Author’s response to reviews

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

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Author’s response to reviews: see over
Dear Editor,

We would like to thank the reviewers for their comments and suggestions on our manuscript titled "The interpretation of meta-analyses: an objective or subjective process?" We have made extensive changes to the manuscript that we believe have improved the manuscript, and address their concerns. 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)

Reviewer: Please define exactly what you mean by meta-analysis.

Answer: We agree with the reviewer that it is important to have precise definitions. We believe that we defined this in the first paragraph “A recommended method is the meta-analysis, i.e. the estimation of a quantitative summary statistic for the measure of effect [2] based on a systematic review of the literature.” We think the confusion for the reviewer arose because of how we later described the packages we sent out (see answer to next point) and that text has now been modified. We would also like to add that although we agree with the reviewer that a meta-analysis does not have to be based on a systematic review, we opted for this definition for the purpose of this study because it is a very commonly used definition and suffices for the purpose of our study; to elaborate more would risk causing unnecessary confusion for the reader.

Reviewer: What is being evaluated in this work is not a meta-analysis by either definition used above. It is described as a package providing everything necessary to write a meta-analysis. But you then describe the packages as containing a meta-analysis(!) This is contradictory and needs to be clarified.

Answer: We have clarified the text to make this clearer. Each reviewer was indeed provided a meta-analysis. In addition to the meta-analysis, we also provided all the material that a reviewer might want to see if they were supervising a meta-analysis done by their own research assistants (i.e. everything else in the package such as data abstractions, etc). We did this because we agree with reviewer #3 that a meta-analysis cannot be interpreted without understanding the context of the question. This includes understanding the strengths and weaknesses of the studies providing data for the meta-analysis.

Reviewer: The packages contain all review articles published prior to the last a RCT in the package. Please clarify the inclusion criteria for such reviews.

Answer: We have made the appropriate changes. The reviews included both clinical and basic science reviews. We believe these types of reviews are important for several reasons, including the reasons pointed out by Reviewer #3 about co-interventions. For example, if a basic science review suggested that the mechanism of action of magnesium is to decrease the effectiveness of platelets, then one might expect the effect of magnesium to be reduced in studies where acetyl-salicylic acid (ASA) is used in patients (i.e. both experimental and comparison groups) because platelets are already inhibited. The other reason for including all the reviews is because meta-analyses are usually done by someone who has background knowledge of the subject. This knowledge is obtained through clinical practice, seminars, research meetings, public media and discussions. If one wants to isolate the process of interpretation from background knowledge, we feel the best way is to provide everyone with the same background knowledge. We accomplished this by instructing reviewers to base their decisions
only on the knowledge provided, and the same knowledge was provided to everyone.

**Reviewer:** Were both random and fixed effects analyses included?  
**Answer:** Yes, as per Table 1. We have now added this to the methods to make it clearer.

**Reviewer:** Outcomes of “mortality and/or arrhythmia” was confusing  
**Answer:** We have clarified the text. Each reviewer was given a meta-analysis for the outcome of mortality, and a meta-analysis for the outcome of arrhythmia for each time point – it was not a composite endpoint. This was done a priori because we did not know the data when the project began and we were not sure how many studies had been conducted for each outcome.

**Reviewer:** What was the comparison treatment?  
**Answer:** We have clarified the text. The comparison treatment was always placebo.

**Reviewer:** equating benefits and harms is welcome but there was no discussion of side effects  
**Answer:** We have clarified the text. In the context of an acute myocardial infarction, serious side effects due to magnesium would be difficult to detect and were generally not reported in the studies. Where they were reported, this was captured in the data abstraction forms provided to the reviewers but we did not do a meta-analysis on side effects.

**Reviewer:** I do not understand why having a discrepancy between meta-analyses and a mega-trial is a desirable aspect of the set of trials used to run this experiment.  
**Answer:** We have clarified the text. First, although the magnesium example may have been well known to Reviewer #1 and #3, the details of the discrepancies between studies were not well-known to the investigators when the topic was chosen. The reason for choosing a topic where a mega-trial disagreed with previous small studies is because one of the reasons often given for discrepancies is the relative weight a reviewer gives to large trials. From the strict meta-analysis perspective, the fixed effects meta-analysis gives more weight to large trials compared to the random effects meta-analysis. However, the presence of a mega-trial may further affect the interpretation of the meta-analysis and the decisions that are made based on it. For example, some people believe that large trials are conducted with more rigor. The meta-analysis itself does not take into account the quality of the study. In direct response to the reviewer’s confusion, we have deleted the phrase that we did not know the details of the original studies. The intention of this phrase was to highlight that we did not specifically choose this topic because we knew what the outcome would be.

