December 03, 2014

Dear editor, dear reviewers,

Please find enclosed the edited manuscript in Word format (file name: 14698-review.doc).

Title: Why meta-analyses are important for complementary and alternative medicine research

Author: Holger Cramer

Name of Journal: World Journal of Meta-Analysis

ESPS Manuscript NO: 14698

The manuscript has been improved according to the suggestions of the editor and the reviewers. Changes are highlighted in red font.

1) Format has been updated.

2) Revision has been made according to the suggestions of the reviewers:

Reply to reviewer 02445972:

1. *I found the publication persuasive and articulate about the issues under consideration and the use of the method. The comments were not over claims but were measured and very accurate representations of the method as well as the research that was reviewed*

HC: Thanks a lot.

Reply to reviewer 02521098:

1. *Meta-analysis is a important tool to summarize the effect of CAM for human health. However, heterogeneity between the trials is a common problem in CAM studies. Can you comment on this issue in detail? The article is well written and should be accepted.*

HC: Thanks a lot for your comments. Heterogeneity between CAM trials and its consequences when conducting a meta-analysis are now discussed.

Reply to reviewer 00910998:

2. *In my opinion this editorial on complementary and alternative medicine research highlights right things, but in a wrong way and with a wrong emphasis. Firstly it assimilates the concept of meta-analysis with that of a re-correct analysis of the data. I think that some of the reported examples, in particular the second, can be explained without a meta-analysis, but only with a proper assessment and evaluation of the published data.*

HC: Thanks a lot for your comments. I now make clear that a re-evaluation of the published data without relying on a published meta-analysis would also help overcome the problems I mentioned. However, a typical clinician who is using the published research as a guide for clinical decision making will often not be able to re-evaluate the data of all published trials. Thus, misleading analyses might result in a biased estimate of treatment effects. Thus, while meta-analyses might not be the only way to address this problem, they are a way that will reach more clinicians than a re-evaluation of single trials; especially since the latter are rarely published.

3. *In addition, it is a little misleading since a meta-analysis increases the power of the analysis, but does not reduce the bias of individual studies. This important issue does not seem to clearly come out.*

HC: I deleted the misleading notion that a meta-analysis can reduce the risk of bias resulting from biased analyses. It is now repeatedly pointed out that meta-analyses cannot reduce risk of bias or compensate for low-quality original research.

Reply to reviewer 14698:

1. *The letter/commentary submitted by Dr. Cramer addresses and important and central issue regarding the research validity of clinical trials and meta-analyses for CAM therapies. The manuscript is well written and precise.*

HC: Thanks a lot.

2. *I would suggest a few additions and changes as follows: However, while these trials are urgently needed to consolidate evidence for interventions that have been – by definition – rarely studied [add in "systematically"] in the past, the research evidence from single trials on CAM is often limited by small sample sizes, unclear methodology, and inadequate statistics.*

HC: Changed as suggested. Thanks for the suggestion.

3. *The author mentions that many CAM trials rely on within-group comparisons as RCT trials. One question to ask then is, are RCT trials the best way to study CAM interventions? How can be increase the validity of such studies? Would a cross-over design potentially solve some of the issues that are mentioned? The author may want to discuss the limitations of RCTs and what other trial designs are better suited. The assumption that meta-analyses will be able to overcome the limitations of RCTs may not hold true depending on the heterogeneity in defining outcomes and especially in regards to the intervention. This should be further discussed by the author.*

HC: I am well aware of this discussion. However, it seems to be a bit out of focus for this editorial. I added a brief section on this topic. I do not believe that the main problem is the choice of a randomized trial design but the lack of adequate methodological training.

4. *The assumption that meta-analyses will be able to overcome the limitations of RCTs may not hold true depending on the heterogeneity in defining outcomes and especially in regards to the intervention. This should be further discussed by the author.*

HC: I now discuss heterogeneity between trials and its consequences for conducting a meta-analysis in more depth.

3) References and typesetting were corrected

I would like to thank the editors and the reviewers for their efforts, encouraging comments and constructive criticism.

Sincerely yours,

Dr. Holger Cramer
Department of Internal and Integrative Medicine, Kliniken Essen-Mitte
Faculty of Medicine, University of Duisburg-Essen
Email: h.cramer@kliniken-essen-mitte.de