PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing bias in osteoarthritis trials included in Cochrane reviews: Protocol for a meta-epidemiological study
AUTHORS	Hansen, Julie; Juhl, Carsten; BOUTRON, Isabelle; Tugwell, Peter; Ghogomu, Elizabeth; Pardo Pardo, Jordi; Rader, Tamara; Wells, George; Mayhew, Alain; Maxwell, Lara; Lund, Hans; Christensen, Robin

VERSION 1 - REVIEW

REVIEWER	Peter Herbison Dunedin School of Medicine University of Otago
REVIEW RETURNED	13-May-2014

GENERAL COMMENTS	I have only very minor comments on this paper. I am aware that pain is measured in various ways. Commonly it is measured by either a visual analogue scale(VAS) or a numeric rating scale and less commonly by more complicated instruments. Do the authors think that results from the VAS may differ from those of the rating scale? One of the reasons why small studies may give different answers from larger studies, is that the participants in small studies may be more homogeneous than those in larger studies. Thus changes with treatment may be more similar, and if they are a more severely affected group the potential for gain may be larger. I was a bit confused about what was meant by study size, and even after this was explained I thought it was a bit unclear. e.g. In table 2 it is not clear whether they mean the number randomised or the number assessed. What will happen when reports of studies only use one or the other?

REVIEWER	Eveline Nüesch University of Bern, Switzerland
REVIEW RETURNED	29-May-2014

GENERAL COMMENTS	I entered yes to question 14 due to a very similar study that has resulted in several publications already, which were not cited in the manuscript. The authors propose undertaking a meta-epidemiological study to

	investigate the extent of different sources of bias in Cochrane reviews of osteoarthritis trials using patient-reported pain as an outcome. Although I completely agree with the authors that assessments of bias in osteoarthritis trials included in Cochrane reviews are important, I have several comments on the proposed study: 1. A meta-epidemiological study in osteoarthritis trials with very similar inclusion criteria and methods has already been performed by myself and colleagues, and has resulted in several publications that addressed many of the proposed research questions already. For example, we addressed the impact of attrition bias (Nüesch et al. BMJ. 2009 Sep 7;339:b3244), the effects of concealment of allocation and blinding (Nüesch et al. Arthritis Rheum. 2009 Dec 15;61(12):1633-41.) and the presence of small study effects (Nüesch et al. BMJ. 2010 Jul 16;341:c3515.) in meta-analyses of osteoarthritis trials. The proposed study will find very similar results because of the high overlap in included studies. Therefore, the authors need to make clear what the proposed study will provide in addition to already published research. 2. The proposed study would benefit from a new research focus and questions that have not been addressed previously. It would be a pity to do all this work of searching trials and extracting and analysing data to repeat previous work, instead of addressing novel research questions. There are still a lot of open questions about biases in osteoarthritis trials. 3. Studying the effects of funding source is important but equally problematic and controversial. In my experience, the assessment of funding source on estimates of treatment benefit in osteoarthritis trials will be very much limited by the very low quality of reporting in these trials. 4. The authors mention looking at the impact of reporting biases as one aim of their study. More details should be provided how reporting biases will be addressed, e.g. whether and how selective reporting of outcomes will be addressed. 5. The authors propose to address attrition bias and consider trials as free of risk of attrition bias event though they had missing outcome data in up to 10% of the participants, which is a lot. We have shown that already excluding any randomised patient could result in bias and increases heterogeneity between osteoarthritis trials (Nüesch et al. BMJ. 2009 Sep 7;339:b3244). Therefore, I suggest that the authors reconsider their definition for incomplete outcome data. 6. I suggest to also do funnel plots to address the effects of trial size in addition to the categorisation into small and large trials based on a sample size of 128 patients.

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1 Peter Herbison

Comment #1:
I am aware that pain is measured in various ways. Commonly it is measured by either a visual analogue scale(VAS) or a numeric rating scale and less commonly by more complicated instruments. Do the authors think that results from the VAS may differ from those of the rating scale?

Author response:
We agree with Mr. Herbison, that the results may differ according to different pain measure instruments. Therefore to reveal whether there are any relevant differences in effect sizes depending

on the pain instrument, we will also combine SMDs derived from each of these instrument categories in a stratified meta-analysis.

