Author's response to reviews

Title: The interpretation of meta-analyses: an objective or subjective process?

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Editor

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Dear Editor,

We would like to thank the reviewers again for their comments and suggestions on our manuscript titled "The interpretation of meta-analyses: an objective or subjective process?" We have made most of the requested changes to the manuscript and we believe this has improved the manuscript, and addressed their concerns. There were some issues we felt were minor where we did not feel the changes would improve the manuscript and our reasoning is provided in the Answers to Reviewers. We would be willing to make these changes if the Editor still feels that they should be done after reading our response.

We have cut-and-pasted most of the reviewer’s comments directly into the Answers to Reviewers to minimize any confusion. In areas where strange characters exist (e.g. “â##” for General comment #3), this came directly from the PDF file we received.

We would like to submit the revised version for further review.

We look forward to hearing from you

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Answers to Reviewers

Reviewer #1 (Alex Sutton)
This reviewer had no further comments.

Reviewer #3 (Tom A. Trikalinos)

Reviewer (Gen #1 and 2, Results #1): The reviewer seems to suggest that we rephrase the manuscript and replace “meta-analysis” with “quantitative systematic review” throughout the manuscript.

**Answer:** We agree with the reviewer that different people use the term meta-analysis differently at times, but we believe that to use his suggestion would make the manuscript difficult to read and unnecessarily wordy. It is important to note that the emphasis of this paper is on the interpretation of the quantitative summary statistics (meta-analysis) and not on whether the literature search and data abstraction were systematic or not. Finally, the implication of the reviewer’s suggestion is that no one should ever use the word meta-analysis and we believe this is an unrealistic expectation. Therefore, we have defined the term “meta-analysis” as suggested and then use “meta-analysis” throughout the text. This is a minor point and we will make the suggested changes if the editor still feels that it is appropriate after reading our response.

Reviewer (Gen 3): “Mention in the results section the apparent tendency for people who probably know the topic very well (such as the 2 cardiologists-specialists and the non-practicing physician - epidemiologist with years of experience??) to be conservative and unconvinced and contrast to the other reviewers who were convinced (as if they were following a â##stick with random effectsâ## heuristic rule)

**Answer:** We have made changes in the manuscript to address this point, but feel that this is more appropriately placed in the discussion. We believe the Results section should report only the results as much as possible, and any interpretations of the results (e.g. why different people responded differently) should be mentioned in the discussion.

Reviewer (Gen #4): “Clarify in the text whether the reviewers were given information on the standard of care at each time period.”

**Answer:** We have made the appropriate changes. This information was given through the summaries of the review articles.

Reviewer (Gen #5): “Please, comment on the limitation of the choice of the topic in the Discussion.”

**Answer:** We have made the appropriate changes.

Reviewer (Abs #1): “The opening sentence is still too strong”

**Answer:** We have made the changes suggested by the reviewer
Reviewer (Abs #2-5, Background #1): These comments are similar to those of Gen #1 and #2.

**Answer:** As per our previous answer, we believe that meta-analysis is an appropriate term once defined.

Reviewer (Background #2): “p4, lines 6 from bottom to 3 from bottom: I cannot understand what you mean here.”

**Answer:** We have reworded the text to make it clearer.

Reviewer (Methods #1): You state that the reviewers were given all pertinent reviews up to the corresponding times per package. How were these identified? Based on the publication type in the corresponding MEDLINE field? How many were there? It seems daunting to go through all reviews that have been written on this topic.

**Answer:** We apologize for the confusion and have corrected the text. We provided the reviewers with “summaries of the review articles”. Our reviews were retrieved by omitting the reference to RCTs in the search strategy – we had originally intended to obtain all observational studies on this topic as well but in fact could not find any. When we retrieved articles, we only included review articles that directly addressed the question of magnesium administration in the early post-operative period or explained the mechanism of action/pathophysiology of magnesium as it relates to heart. We did not include all review articles discussing other aspects of magnesium. These reviews were summarized by the research assistant abstracting the data. For more recent reviews, the research assistant only included new information in the summary. If there was no new information, the article was briefly summarized in a couple of sentences. We have added the number of reviews in the text for the first package and the 2nd package because the text allowed for this without breaking up the natural flow. There were 23 review articles summarized in the first package and 6 review articles summarized in the 2nd package.