**Reviewer:** Struggling to understand and interpret the findings. There is so much going on it is hard to reach any conclusions.
**Answer:** We agree with the reviewer. We had hoped that the notes accompanying the answers would yield enough information to tease out some of the possible reasons but this did not occur. We have now developed a protocol to study the process using a mixed-methods design in which reviewers are interviewed each time after being shown a set of simulated data. There are of course many variables one can manipulate in a simulation study, and we plan to address each over the course of several studies. That said, the importance of the manuscript currently under review is that the results show very discrepant interpretations even when there is homogeneity in the data and appropriate sample sizes and that the discrepancies in interpretation are not solely due to heterogeneity or a preference of fixed vs random effects. In addition, there are many clinical situations where there are less than 10 RCTs involving less than 4000 patients and clinical decisions are necessary. Are 10 RCTs involving 4000 patients with homogeneous results not enough? Our results suggest it is not and that different people will continue to interpret the findings differently, and that some of the expectations of the EBM movement may not be realistic.

**Reviewer:** I have concerns that question 2 asked is not really helpful.

**Answer:** We respectfully disagree with the reviewer. Our interest was about how meta-analyses are used to guide clinical decisions, rather than the intentions of those who originally developed the methodology. Question 2 reflects the reality that clinicians are often provided evidence of the effectiveness of a treatment but do not prescribe the treatment because they prefer to wait for longer follow-up or more trials (one reason for slow-adopters versus quick-adopters of new treatments). Therefore, this question was included because we believed that some individuals might not yet recommend treatment even though the first studies suggested it was beneficial. Alternatively, some individuals might prescribe a treatment that was not yet proven beneficial because they believed the risks were minimal. Since one of the goals of the EBM movement is to help clinicians choose the most effective treatment, we believe it is important to note when they do not make that choice. We believe our results will be useful to others who are conducting research in this area.

**Reviewer:** Surely the recommendation of a treatment depends on the alternatives (related to Question 3).

**Answer:** We agree with the reviewer and add that it also depends on the particular patient characteristics for prognosis, other co-morbidities, etc. This is why the question was phrased in a general manner and the respondents were allowed to specify specific situations where they would use the treatment or not.

**Reviewer:** Interpreting a meta-analysis and making a decision for future patients are two different processes.

**Answer:** We agree with the reviewer. Our question #1 (proven effective?) is about interpreting the meta-analysis. Our question #3 (recommend treatment?) is about decision making. Our question #2 (would eventually be proven effective?) is an attempt to understand why someone might recommend treatment if they
don’t believe the treatment is yet proven effective (this is a very common occurrence in medicine).

**Reviewer:** systematic reviews increase transparency and reproducibility and this should be mentioned in the introduction.

**Answer:** We agree with the reviewer and have made the appropriate changes

**Reviewer:** What is the delineation between process and interpretation?

**Answer:** We have made changes to clarify the text. We believe that different people will make different distinctions. In the context of the current manuscript, process refers to everything up to the presentation of the data to the person who will interpret it. Therefore, the example given about reading 6000 abstracts refers to the application of inclusion / exclusion criteria, and as in any other study, this is a process issue.

**Reviewer:** Include the Ades et al reference on the interpretation of random-effects meta-analyses

**Answer:** We were aware of this article but did not include it because the discussion is tangential to the focus of our manuscript. This article is a prescription for how to interpret heterogeneity. Our manuscript is about how people actually interpret the results. The analogy is similar to language – there are rules about grammar and many people will edit writing so that it conforms to these rules. Linguists however study how language is used and not how it is “supposed to be used”. These are very different questions and our focus was on the current use rather than the prescribed use.

**Reviewer:** Include a forest plot that includes the meta-analyses of all 23 studies with cumulative pooled results at the various package levels.

**Answer:** We have preferred not to add the forest plots because it would require considerable space to have one for each of the 5 packages. The Table already provides the summary information that includes 1) number of subjects, 2) fixed and random effects odds ratios, and I² value. If the editor believes the extra figure would be worthwhile, we would be happy to include it.

**Reviewer:** Table 1 should still have the results of the first study.

**Answer:** The first study measured infarct size and mortality was not the outcome. There were no deaths reported and so we did not report an effect estimate.

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**Reviewer #2 (Malinee Laopaiboon)**

No comments

**Reviewer #3 (Tom A. Trikalinos)**

**Reviewer:** It is unclear exactly what detail the reviewers had and whether it included the co-interventions that constituted standard of care.
**Answer:** We have clarified the text. The only inclusion criterion was a RCT on the effects of intravenous magnesium in the immediate post-MI period. Where there were co-interventions because it was part of the standard of care, these were provided to each reviewer as part of the standardized data abstraction.

**Reviewer:** The choice of the meta-analysis worked example should be further supported.

**Answer:** We have made the appropriate changes in the introduction. In brief, when the protocol and study began, we were not as aware as BMC reviewers about the details of the studies that were eventually included in this meta-analysis. We were aware that a mega-trial contradicted previous RCTs. We were interested in whether this would be a defining feature in the discrepancies between reviewers. Our findings suggest it was not because there was considerable discrepancy even when there were only 10 RCTs and homogeneity between studies.

