such a policy could also be a proxy for a well-designed project where project plans are described clearly, thereby engendering confidence in entrusting data for analysis. A project that gives due consideration to considering/rewarding others at the outset may also reflect a more collaborative ethos, which in my experience is vital to IPD-MA success.

Response: Thank you for this comment, this is a very good point. We have further explored the influence of authorship policy in an additional sensitivity analysis presented in the Statistical Appendix. This analysis shows that both individual and collaborative group authorship is positively associated with obtaining 80% or more IPD but it is only individual authorship which is positively associated with obtaining 100% IPD.

We have added this finding into our results and an additional paragraph into the discussion elaborating on the importance of an authorship policy.

Minor specific comments:

In the ‘what is known’ section I would qualify the first bullet point by adding and the data obtained are unrepresentative.

Response: First bullet point changed as suggested.

Page 6: I am curious about the IPD-MA with 16 participants ?!

Response: Yes, our inclusion criteria were broad and we did not limit by sample size. This IPDMA in question considered case reports and case series of a rare form of refractory skin ulceration aiming to identify effective treatments (proportion of patients achieving remission of ulcers).

No changes made to the manuscript.

Page 6: In the numbers reported it would be helpful to state (here or in the methods section) how projects that carried out multiple IPD-MAs (series of related questions/comparisons reported in a single communication) were counted – as one IPD-MA or as the number of individual comparisons.
Response: We have outlined in the Study Flow Diagram the number of distinct IPD-MA (i.e. that 1280 IPDMA were reported in 1278 articles). By this we mean different research questions were considered with cohorts of eligible studies for IPDMA. We did not consider multiple analyses reported within an IPD-MA (e.g. if IPD was used to analyse several outcomes), we extracted only information on the maximum amount of IPD was provided for the IPDMA as a whole (regardless of exactly how IPD was used in analysis).

We have added an extra couple of sentences to the Methods (data extraction) to make this clear.

Page 12/13 Data sharing platforms will only provide a clear communication between data requestors and providers if facilitating mechanisms are included in the platform and if data providers use the platforms – something that is not currently the case for academic trials. I suspect that for a variety of reasons academics may prefer to share data on an individual basis for specific projects.

Response: Yes, we agree with this comment and we have edited the paragraph in question to reflect that data sharing platforms are only useful if the research community buy into them and are proactive in their use (by data providers and data users alike). At the time of writing, these platforms are limited to only pharmaceutical data, but we will see what the future brings.

Additional Questions:
Please enter your name: Lesley Stewart

Job Title: Director and Professor of Evidence Synthesis

Institution: Centre for Reviews and Dissemination University of York

Reviewer: 2

Recommendation:

Comments:
In general I found this to be a well written and clear paper examining the interesting topic of why IPD is not always obtained in reviews, and whether there have been changes over time. My main concerns are that the topic is somewhat specialised, and perhaps not of great interest to the full BMJ readership, particularly as previous papers on IPD analysis have already discussed that few IPD reviews obtain all the relevant IPD. Much of the paper is given over to anecdotal discussion of the authors’ experiences, from which it is difficult to take any clear message.

Response: Thank you for your comments.

Please see our above response to the Editors comment regarding whether our main findings are novel. To expand on our objectives, we hope that our detailed documentation of the IPD requesting process may provide some insight for those who have conducted or those planning to conduct IPDMA and also some early insight on the impact of changes in attitudes and mechanisms of data sharing on a ‘real’ project. This reflection also provides a different perspective to the clinical results of our work in Epilepsy, which we believe will aid the interpretation of the results of such a large project.

While our experiences in epilepsy are by nature anecdotal, we have provided factual numerical supportive data on the time taken to retrieve IPD (Figure 3) and the reported reasons why IPD was not made available to us (Supplementary Table 1). We also have retained all of the documentation (emails etc.) behind this table and figure which can be made available on request.
The messages to be taken from these reflections are the processes followed in the requests of IPD, the substantial time taken to retrieve IPD in this project (Figure 2), the decline in our success rate and the apparent changes in reasons for lack of data availability (Supplementary Table 1 and Discussion).

