Author's response to reviews

Title: Treatment of depressive disorders in primary care - protocol of a multiple treatment systematic review of randomized controlled trials

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Author's response to reviews: see over
Editors
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Dear editors,

enclosed we submit a revised version of our manuscript

Treatment of depressive disorders in primary care – protocol of a multiple
treatment systematic review of randomized controlled trials

for publication in BMC Family Practice. Please find our point by point responses
to the reviewer’s comments below. We also attach an additional version with
changes in track. We hope that you will find this new version acceptable

Sincerely
Klaus Linde
Comments by the reviewer

My interpretation is that it is a protocol for a meta-analysis of RCT of treatments of depression in primary care although the authors refer to systematic review in some part of the paper and meta-analysis in another. The methods for search and selection of papers, and the statistical methods for the meta-analysis are clearly described standard methods, but there is insufficient details on how outcome data will be pooled together for the meta-analysis, and how the results can answer the research question of "how the available treatment options compare with each other" better than the many reviews that are already available. The results of multiple treatment meta-analysis should be most original and useful but the authors regard it to be exploratory. The biggest uncertainty of the success of this study is whether there are enough good quality studies in primary care to make a meta-analysis meaningful.

1. Please state more clearly whether the proposed study is a systematic review or meta-analysis.

2. Please explain more clearly the meaning of the research question "how the available treatment options compare with each other". Does it mean that the study will try to rank the relative effectiveness of different treatments? A more specific and detailed review of the literature on what is known about the effectiveness of each treatment should be provided.

Response: We apologize that we have been unclear in our initial submission. Based on the comments we considerably revised the introduction. On page 4 we now introduce the concept of network meta-analysis in more detail. On the top of page 5 we describe key criteria for the validity of network meta-analysis (homogeneity, similarity and consistency) and our concerns that these might not be met in case of our project. These concerns are the reason why we prefer to describe our project as multi-treatment systematic review which might possibly include a network meta-analysis at least for some interventions (e.g. the different types of medications). We believe that this is correct and sincere – we should not promise something which might turn out to be unrealistic or invalid.

There is no mentioned of the Cochrane and NICE reviews on psychological treatments of depression.

Response: We have cited in our introduction the most relevant systematic reviews of primary care trials including two on psychological treatments (ref. 11 & 12). So far the Cochrane Library only includes a completed review on family therapy for depression and one on relaxation – both have been cited (ref. 22 & 23). All other reviews of psychological therapies are not yet completed with only protocols available (we are in regular contact with the coordinating editor of the Cochrane Depression, Anxiety and Neuroses Group, Rachel Churchill for mutual information). None of the reviews will be restricted to primary care patients. Also, the NICE reviews are not restricted on primary care. Nevertheless, we now cite the clearly highly important NICE guideline as reference 7 instead of the paper by Härter et al.

3. Explain why trials that compare with placebo or no treatment will be included if the study aim is to compare treatments with each other?

On page 4 we now explain that based on two separate comparisons of treatment A vs. placebo and treatment B vs. placebo it is possible to make an indirect comparison of the treatments A and B.

4. Please define the primary outcome measure better, is it the proportion of subjects who responded to the treatment? If it is, please define "responders" more clearly for studies that did not use the HAMD or CGI as the outcome measure including those that used change in depression scale scores as the outcome measure.
We now explicitly state in the “synthesis” section that the primary outcome measure is the proportion of subjects who responded to treatment. In the “data extraction” section we now describe that response according to HAMD (we document which criterion has exactly been used as these vary slightly) is our first preference as outcome, after a discussion in the group we decided to add response according to the MADRS as second preference and use the CGI improvement scale as third preference. We did not predefine our exact approach if other types of responder data are reported as we simply do not know yet what will be available. We consider it reasonable to not predefine further response outcomes. However, we added that we will estimate response data from metric scales if no such data are presented in a study.

5. As explained above, the results of multiple treatment meta-analyses should be most useful in addressing the research question. Therefore, the multiple treatment meta-analysis methods need to be described more fully.

As described in our response to the general comments and the comments 1 & 2 we are uncertain whether a valid network meta-analysis will truly be possible (maybe for the different types of drugs). We have now added a phrase indicating that, in case network meta-analysis is possible, analyses will be done and interpreted based on a Bayesian analysis using WinBUGS code following Lu and Ades (2006), as mentioned on page 13 of the revised manuscript.