Action item:
[Data collection process and data items; now added]

We anticipate that pain will be measured in various ways, and thus different instruments will be applied to monitor the changes during any given trial period {REF}. Commonly pain is measured by either a visual analogue scale (VAS) or a numeric rating scale (NRS) and less commonly by more complex item-based instruments (e.g. WOMAC, KOOS, and ICOAP).

[Data synthesis; now added]
To explore whether the choice of pain instrument (i.e., VAS, NRS, or item-based scores) interacts with the apparent treatment effect, we will also combine SMDs derived from each of these instrument categories, in a stratified meta-analysis. This will reveal whether there are any relevant differences in effect sizes depending on the pain-instrument chosen.

Comment #2:
One of the reasons why small studies may give different answers from larger studies is that the participants in small studies may be more homogeneous than those in larger studies. Thus changes with treatment may be more similar, and if they are a more severely affected group the potential for gain may be larger.

Author response:
We thank the reviewer for highlighting that participants in small studies may be more homogeneous than those in larger studies. We agree that this difference may give diverging answers from the larger studies and that the potential for gain may be larger according to the more similar treatment, or more severely affected group.

Action item:
[ETHICS AND DISSEMINATION; now added]

As previously described by Nüesch et al the presence and extent of small study effects in OA research might distort the overall evidence from meta-analyses {REF}. Thus the influence of small trials on estimated treatment effects might be considered a novel risk of bias domain that needs to be addressed in the future. However, one of the reasons why small studies may give different answers from larger studies is that the participants in small studies may be more homogeneous than those in larger studies. Thus changes with treatment may be more similar, and if they are a more severely affected group the potential for gain may be larger. This work will facilitate consensus on the need for mandatory sensitivity analyses before making conclusions of a meta-analysis if the overall result is not consistent with those of the largest trials {REF}.

Comment #3:
I was a bit confused about what was meant by study size, and even after this was explained I thought it was a bit unclear. e.g. In table 2 it is not clear whether they mean the number randomised or the number assessed. What will happen when reports of studies only use one or the other?

Author response:
We appreciate this observation and we have corrected the vague description in table 2. The judgement of whether a trial is small or large trial attributes to the number of randomised patients according to the Cochrane review.

Action item:
[Table 2. Risk of bias assessment table; now added]

…patients (according to the Cochrane review),…

REVIEWER #1 Eveline Nüesch

Comment #1:
I entered yes to question 14 ("To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)?") due to a very similar study that has resulted in several publications already, which were not cited in the manuscript.

The authors propose undertaking a meta-epidemiological study to investigate the extent of different sources of bias in Cochrane reviews of osteoarthritis trials using patient-reported pain as an outcome. Although I completely agree with the authors that assessments of bias in osteoarthritis trials included in Cochrane reviews are important, I have several comments on the proposed study:

A meta-epidemiological study in osteoarthritis trials with very similar inclusion criteria and methods has already been performed by myself and colleagues, and has resulted in several publications that addressed many of the proposed research questions already. For example, we addressed the impact of attrition bias (Nüesch et al. BMJ. 2009 Sep 7;339:b3244), the effects of concealment of allocation and blinding (Nüesch et al. Arthritis Rheum. 2009 Dec 15;61(12):1633-41.) and the presence of small study effects (Nüesch et al. BMJ. 2010 Jul 16;341:c3515.) in meta-analyses of osteoarthritis trials. The proposed study will find very similar results because of the high overlap in included studies. Therefore, the authors need to make clear what the proposed study will provide in addition to already published research.

Author response:
We acknowledge the comprehensive work prepared by Nüesch et al. We are very sorry for not making this clear in our protocol. We thank the reviewer Dr. Nüesch for pointing this out.

Action item:
[Description of the problem or issue; now added]

REF: the effects of concealment of allocation and blinding (Nüesch et al. Arthritis Rheum. 2009 Dec 15;61(12):1633-41.)

[Description of the methods being investigated; now added]

REF: the presence of small study effects (Nüesch et al. BMJ. 2010 Jul 16;341:c3515.)

[Why this review is needed; now added]

REF: the presence of small study effects (Nüesch et al. BMJ. 2010 Jul 16;341:c3515.)