**Reviewer:** Why did the authors go to such lengths to run a comprehensive search…one could simply obtain the studies using references lists of an existing meta-analysis…?

**Answer:** After completing the review, we agree with the reviewer. However, the originally funded grant was written without knowing the studies. In addition, different meta-analyses on the same topic often have different inclusion/exclusion criteria and we wanted to be as inclusive as possible.

**Reviewer:** Why did the authors examine a single example?

**Answer:** The study described in the manuscript actually represented only one part of our project. The entire project was also designed to answer questions based on a meta-analysis of all the observational data, and a systematic review that included all the basic science data. However, for the magnesium question, we could not find any observational data examining magnesium in the post-MI period (there were studies looking at magnesium supplementation as preventative). The project also was designed to examine discrepancies based on meta-analyses of the effects of HRT but that systematic review has only recently been completed because the original research assistant moved and we had difficulty finding an appropriate replacement. Given that it takes considerable time for reviewers to go through each meta-analysis package and provide answers, we do not expect to have data to analyze for another year and we feel that the results from the current analysis are interesting and important enough to be published now.

**Reviewer:** Please provide more details on the “exact information” the reviewers were given.

**Answer:** We have made the appropriate changes to the Methods section. In brief, reviewers were given the meta-analysis, and in addition, all review articles, the standardized data abstraction from the article and a copy of the original article itself (in case they wanted to look something up).

**Reviewer:** “If you just provide statistical output on effect sizes,…..then this boils down to what people understand from meta-analysis statistics rather than the interpretation of the meta-analysis results!”
**Answer:** We agree with the reviewer and this is why we also provided the standardized data abstractions, original articles, and also review articles on the topic that were published at the time. We feel that most meta-analyses are conducted by people who have some clinical knowledge about the field, and this is in fact the motivating factor behind the meta-analysis. By providing our reviewers with the clinical and basic science reviews on the topic at that time, we were able to simulate the knowledge a meta-analyst would have had at that time. Further, we believe this is a best-case scenario because some people conducting systematic reviews limit themselves only to RCTs and fail to understand the current understanding of pathophysiology and clinical care at the time.

**Reviewer:** I also found kind of strange the choice to provide publication bias tests, but I presume that they may have been asked by the reviewers themselves

**Answer:** The decision to include publication bias tests was made a priori. Although there are well-known weaknesses to the publication bias tests, they are still considered one component of a systematic review and we felt it was important to provide the reviewers with whatever information would be included in a meta-analysis.

**Reviewer:** Please streamline the discussion.

**Answer:** We have cut the discussion down from 4 pages to 3 pages (1195 words to 983 words).

**Reviewer:** The reviewer suggested that the opening statement of the abstract is not accurate and we provide data to support it or rephrase.

**Answer:** The statement in question is “The discrepancies between the conclusions of different meta-analyses are generally believed to be due to different methodologies.” We have referenced the statement in the text (Jadad AR, Cook DJ, Browman GP: A guide to interpreting discordant systematic reviews. CMAJ 1997, 156(10):1411-1416.). Based on the results of our study, we obviously agree with the reviewer that there are other reasons for the discrepancies but we also believe that many people do not understand this.

**Reviewer:** The interpretation thereof is *by definition* subjective. Consider deleting or rephrasing to “Is the *interpretation* of a meta-analysis objective?”

**Answer:** We have made the appropriate changes. The text now says “Is a meta-analysis (procedural and/or interpretations) objective?”. We have preferred to keep both issues together at this point in the Background because we feel it improves the flow of the manuscript. The argument in favor of meta-analyses is often that it is objective, and the people putting forth these arguments do not separate out procedural issues from interpretation. Therefore, we feel that we should first repeat the statement and then show that it is important to distinguish between them. Further, the reviewer also suggested that the procedural issues of a meta-analysis are as objective as possible. We agree with the reviewer, but “as objective as possible” does not mean they are objective. As an example, we highlight the comment by Reviewer #1 that the delineation between process and interpretation is
sometimes difficult. Reviewer #1 asked if two reviewers disagree on the application of inclusion / exclusion criteria, is this process or interpretation? We add that most meta-analyses have a third person to rule on differences of opinion or say that differences were “resolved by consensus”. If these were truly objective processes, we should not be requiring methods to resolve disagreements.

**Reviewer:** Please make a better distinction between technical and interpretation in the introduction and throughout the manuscript.

**Answer:** We have made changes throughout the text to improve the clarity.

**Reviewer:** Reword the preamble to the appendix

**Answer:** Although we understand the reviewer’s comment, the appendix is a copy of the actual questionnaire (which included the preamble) given to the reviewers. It would not be appropriate to modify it at this time.