BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials
AUTHORS	Mulla, Sohail; Buckley, D; Moulin, Dwight; Couban, Rachel; Izhar, Zain; Agarwal, Arnav; Panju, Akbar; Wang, Li; Kallyth, Sun; Turan, Alparslan; Montori, Victor; Sessler, Daniel; Thabane, Lehana; Guyatt, Gordon; Busse, Jason

VERSION 1 - REVIEW

REVIEWER	Andrew Moore Pain Research Nuffield Division of Anaesethetics University of Oxford The Churchill Oxford UK
REVIEW RETURNED	24-Jul-2014

GENERAL COMMENTS	This is an issue of philosophy, and I believe that the 15 authors have got almost, but not completely, exactly wrong. They propose to take all neuropathic pain conditions, and all treatments, and pool them in a network analysis. Fine, except that: Neuropathic pain conditions are different - many treatments work in painful diabetic neuropathy - almost none in HIV neuropathy. No doctor treats "neuropathic pain". So the analysis is irrelevant. Almost all data, as the authors say, is in placebo controlled trials. So the network is really an indirect comparison with a common comparator - placebo. There are many reviews that can be consulted, and overviews. They make no mention of the criticality of outcome desired by patients, no mention of the major biases from imputation method and small size, or duration of the trial, or of a range of other potential biases. There is no possibility of the review being remotely useful, because they will resort to relative outcomes, of some passing statistical interest but no value to clinical practice. Why would anyone bother? The fact is that right now you could go to the Cochrane library, or BMJ, or JAMA, and find most of what one wants to know, properly done, and with relevant outcomes. This just makes me want to weep, that after 20 years of reaearch in evidence in pain people can still think this is a useful enterprise.

REVIEWER	Avinesh Pillai

	Department of Statistics University of Auckland New Zealand
REVIEW RETURNED	02-Oct-2014

GENERAL COMMENTS	Typically, in a protocol for a meta-analysis, no data is presented but a detailed plan is, including the outcomes of interest and the methods of analyses. The authors have described the analyses they will carry out, but the outcomes of interest have not been defined yet and will be defined using IMMPACT guidelines. It remains to be seen whether the analyses suggested are able to be carried out fully with the outcomes collected, especially for multiple treatment comparisons. The authors touch on the limitations of the study, but these limitations will need to be reevaluated after data collection. Especially since no review has evaluated all interventional studies for chronic neuropathic pain. It important that the authors do not select too many outcomes for analyses, because of the increased risk for false finding false positive results. Overall, a good solid plan for a meta analyses. It will be very interesting to see which outcomes the authors end up selecting for analyses.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Andrew Moore

This is an issue of philosophy, and I believe that the 15 authors have got almost, but not completely, exactly wrong. They propose to take all neuropathic pain conditions, and all treatments, and pool them in a network analysis. Fine, except that: Neuropathic pain conditions are different - many treatments work in painful diabetic neuropathy - almost none in HIV neuropathy. No doctor treats "neuropathic pain". So the analysis is irrelevant.

Response: Dr. Moore is convinced that there are major differences in response to treatment across neuropathic syndromes. There are those who agree with him. For instance, the European Federation of Neurological Societies (EFNS), recommend treatments for individual neuropathic pain conditions. There are others who disagree. For example, the Canadian Pain Society (CPS) and the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG), group peripheral and central neuropathic pain conditions and issue recommendations accordingly.

In our review, we are not prejudging the issue. Dr. Moore, in his comments, does not seem to understand the methodology of our review. A key a priori subgroup analysis for the direct comparisons will be that chronic neuropathic conditions that are a result of lesions or diseases within the central nervous system will differ in their effects from peripheral neuropathic pain conditions.

Almost all data, as the authors say, is in placebo controlled trials. So the network is really an indirect comparison with a common comparator - placebo. There are many reviews that can be consulted, and overviews.

Response: Because of the limited number of head-to-head comparisons, there is little information addressing the comparative effectiveness and safety of therapies. The network meta-analysis, utilizing direct and indirect evidence, will provide new insights into the issue.

In addition, previous reviews have methodological limitations that our review will address. These include: focusing on specific therapies rather than being comprehensive; lack of comprehensive searching; suboptimal assessment of risk of bias; and failure to use the state-of-the-art GRADE approach to evaluating certainty of treatment effects.

They make no mention of the criticality of outcome desired by patients…

Response: Such a remark makes us wonder about the care, or perhaps the objectivity, with which Dr. Moore has read our protocol. As we state in our manuscript, we will, because they are important to patients, collect data across nine core outcome domains that are recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).