Reviewer (Methods #2): “Please, state how long did it take the reviewers to do this? Minutes, hours, days or weeks?”

**Answer:** We did not keep track of time while reviewing the articles. Some reviewers would review all the information at once, and some reviewers would split the work up over several sessions especially when there were more articles to cover. We estimate that it required between 1-8 hours per package depending on how many articles and have added a sentence to this effect in the results. The delay between sending the package and receiving the answers to the questions ranged from days to months depending on the package, and other commitments of the reviewers, but we did not include this information because it is tangential to our results and we believe would be distracting from the main message.

Reviewer (Results #2): “Please, provide 2 graphs (forest plots), one with fixed and one with random effects models. The layout should summarize the information succinctly”

**Answer:** We have provided one figure with the requested information in order to
supply the information as succinctly as possible. We did not feel it necessary to provide separate figures for random and fixed effects because the forest plots and individual study odds ratios are exactly the same – the only difference is in the weighting of the individual studies. Therefore, we created a figure in Review Manager for fixed effects, and one for random effects. We then exported the figures as RTF and combined the diamonds and summary effect estimates into one figure. This figure also shows the data for each study at each time point. This seems repetitive but we felt that if we just added the additional studies at each time point and omitted the earlier ones, it might be too confusing. There is a summary diamond for each package and the summary diamond for 23 RCTs is the final diamond. The ISIS-4 trial is clearly indicated. Reviewers were also given packages with forest plots for arrhythmias but we have not provided these. Finally, it is important to note that during the process of reviewing the meta-analyses, some authors noted a couple of data entry errors. Because some authors had already reviewed the material, and the changes were minor and would not realistically affect the responses, we did not ask reviewers to go back and redo those packages. In order to be transparent, we provide the summary statistics shown to the reviewers in the table as before (numbers the same as previous versions) and provide the corrected data in the figure.

Reviewer (Results #3): “Summarize in 3-4 lines the thoughts/comments of the various reviewers on the discrepancies between ISIS-4 and the smaller RCTs. I understand that there was room for such comments in the forms the reviewers filled in. If none of the reviewers commented on this, this is very interesting to know and please state it.”

Answer: We have made the appropriate changes and focused on the changes in opinions when moving from 10RCT package to the 20 RCT package (i.e. before and after ISIS-4).

Reviewer (Results #4): “Relevant to my general comment #4, please indicate if any of the reviewers commented on the differences in the standard of care over time periods.”

Answer: We have made the appropriate changes.

Reviewer (Discussion #1): “The Jadad scale is at best indicative, and scores reporting quality to a large extent.”

Answer: We are not sure what changes the reviewer would like. We have now changed the sentence to read “Finally, even though we provided everyone with the quality score of reporting for each study based on the Jadad scale [16], it is possible that the reviewers differentially judged the quality of the studies.”

Reviewer (Discussion #2): “Page 11, 1st paragraph: Comment here on the problems stemming from the choice of this particular example.”

Answer: This paragraph discusses evidence-based medicine in general and we believe the appropriate location for a discussion of the problems stemming from our choice to use this topic is in the limitations section.
**Reviewer (Discussion #3):** “Please drop the 2nd paragraph in page 11, to shorten the discussion. The comments in this paragraph are not essential to this project. Moreover, if you were to open this can of worms you also have to explicitly refer to decision analysis and decisions under uncertainty.”

**Answer:** We have left this paragraph in because we feel that it raises important issues that most consumers of meta-analyses (and authors currently discussing discordant interpretations of meta-analyses) are not aware of. We have not added any text about “decisions under uncertainty” because all clinical and policy decisions (i.e. the decisions that would be based on meta-analyses) are made under uncertainty – it is only a question of the degree of uncertainty.

**Reviewer (Discussion #4a-d):** “Page 12, in the study limitations, you do not really discuss the study limitations.

a. I suggested to discuss the limitation of the topic choice earlier on and you can briefly remind this here.
b. There was only one topic analyzed â## but there were objective constraints
c. One cannot really tell someone to forget what he/she knows about the topic â## but again there is no other way around this problem short of picking an unknown topic
d. There was no qualitative analysis of the reviewersâ## written comments, as done in qualitative research designs”

**Answer:** We have added a discussion of the limitations the reviewer suggests to the ones mentioned in our previous submission.