Author’s response to reviews

Title: Protocol registration or development may benefit the reporting, design and conduct of dose-response meta-analysis: Empirical evidence from a literature survey

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Author’s response to reviews:

Juan Ruano Ruiz (Reviewer 1)

Summary:

The manuscript "Does registration benefit the reporting and methodological quality? A propensity score matching analysis on dose response meta-analysis" is an original research-on-research article exploring if there are differences of methodological and reporting quality, assessed using modified versions of AMSTAR tool and PRISMA checklist respectively, between meta-analyses of dose-response interventional studies (DRMAS) conducted after an a priori protocol has been published in a scientific journal or registered in a public repository as compared with those reviews conducted without an a priori protocol.

They found that only a minority of DRMAS were conducted after publishing or registering a protocol. This group showed higher reporting quality but without differences in methodological quality as compared with DRMAS conducted lacking an a priori protocol.
The methodology is sound but there are some confusing aspects that authors should clarify. The results are innovative because it is the first time that protocol utility to improve methodological and reporting quality is evaluated. However, using such a small sample and focusing only on a rare subtype of meta-analysis hamper the confidence and external validity of the results.

My conclusion is that this manuscript must be scientifically improved before I can recommend to publish this manuscript in your journal. For that reason, authors must consider to address some of the following questions/suggestions:

Response: We’d like to express our deep appreciation to you for the valuable comments on the manuscript, which indeed helps us improve our manuscript. We have carefully revised the manuscript according to the comments, as below.

1: In the Title:

-"Does registration benefits the reporting and methodological quality? [...]" should be read "Does registration benefit the reporting and methodological quality? [...]"

-I do not believe that including "propensity score matching analysis" in the title will be of added value as it is only an operational method to match studies and no analysis to compare results with other matching methods has been performed. In my opinion this sentence should be removed and formulating a new declarative title describing the results specifying the subtype of MAs analysed is suggested.

Response: Thanks very much for this valuable suggestion. We’ve revised the title accordingly, and the new title is “Protocol registration or development may benefit the reporting and methodological quality of dose-response meta-analysis: Empirical evidence from a literature survey”.

2: Other factors that could influence methodological or reporting quality should be considered when creating univariate and multivariate regression models [founding sources (pharma vs academic), authors’ conflict of interest, journal's adherence to PRISMA statement, page number,

Response: Thanks for this in-depth suggestion. We agree with that these variables may also important confounders. We also have referred the article you mentioned, see ref.23. The variable “use of any reporting checklist” was added in the regression model in the revised manuscript, and the results keep unchanged. However, we have some reasons why we did not consider some of the variables:

1. In our database of the 529 DRMAs, 377 of which received financial support, only one was supported by company, therefore, it is not possible to consider the founding source in current study.

2. For conflict of interest, which is already a component of AMSTAR statement that was contained in the dependent variable of total quality score. Therefore, we did not treat it as independent variable in the regression model.

3. For page number, we agree that the page numbers may influence the quality, the agreement is that page number may be not a good predictor since the number of Figures, Tables, text sizes, even number of references (and so on) together would largely influence the page numbers. Therefore, page numbers is more likely as a “media variable”.

4. For Cochrane vs non-Cochrane reviews, the current database of 529 DRMAs, none of them were Cochrane reviews since majority DRMAs were based on observational studies.

3: Authors have removed the item "structured summary" from PRISMA checklist arguing that the structure of summary varies considerably and unstructured summaries report sufficiently detail. However, there some reasons for not to exclude this item: "Free format abstracts were most sensitive to the increase of text complexity as compared with more structured abstracts (IMRAD or eight-heading formats), yielding opposite effects on their quality and completeness depending on the methodological quality: a worsening in low quality reviews and an

Response: Thanks for this in-depth suggestion. We’ve added the item “structured summary” in the revised manuscript, and the final regression results did not change. And the article mentioned also listed as a reference in the revised manuscript, as ref.31

4: Pg 7, ln 15: 'PRIMSA' must be read 'PRISMA'. Please, fix it.

Response: The error has been revised.

5: In the Results section (pg 8, ln 18), authors explain that '4 (studies) provided a supplemented protocol'. As these are not a priori published or registered protocols, in my opinion should have not been included in the study. In any case, a sensitivity analysis (without these studies) should be performed address this issue.

Response: We’ve added a post hoc sensitivity analysis by excluding the 3 studies (and the matched 6 studies) in the results part (regression), there were no substantial changes observed. There is an error after we checked the registration information that there were 3 provided a supplemented protocol, while the other provided protocol at website.

6: In addiction, authors include 'DRMAS with protocol registration or published' expression throughout the manuscript when in fact no include review has an a priori protocol published in a scientific journal -see comment #5.

Response: Thanks very much for this in-depth consideration. There may be a misunderstanding for the expression. In the data collection and quality assessment part, we’ve defined the scope of “DRMA registered or published a protocol”, which refers to “if they provided a registration ID, an attachment protocol, or a web linkage of the protocol.”
We’ve changed “published” to “developed” in the revised manuscript.