REF: the effects of concealment of allocation and blinding (Nüesch et al. Arthritis Rheum. 2009 Dec 15;61(12):1633-41.)

REF: the impact of attrition bias (Nüesch et al. BMJ. 2009 Sep 7;339:b3244)

Comment #2:
The proposed study would benefit from a new research focus and questions that have not been addressed previously. It would be a pity to do all this work of searching trials and extracting and analysing data to repeat previous work, instead of addressing novel research questions. There are still a lot of open questions about biases in osteoarthritis trials.

Author response:
We agree with the reviewer that our study could benefit from a reformed research question. It indeed would be a pity to re-do what is already has been undertaken.

Action item:
[Objectives; now added]

Our objective was to evaluate the association between estimates of treatment effects with different study characteristics including both well-recognised domains as well as novel bias-related aspects in meta-analyses of interventions used for treating pain in OA.

Comment #3:
Studying the effects of funding source is important but equally problematic and controversial. In my experience, the assessment of funding source on estimates of treatment benefit in osteoarthritis trials will be very much limited by the very low quality of reporting in these trials.

Author response:
We agree that source of funding are in risk of being limited by the low quality of reporting. We do too see a possibility for undergoing a large amount of trials and the influence on effect sizes of source of funding. From the assessment of unclear, for- and non-profit assessment, we won't be able to detect why trial authors do not the report funding, but we will be able to detect whether there is a difference in effect sizes from those reporting source of funding (i.e., for- and non-profit funding) and from those not reporting the funding (i.e., unclear funding). We agree with the reviewer that it prospectively would be very interesting to examine the unclear source of funding and the reason for.

Action item:
[Nothing added]

Comment #4:
The authors mention looking at the impact of reporting biases as one aim of their study. More details should be provided how reporting biases will be addressed, e.g. whether and how selective reporting of outcomes will be addressed.

Author response:
We thank the reviewer for highlighting the lacking information on reporting bias. We are very sorry for not having corrected this information after reconsidering our initial plan of to assess the impact of reporting bias. This is also the reason for the missing description of how the bias would be assessed. We decided not to examine reporting bias due to the fact, that our inclusion criteria was patient reported pain, which is the primary outcome for far the most intervention studies for treating pain in OA trials. As the definition of adequate reporting is that the study reports all expected outcomes, we would assess all the included trials 'adequate'. Otherwise, they would not have been available through our search. We therefore decided not to assess reporting bias in this study.

Action item:
[Description of the problem or issue; now removed]

…: attrition bias, (reporting bias), the issue of single centre vs. multicentre trials, and funding.

Comment #5:
The authors propose to address attrition bias and consider trials as free of risk of attrition bias event though they had missing outcome data in up to 10% of the participants, which is a lot. We have shown that already excluding any randomised patient could result in bias and increases heterogeneity between osteoarthritis trials (Nüesch et al. BMJ. 2009 Sep 7;339:b3244). Therefore, I suggest that the authors reconsider their definition for incomplete outcome data.

Author response:
We thank the reviewer for pointing out that our definition of attrition bias is in risk of flawing our results. We agree with the reviewer that Cochranes definition of low risk of attrition bias is defined as 'no missing outcome data'. Further, Cochrane define a low risk of attrition bias due to a balanced numbers of missing data across groups with similar reasons for drop out. To ensure a systematic and standardised bias assessment, we defined this 'balanced number of missing data across groups' to be of a maximum of 10%. We have not been able to detect any information on how large the exclusion of patients from the analysis were allowed to be before impacting on the effect estimates. Only the study from Nüesch et al 2009, BMJ, discussed that exclusion of a small proportion of patients from the analysis were unlikely to impact on the estimates of treatment benefits.

Action item:
[nothing added]

Comment #6:
I suggest to also do funnel plots to address the effects of trial size in addition to the categorisation into small and large trials based on a sample size of 128 patients.

Author response:
This is a good suggestion. We agree on including funnel plots to address the effects of the trials size in addition to the categorisation of small and large trials.

Action item:
[Data synthesis; now added]

To address the effects of trial size in addition to the categorisation of small and large trials we will do funnel plots based on sample sizes. If small study effects are present, funnel plots will be asymmetrical.