Originality: As the authors note there have been several reviews of IPD practice, which have considered success at obtaining IPD. This paper is the first to try and investigate and model whether success in obtaining IPD is linked to characteristics of the review.

Response: It is encouraging that the reviewer has also recognised that our research is the first to attempt to investigate characteristics that could predict success in obtaining IPD. We would also draw attention to the fact that our data set represents the largest, most comprehensive cohort of IPDMAs published to date.

Importance: That IPD reviews often do not obtain IPD has been widely reported in previous articles and reviews. As such the conclusions of this paper are unlikely to surprise anyone familiar with the field, although the analyses to identify where IPD retrieval is less successful are helpful. The section on the authors’ own experiences in epilepsy are rather long (longer than the review and analysis), and inevitably anecdotal. As such I could not draw any real conclusions from this section. I would recommend that this section be substantially shortened, to focus only on how the authors’ experience compares with what they found in their review.

Response: Thank you for the comment. We are disappointed that the reviewer could not draw any conclusions from our experiences.

As outlined in our responses to earlier comments, our objective in this section was to provide a detailed account of the IPD requesting process as an insight for those who have conducted or those planning to conduct IPDMA. Such information is often lost when publishing results of IPDMA, in favour (quite rightly) of dedicating limited words in journal publications to clinical conclusions and implications. We will publish the clinical results of our work in the near future, but we are keen that the work that went on in the background is not lost as it provides an alternative perspective of the work which has implications for the interpretations of the results and on future work.

If the reviewer and the Editorial Team feel that this section is too long, we can reduce the length; however this would detract from our objective to provide a detailed documentation of the IPD requesting process.

Methods: The review process appears to have in well conducted, and the methods used appropriate. The results are reasonable and all conclusions suitable given the data.

Response: Thank you for your feedback.

I give some specific comments below:

1. It would be helpful to present at least some of the data in Table 1 in figures, such as stacked bar charts. This would allow a more granular presentation of the data (100% IPD, 80-100%, 50-80, <50, not reported, for example). Even if this is not possible numbers where IPD was unreported/unclear should be reported separately in the tables.

Response: We agree that presentation of the characteristics of IPDMAs where proportion of IPD is not provided is important, therefore we have edited Table 1 to present all IPDMA, 100% IPD, >80%,
<80% and not reported. To break down the numbers further than this (e.g. 50-80%, <50% etc.) would result in small numbers which would not be as useful for interpretation.

We have also presented some additional bar charts of the Characteristics included in the logistic regression model as a Supplementary Figure. We have presented these bar charts in the same format as Figure 2 (IPD retrieval rate by year) rather than in a ‘stacked’ format; we considered a ‘stacked’ format for Figure 2 but felt that the different proportions of IPD retrieval were not reflected well in the stacked scale of the bars and opted for the current presentation. We hope that the Supplementary Figure further aids the interpretation of these Characteristics.

We have also updated Figure 2 to reflect 100% IPD retrieval, 80%-99% retrieval, < 80% retrieval and unknown proportion retrieved.

2. Using logistic regression has obvious limitations for percentage data, including the arbitrary choice of 80% as a cut-off, the loss of information from making percentage data into binary data, and including unknown proportions in with the <80% group. I think some sensitivity analysis is needed here, such as analyses at more cutoffs, or excluding reviews where numbers were unreported (which may introduce reporting bias, of course). Perhaps multinomial regression, beta regression, or other methods for analysing percentage data might also be considered.

Response: Our choice of 80% cut off was not completely arbitrary, it was chosen to allow comparison with previous reviews conducted by Riley et al, Huang et al and Simmonds et al on this topic. This reasoning has now been added to the Statistical Appendix. As outlined above, due to small numbers (less than 10% of IPDMA retrieved less than 50% of IPD), examination of characteristics with a cut off of 50% was not deemed appropriate.