Such information was collected from the context the authors reported. If the authors did not claim they published their protocols in scientific journal, it is hard to collection this information since the authors, the titles may change from the protocol to the final article publication. We’ve added this as a limitation in the discussion part.

7: Method for clustering journal was not defined in the Method section.

Response: Thanks for this suggestion. The clustering has been defined in the statistical analysis part.

8: English writing of the Discussion section must be reviewed.

Response: We’ve carefully revised the wording of the discussion section.

9: It would be interesting to expand the Discussion about the PRISMA items that discriminate reviews with registered vs non-registered protocols. Three out four items were related with risk of bias assessment or source of funding of primary studies. This may be another argument to question #2.

Response: Thanks for this in-depth suggestion. We agree that this is an interesting point. In the PRISMA, the item related to protocol registration is “Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.”, which contains both registered and non-registered protocols. We have no evidence support there is difference on the quality for registered vs non-registered protocols due to the limited eligible studies. And we’ve discussed this in the limitation section.
Katharina Allers (Reviewer 2)

Thank you for the opportunity to review this manuscript. The authors have conducted a study to investigate the prevalence of registration among dose-response meta-analyses (DRMA) and to compare the reporting and methodological quality of DRMA with and without a registration or published protocol.

While I think this is a relevant topic and an interesting study, there are some major issues I am concerned about.

The authors limited their study to DRMA, which leads to a very small number of included studies (n = 45). I think the study and its significance would be improved by a wider inclusion of meta-analyses. The definition of registration and published protocol is rather broad including heterogeneous registration methods. Almost half of all included DRMA with a registration or a published protocol were funded by the World Cancer Research Fund UK with a study protocol reported at their website and 14 of the studies were published by the same first author, which might limit the generalizability. Presentation of methods and results is partly unclear.

Response: We’d like to express our deep appreciation to you for the valuable comments on the manuscript, which indeed helps us improve our manuscript. We have carefully revised the manuscript according to the comments.

1) Introduction:

Overall, this is a clear and well written introduction, only the limitation to DRMA does not seem reasonable to me. How exactly should these DRMA differ to other meta-analyses, e.g. those on efficacy.

Response: Thanks for this in-depth comment. This is because the current study is a part of a project that aims to collect evidence that could influence the design, conduct, and reporting quality of dose-response meta-analysis in order to develop evidence-based guidelines for dose-response meta-analysis. The results of current study therefore main focus the value on dose-response meta-analysis.
2) Methods:

a) How did the authors define meta-analysis and was a thorough systematic review component required? Otherwise some items of the PRISMA and AMSTAR checklists might not be applicable. This could lead to a difference between cases and controls (with more meta-analyses without a thorough systematic review component in controls) which would affect the results.

Response: Thanks for this in-depth comment. The meta-analysis is defined that a thorough systematic review component required, which did not contains pooled analysis. We’ve added the definition in the revised manuscript.

b) Page 4, line 15-25: The authors only write about registered DRMA but also included those meta-analyses with a published protocol but no registration, as this is a difference, I would prefer to mention both or otherwise be consistent and explain once that registration means that a DRMA had a prospective protocol (registration or protocol publication) and use the same term throughout the manuscript (see also title and abstract).

Response: Thanks for this valuable suggestion. We’ve unified them throughout the manuscript, we choose to mention both of them (in order to distinguish the different two ways).

b) Did the independent variable has to be continuously (e.g. sleep duration in minutes) or could it also be a categorical variable (e.g. sleep duration in 2-hour intervals)?

Response: The variables extracted from the original article is generally categorical one (e.g. sleep for 6-8 hours), however, based on current methods, this should be treated as continuous; generally, the median/mean/middle point of the interval was used in the DRMA model so that this can be treated with continuous. However, it is also possible to use a categorical variable, we are attempting to develop such a model.

c) Please be more precise about the inclusion criteria of included meta-analyses: Did you include meta-analyses on all kinds of included studies, meta-analyses on RCTs and cohort studies but also on observational studies?
Response: Thanks for this valuable suggestion. We did not limit the type of original studies, if a meta-analysis meet the definition of dose-response meta-analysis, it then included, regardless if it is based on RCTs or cohorts. However, it is interesting that for the 529 dose-response meta-analyses we included, there were 527 based on observational studies, and only 2 based on RCTs. We’ve added an illustration in the inclusion criteria part.

d) Consider to explain why you limited your search to studies published after 2010 (because PROSPERO was launched in 2011? Very few DRMA were published before 2011?), in this way, it will be easier for the reader to understand the rationale for this limitation of the period of time.

Response: We’ve added the reason why we limited our search after 2010. This is because there were very few dose-response meta-analysis published before 2011.

e) The search terms mentioned in the methods section are not consistent with the search strategy in the appendix (but rather limited to one part of the search). Consider just referring to the appendix or otherwise you should describe your search terms in a more comprehensive way.

Response: Thanks for this valuable suggestion. We’ve revised it and only referring to the appendix.

f) Study selection process: "...they read the full texts together to check against the eligibility criteria ... For each of the steps, the authors carefully cross-checked the assessment of eligibility, collected data, and assessed the methodological and reporting quality."