Further, we are going to facilitate interpretation of our results by contextualizing values of our meta-analyses, i.e. weighted mean difference, and standardized mean difference, by noting the corresponding minimally important difference (MID) – the smallest change in instrument score that patients perceive is important, and using this threshold to derive a relative risk and number needed to treat.

However, we have modified our protocol to consider more stringent thresholds than the MID:

"Patients may be interested in the ability of a given intervention to provide more than an MID – to produce improvement that allows patients to feel much better (i.e. substantially greater than the MID), Thus, for our analyses, for studies that report percentage reduction in pain, we will also use thresholds of ≥20%, ≥30% and ≥50% reduction of pain from baseline to calculate the proportion of patients who have benefited in each trial, and derive RRs and risk differences."

… no mention of the major biases from imputation method…

Response: We presume the reviewer is referring to imputation in cases of missing participant data from the individual trials. As we state in our manuscript, "we will use recently developed approaches to address missing participant data for dichotomous outcomes and continuous outcomes.[90, 91] When plausible worst case scenarios reverse the treatment effect, we will rate down for risk of bias." These analyses are not intended to generate best estimates of effect, which will come from the complete case analysis, but rather to establish the vulnerability or robustness of results to the missing outcome data.

… and small size…

Response: We presume the reviewer is referring to the fact that smaller trials generate more imprecise results. As we describe in our manuscript, we will use the GRADE approach to determine whether to rate down confidence in the body of evidence. A key domain of the GRADE system is imprecision, which we will contextualize using the optimal information size (OIS) – the number of patients generated by a conventional sample size calculation for a single trial. In cases in which our meta-analysis suggests benefit but the sample size is less than the OIS, we will follow GRADE guidance and rate down confidence in effect estimates for imprecision. For the purposes of calculating the OIS, we will assume, for binary variables a relative risk reduction (delta) of 25%, an alpha of 0.05, and a beta of 0.20, and a baseline risk from observational studies of representative patients. For continuous variables, we will use the same alpha and beta, the largest standard deviation from the available studies (thus ensuring a conservative estimate of OIS), and for the delta the minimal important difference (if established) or an effect size of 0.2 standard deviations.

… or duration of the trial…

Response: As we describe in our manuscript, one of our a priori subgroup hypotheses is that trials with longer follow-up times will show smaller treatment effects than trials with shorter follow-up times. Thus, we will explore duration of trial as a possible effect modifier.

or of a range of other potential biases.

Response: We would be happy to consider other specific biases that we have not already considered in our analytical plan. If the reviewer has specific suggestions, we would be happy to consider them.

There is no possibility of the review being remotely useful, because they will resort to relative outcomes, of some passing statistical interest but no value to clinical practice. Why would anyone bother? The fact is that right now you could go to the Cochrane library, or BMJ, or JAMA, and find most of what one wants to know, properly done, and with relevant outcomes. This just makes me want to weep, that after 20 years of research in evidence in pain people can still think this is a useful enterprise.

Response: We note, with concern, Dr. Moore's emotional language. With regard to "relative outcomes", we are not certain what Dr. Moore means, but as we have noted we will estimate both relative and absolute measures of effect. We have noted above what our study will add to existing analysis: comparative effectiveness assessment through use of direct and indirect evidence, and addressing methodological limitations of prior reviews.

Reviewer Name: Avinesh Pillai

Typically, in a protocol for a meta-analysis, no data is presented but a detailed plan is, including the outcomes of interest and the methods of analyses. The authors have described the analyses they will carry out, but the outcomes of interest have not been defined yet and will be defined using IMMPACT guidelines. It remains to be seen whether the analyses suggested are able to be carried out fully with the outcomes collected, especially for multiple treatment comparisons.

The authors touch on the limitations of the study, but these limitations will need to be reevaluated after data collection. Especially since no review has evaluated all interventional studies for chronic neuropathic pain.

It important that the authors do not select too many outcomes for analyses, because of the increased risk for false finding false positive results.

Overall, a good… [comments are cut off]

Response: The reviewer is correct that it remains to be seen how many of the IMMPACT outcomes the data will allow. We disagree, however, with the suggestion that we limit addressing outcomes because of the risk of false positive results. We believe that we should try and address all outcomes that are important to patients, and the IMMPACT statement provides a reasonable guide. The issue, we believe, is care in interpretation of results. If, for instance, 8 of 9 outcomes show no suggestion of a treatment effect and the 9th shows a small effect of borderline statistical significance, the appropriate interpretation would be skepticism about patient-important effects on any of the 9 outcomes.

References

1. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. The

American journal of medicine. Oct 2009;122(10 Suppl):S22-32.
2. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane database of systematic reviews (Online). 2013;11:Cd010567.