Response to reviewer comments

Dear Dr. John Fletcher,

Thanks a lot for reviewing our article and offering us a precious opportunity to revise our manuscript (Title: The methodological quality of individual participant data meta-analysis on intervention effects: A systematic review; ID: BMJ-2020-058077.R1). We found comments from Prof Riley invaluable for improving our manuscript. We have addressed each comment in a point-to-point format below, and we have also revised the manuscript according to these comments by tracking changes. A clean version of the revised manuscript has also been resubmitted.

We would like to express our gratitude to your input to our submission. Please do not hesitate to contact us if further information is needed.

Yours sincerely,

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Reviewer 1

Comments:
I thank the authors for addressing my comments. Their revision is much improved and will provide a useful reference for those aiming to improve the quality of IPD meta-analyses in the future. It is good that they combined AMSTAR with the Tierney checklist, and even provide a summary of these tools alongside their final checklist items. I only have minor remaining comments.

Response to comments
Thank you very much for your comments and all your kind help. We have revised the manuscript according to your comments. Our point-to-point response to your comments were listed below.

1) “As many as 126 (39.0%) IPD meta-analyses failed to obtain a large proportion of IPD from the eligible trials” – please define large

Response to comment 1)
Thanks for your comment. Stewart and colleagues(1) have proposed a proportion of 90% IPD retrieval as an acceptable target. A proportion of 90% IPD retrieval was used as the cut-off for a large proportion of IPD retrieval in this study accordingly. We have revised the manuscript accordingly.

As many as 126 (39.0%) IPD meta-analyses failed to obtain IPD from ≥90% of eligible participants and/or trials, among which only 60 (47.6%) provided reasons and 21 (16.7%) undertook certain strategy to account for the unavailable IPD.

2) In the abstract, the %s should be reported with CIs in this sentence: “The sampled IPD meta-analyses showed low compliance in using a satisfactory technique to assess the risk of bias of the included RCTs (43.0%), accounting for risk of bias when interpreting results (39.6%), providing a list of excluded studies with justifications (32.2%), establishing an a priori protocol (30.7%), pre-specifying methods for assessing the overall effects (44.3%) and participant-intervention interactions (31.3%), assessing and considering the potential of publication bias (30.7%), and conducting a comprehensive literature search (18.9%).”
Response to comment 2)

Thanks for your comment. The %s have been reported with CIs in the abstract accordingly.

The sampled IPD meta-analyses showed low compliance in using a satisfactory technique to assess the risk of bias of the included RCTs (43.0%, 95% CI: 37.6% to 48.5%), accounting for risk of bias when interpreting results (39.6%, 95% CI: 34.3% to 45.0%), providing a list of excluded studies with justifications (32.2%, 95% CI: 27.1% to 37.3%), establishing an a priori protocol (30.7%, 95% CI: 25.6% to 35.7%), pre-specifying methods for assessing the overall effects (44.3%, 95% CI: 38.8% to 49.7%) and participant-intervention interactions (31.3%, 95% CI: 26.2% to 36.4%), assessing and considering the potential of publication bias (30.7%, 95% CI: 25.6% to 35.7%), and conducting a comprehensive literature search (18.9%, 95% CI: 14.6% to 23.2%).

3) “IPD meta-analyses have increased over time, from eight publications in 1994 to eighty eight in 2014” – please rewrite, as it sounds like there are 88 IN TOTAL (across all years) by 2014, but I think the authors refer to per year here. Anyway, there are more than 88 published in 2014 – the authors perhaps refer to IPD MAs looking at treatment effects? Need to be more specific.

Response to comment 3)

Thanks for your comment. We have re-written the sentence for clarification. Yes, we refer to the number of published IPD meta-analyses per year here. These numbers were cited from Nevitt and colleagues’ study in 2017.(2) Eighty-eight publications in 2014 only referred to those IPD meta-analyses that were included in systematic reviews, the number could be larger when IPD meta-analyses that were not incorporated in systematic reviews were accounted for as well. Hence, the 88 published in 2014 did not restrict to research question, including therapeutic, diagnostic, and prognostic questions. The manuscript has been revised accordingly.

The number of yearly published IPD meta-analyses have increased over time, from eight in 1994 to eighty-eight in 2014.(2) These numbers only referred to IPD meta-analyses that were included in SRs, even larger number per year were found when IPD meta-analyses without SRs were accounted for.(2)

4) “Only around half (53.9%) IPD meta-analyses reported information related to intervention harms, with IPD meta-analyses on pharmacological interventions (61.8%) performing better in reporting harm
than that of IPD meta-analyses on non-pharmacological interventions (36.6%)” … the word ‘better’ is ambiguous – be clear that you mean better in reporting harms.

Response to comment 4

Thanks for your comment. We have revised related expressions in the manuscript accordingly.

Only around half (53.9%) IPD meta-analyses reported information related to intervention harms, with more IPD meta-analyses on pharmacological interventions (61.8%) reporting intervention harms than that of IPD meta-analyses on non-pharmacological interventions (36.6%) (Table 2).

5) In the Methodological Quality section of the Results, I think all %s should be reported with 95% CIs in the main text as well as the tables.