We accept the limitation of dichotomising percentage data. As noted in our Statistical Appendix, this approach was taken due to the complex distribution of the dependent variable which was highly skewed even following attempts at transformation. Also, such an approach was considered the most appropriate to also to allow for a widely accessible interpretation of our results, avoiding too much statistical complexity. We also believe that the loss of information from dichotomising our dependent variable is counteracted, in part, by the size of the cohort used in our analysis. We have added a paragraph on this limitation to the Discussion.

As suggested, we reconsidered the modelling of percentage data and applied fractional logistic regression (beta regression as suggested by the reviewer does not allow the dependent variable to take the value of 1 so was not appropriate for the IPDMAs within our cohort retrieving 100% of IPD).

We present the results of this additional sensitivity analysis in Appendix 3. Conclusions of this analysis were mostly similar to those of the primary analysis, but indication here that IPD retrieval rates may actually be getting worse (older publications were associated with a higher proportion of IPD retrieved).

We have also considered a number of other sensitivity analyses to account for assumptions that we have made (including a range of scenarios for the 257 IPDMA where proportion of IPD could not be reported). Results of these analysis are mostly similar and conclusions unchanged, demonstrating that our primary results and conclusions are robust to changes in assumptions made. Full results of all sensitivity analyses are presented in Appendix 3, and we have made it clearer in our methods and results sections that sensitivity analyses have been conducted.
3. It would also be helpful to model non-reporting as an outcome, to see if this is related to any of your covariates.

Response: As suggested, this analysis has been added to Appendix 3.

Results of this additional analysis indicate that the odds of the proportion of IPD retrieved being reported are significantly higher in more recently published IPDMA, IPDMA including IPDMA only and IPDMA without an authorship. There was no association between publication as a Cochrane IPDMA and the source of funding on the reporting of the proportion of IPDMA.

4. You found that having an authorship policy increased retrieval rates, but this doesn’t seem to be the case for collaborative groups (at 100% retrieval). Could you comment on this?

Response: Yes, this is correct. Reviewer 1 has also commented on the importance of authorship policy so we have added an additional explorative analysis examining authorship policy (individual or collaborative group) to Appendix 3 and discussed the implications of this analysis in the discussion.

5. One likely reason for the general decline in IPD retrieval rates over time you miss is that IPD analysis is becoming more common, and is used in a wider range of fields (not just treatments for cancer). It would seem inevitable then that more IPD reviews are being done in areas where getting all the IPD will be difficult, where in the past the focus was on areas where getting IPD was feasible. I wouldn’t consider that to be a problem, just a natural consequence of IPD becoming more popular. Larger and better managed databases and searching techniques probably also increase identification of hard-to-obtain studies.

Response: Thank you for this comment, two good points are raised here which we had previously not articulated clearly enough in our findings. The first two paragraphs of the discussion have now been reworded (also taking account of a comment by Reviewer 4).

We also note that IPD retrieval is likely to be related to the data collection methods used within the IPDMA (see response to Editors comments above) and have added a paragraph to the limitations section on this.

6. Might Review type (systematic vs opportunistic) be an important covariate to consider, if you extracted this data?

Response: Our original search included ‘opportunistic’ analyses, however our main focus was on systematic IPDMAs and the characteristics associated with IPD retrieval where IPD is not available to reviewers.
As outlined in our discussion we feel that non-systematic IPD meta-analyses are a different type of analysis and outside of the main focus of our review so we have not considered their characteristics in any detail. This may be an interesting focus for future work.

No changes made to the manuscript.

7. IPDMA is sometimes singular, sometimes plural and sometimes IPDMAs in the text. Please make this consistent.

Response: We have given the manuscript a further proof read and hope to have eliminated all such errors.
8. There are several typos or editing errors (e.g. “should therefore which could” line 20, page 2). Further proof reading is needed.

Response: We have given the manuscript a further proof read and hope to have eliminated all such errors.

Dr Mark Simmonds
Centre for Reviews and Dissemination, York

Reviewer: 3

Recommendation:

Comments:
This is cutting edge research that should aid patients across several disease spectrums.

Response: Thank you, we appreciate your feedback.