Was the full-text screening (and data extraction) done independently by the authors or together?

Response: The two reviewer screen the full-text independently. We’ve revised the error in the manuscript.

g) "Those DRMAs claiming registration or protocol publication, which failed to provide any details and cannot be obtained by our further attempt (searching the websites of the institution of the first and corresponding author), were not treated as such."
I am not sure if searching the websites of the institutions of the first and corresponding author is sufficient. Searching PubMed and PROSPERO seems to be a better way to identify further protocols.

Response: Thanks for this valuable suggestion. We did not searched the PubMed and PROSPERO. We did some attempt by searching the supplementary file, first/corresponding author’s websites. This is because these DRMAs have mentioned the information, but also claimed that the protocol is unattainable currently.

h) Page 7, line 12-15: What is about the option „not applicable”? Some of the items might be not applicable for some meta-analyses.

Response: We did not set “not applicable” option, but used “Can't answer” instead, which we have illustrated in our previous article [J Clin Epidemiol. 2018 Nov 13. pii: S0895-4356(18)30455-4]. While for the situation that the information was “Can't answer”, we treat it as “No” in the analysis as previous research suggested [JAMA 1995; 273:408-12.]

i) Please specify which test for normality was used.

Response: We’ve specified the test method for normality. (Skewness-Kurtosis test)

j) The definition of registration and published protocol is rather broad including meta-analyses with a supplemented protocol and those referring to a protocol reported on a homepage. Though you discuss this point as a limitation of this study, you should also explain the rationale for this definition in the method section, especially, as the introduction is just referring to the advantages of RROSPERO (page 4, line 31-35).

Response: Thanks for this valuable suggestion. The definition is refers to the PRISMA checklist of the reporting item “registration and protocol”, we have illustrated the rationale for it in the revised manuscript.
3) Results:

a) It would be interesting to analyze how the proportion of registered DRMA compared to those not registered changed over the years. It would be expected that this proportion increased during the last years.

Response: Thanks very much for this valuable suggestion. We’ve added the information in revised manuscript. It is true that proportion of registration is increased in 2017 compared to 2013-2016 (see figure below). The proportions were 17.14%, 18.18%, 7.14%, 5.13%, 3.33%, 5.88%, and 16.67% from 2011 to 2017.

b) Table 1: How did you differentiate between general and specialist journal?

Response: A general journal means it published articles on all areas (e.g. plos one) or focus on medicine area (e.g. BMJ open). For specialist journal, we treat it as those publish article only on a certain type of disease (e.g. cancer) or a certain body system (e.g. urology). We’ve added this illustration in the foot note on Table 1.

c) Table 1: Why did you not calculate a p-value for the AMSTAR and PRISMA score at the end of table 1?

Response: This is because I presented the median (quartile ranges) for AMSTAR and PRISMA score, so the p-value was not calculated. However, we’ve given the p-values for them in the context.

d) Appendix 4: Please check the appendix table 4. The column for the registration information does not fit to most of the studies (e.g. Aune et al. registered their protocol not within PROSPERO but have a protocol at the website of the WCRF, the protocol of Kelly et al. is registered within PROSPERO and not at the website of the WCRF…).

Response: We’ve carefully checked the appendix table 4 and revised the registration information accordingly.
e) What did you do if a DRMA had two different registrations or if a protocol was registered and published? For each study there was just one registration mentioned but e.g. Ju et al. registered their protocol at PROSPERO and clinicaltrials.gov.

Response: Thanks for this valuable suggestion. A DRMA had two or more different registrations was also treated as registered, while for those registered at PROSPERO and clinicaltrials.gov, we treat it as PROSPERO which is designed for registration for SR/MA.

f) Table 2: Consider providing proportions and p-values for cases and controls instead of the numbers and rate differences (as these are no rate differences), this could improve readability.

Response: Thanks for this valuable suggestion. We’ve revised Table 2 accordingly.

g) Page 9, line 10: What do you mean by „mean score of methodological quality“? Did you mean the mean score of AMSTAR? How can there be a difference in the mean score of methodological quality but not in the median score of AMSTAR?

Response: The mean score of methodological quality is the mean score of AMSTAR. There is difference for the mean score and median score because although we have evidence that the total score of methodological quality can be treated as normally distributed, however, it is not as ideally as standard normal distribution. So, the mean score may have litter difference to the median score.

h) The presentation of the results in the result section is much too detailed (many numbers, confidence intervals and p-values) especially with regard to the small number of included studies you might consider to refer to the numbers in the tables more often instead of mention all of them in the text.

Response: Thanks for this valuable suggestion. We’ve removed the section of “Fully compliance rate between AMSTAR and PRISMA” to make it more concise.
4) Discussion:

a) It should be critically discussed that many of the included DRMA are from the same authors, as the quality of a meta-analysis will in the first line depend on the authors conducting it rather than from the registration alone.

Response: We’ve added this in the limitation part.

b) Page 11, line 31: "AMSTAR and PRISMA checklist were wildly used…” I guess you mean "widely" instead of "wildly"

Response: We’ve revised this typo error.