Response to comment 5

Thanks for your comment. All the %s have been reported with 95% CIs in the main text as well as in Table 2, Table 3, Table 4 and Table 5.

6) The ‘basic characteristics’ section is very broad, and it would help the reader to have sub-headings, for example for search strategy, amount of IPD retrieved, etc

Response to comment 6

Thanks for your comment. Sub-headings have been added in the ‘basic characteristics’ section accordingly.

7) Risk of bias is discussed in the basic characteristics and then again in methodological quality sections, which is confusing. I would move the text in the former (“The most popular tool for assessing the risk of bias of included RCTs was the Cochrane risk of bias tool (44.9%). It is worth noting that 97 IPD meta-analyses (30.0%) did not perform any critical appraisal of the included RCTs, while 56 (17.3%) did not report the tool they used for critical appraisal (Table 3.” to the latter section (and also give CIs)

Response to comment 7

Thanks for your comment. Results about risk of bias have been combined into one paragraph in “Critical appraisal results on general items” section.
The sampled IPD meta-analyses showed unsatisfactory performance for the six critical items in AMSTAR-2 that were applicable to IPD meta-analyses. Only 43.0% (95%CI: 37.6% to 48.5%) IPD meta-analyses used a satisfactory technique for assessing the risk of bias of included RCTs. It is worth noting that 97 IPD meta-analyses (30.0%, 95%CI: 25.0% to 35.1%) did not perform any critical appraisal of the included RCTs, while 56 (17.3%, 95%CI: 13.2% to 21.5%) did not report the tool they used for critical appraisal (Table 3). The sampled IPD meta-analyses had less than 40% compliance for the remaining five critical items—accounting for risk of bias when interpreting results (39.6%, 95%CI: 34.3% to 45.0%); providing a list of excluded studies with justifications (32.2%, 95%CI: 27.1% to 37.3%); establishing an a priori protocol and justifying any deviations (30.7%, 95%CI: 25.6% to 35.7%); assessing and considering the potential of publication bias (30.7%, 95%CI: 25.6% to 35.7%); and conducting a comprehensive literature search (18.9%, 95%CI: 14.6% to 23.2%).

8) Page 11: “To be specifying…” – change to “To be specific …”?

Response to comment 8)

Thanks for your comment. “To be specifying…” has been revised as “To be specific …” in the manuscript accordingly.

9) On a few occasions, one-stage and two-stage statistical methods for meta-analysis are mentioned. The authors might want to explain briefly what this refers to. Also, the authors have not investigated whether these statistical methods were applied correctly. For example, did the 1-stage methods account for clustering? Did it adjust for ecological bias? And so forth. I am not saying they should do this, but their discussion should refer to other papers that already show that many IPD Mas are sub-standard in their use of one-stage methods. For example, see the following 1-4

Response to comment 9)

Thanks for your comment. Explanations about one-stage and two-stage statistical methods have been added in the introduction and discussion on no investigation on whether the statistical methods were applied correctly has been mentioned as limitation in the discussion section. We have revised the manuscript accordingly.
Introduction

Available evidence has demonstrated that the published IPD meta-analyses were conducted based on inconsistent standards in terms of methods used to estimate intervention effects (e.g., one-stage method, with which IPD retrieved from eligible studies are analyzed simultaneously, or two-stage method, with which IPD are first analyzed within each study separately and then combined with a traditional meta-analysis method(3, 4)), methods used to explore participant-level covariates (e.g., by-participant subgroups, by-trial subgroups, or meta-regression), and whether trial variation was accounted for when combining IPD (e.g., some IPD meta-analyses treated IPD from different trials as a mega-trial).(5, 6)

Discussion-Strengths and limitations

Third, the assessment only considered the execution of the methodological items, without further inspection of its actual achievements. For example, regarding the risk of bias assessment, we only assessed whether a satisfactory technique was used. However, using a satisfactory technique to assess the risk of bias is not equal to assessing the risk of bias appropriately, which was beyond the scope of this study. Likewise, information on statistical methods used for IPD meta-analyses were solely based on the description of the publications. No further investigation on whether the statistical methods were applied correctly was conducted in this study. It is worth noting that studies(5, 7) have indicated that the use of one-stage methods were sub-standard among many IPD meta-analyses. Further assessments are warranted on i) whether clustering was correctly accounted when one-stage method was used(3); ii) whether within-trial interactions were appropriately separated from across-trial interactions to reduce ecological bias when investigating effect modifiers(8, 9); and iii) whether model assumptions (e.g. choice of random or fixed effects) were properly checked and ensured.(4) In addition, no assessment of publication bias is necessarily equal to the existence of publication bias. However, the authors of IPD meta-analyses are requested to provide related information to facilitate evidence-based decision making. Otherwise, a re-assessment of publication bias is needed for evidence users. (10)

10) Table 2 – the results column needs to define what is presented in the column heading (e.g. frequency (%, 95%))
Response to comment 10)

Thanks for your comment. The results column in Table 2, Table 3, Table 4 and Table 5 had defined as frequency (%, 95%CI) accordingly.
References