Additional Questions:
Please enter your name: YASMEEM WATSON

Job Title: RESEARCH ADVOCATE

Institution: NA

Reviewer: 4

Recommendation:

Comments:
This study reports a massive research project investigating trend in IPDMA research. The research question is: did the success rate in obtaining IPD change over time? A systematic review of published IPD and an example from the epilepsy field are used to answer the question. Predictors of success/failure are analyzed. The study is robust, and result might in principle inform willingness to contribute data and regulation to make data access easier or more complex. Some of the limitations of the study are address in the paper, some other are intrinsic in the voluntary nature of data sharing, in the many different economical and intellectual interests at play, in the difficult line where the cost-benefit ratio lies.

No major changes are requested, but some observations are offered to author’s consideration

Page 2, 10-11: the last sentence is not really supported by data, and it is more wishful thinking than drawn from evidence. I would suggest rewriting

Response: Sentence reworded to the active rather than passive voice (i.e. ‘we hope…’) to match the main conclusions.

Page 2, 14: change of verb from singular to plural

Response: This sentence is corrected.
Page 2, 20: sentence does not stand

Response: This sentence is corrected.

Page 5, 15-17: “agreement was good” sound very approximate for a study of this level – also, one would expect declaring the method used to measure agreement in the methods section (i.e. here) and the level of agreement reported instead in the results section

Response: We did not formally record agreement between data exactors as this was not the aim of the work. So our assessment of agreement between data extractors was approximate and we state ‘good’ as we did not have any causes for concern following independent data extraction and most importantly where any discrepancies or uncertainties were noted, we were able to resolve them by discussion to ensure accurate data extraction.

No changes made to the manuscript.

Page 8, 19-20: the sentence is syntactically wrong

Response: We have corrected this sentence.

Page 11, line 16-18: alternative hypotheses could be that non-cochrane authors might be part in specific research communities and therefore more likely to obtain participation – or non-Cochrane reviews being more commonly funded – please discuss – also, I think it would be possible to substantiate your hypothesis by counting the average/median number of trials/participants included in Cochrane vs non Cochrane trials – if your hypothesis is true, Cochrane should be on average larger

Response: In fact, Non-Cochrane reviews tended to be larger than Cochrane Reviews, both in the number of participants and number of trials included. This is may reflect the restriction of Cochrane Reviews (traditionally at least) to randomised controlled trials (although when restricting our cohort to IPDMAs of randomised trials only, the number of eligible participants is still higher in non-Cochrane reviews – both have a median of 11 eligible studies), so perhaps there is also a reflection of different types of research questions considered in Cochrane and Non-Cochrane reviews.

We have reworded this section of the Discussion based on this comment and the comment of Reviewer 2.

Page 11, 23-28: on the issue of cost, I think it would be honest and worth tackling the issue of the many options for funds “scamming” that are camouflaged under privacy and data protection – like in RCT conduct, the cost has ramped up over the last few years for layers and layers of “quality control” that are more aiming at creating revenue generating streams than objectively impacting privacy and quality - it would be a tough argument, but much more valid than the current “superficial” approach – however, there might be political reasons not to touch those strings...

Response: Such a discussion around cost could provoke an interesting debate but we agree that this isn’t the place for it, for the political reasons you mention.

No changes made to the manuscript.

Page 12, 1-9: this concept of shift of time requirements and typology of activities in IPDMA practice over time would be worth mentioning in the highlights
Response: An additional highlight has been added as requested.

IS there a reasons why the following paper (co-authored by the first author) is not cited?

Response: At the time of writing this manuscript, the Cochrane review had yet to be published. It is now cited in the introduction section.

Figure 2 would gain by also showing the n of IPD as proportion of the total number of research articles/systematic review published over the same time span – absolute numbers are just a part of the picture.

Response: It would require a large amount of work to obtain an accurate figure (or a large number of assumptions to obtain an approximate figure) for the number of systematic reviews /research articles published each year to inform such a calculation and have decided to leave Figure 2 as a summary of the absolute numbers which is also consistent with other previous published reviews of IPDMA.

No changes made to the manuscript.

Additional Questions:
Please enter your name: Alfonso Iorio

Job Title: MD, PhD, Associate Professor

Institution: McMaster University