Responses to reviewer and editor comments

We are not sure that most readers are familiar enough with the core outcome project to value this paper properly. You could improve the presentation of the background of this paper, and explain why these findings are of relevance for non-rheumatologists.

>> Text has been added to address this comment.

Screening and assessment is made by a single reviewer. How much of a concern should this be?

>> Please see response to reviewer 2 on these issues.

Published reports of completed trials were identified only via the trial registry. Should not a more comprehensive search for papers have been carried out (eg. by searching via Medline etc for specific authors)?

>>Please see response to reviewer 2 regarding the same comment.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
The paper is written in a very dry style but is straightforward and readable. The inclusion of an anecdote or two may add a little colour for the reader.

The topic has significant relevance, as the adoption of core outcome sets is vital to improve and standardize future drug trials. Unless readers are familiar with what core sets are and the OMERACT process, the article's appeal to a wider readership may be limited. Some additional commentary on these two matters would be a useful improvement.

>> Text has been added to address this comment.

The time lag between OMERACT decisions, trial adoption and measured outcomes are many years. As such the 1992 core outcome sets have been further developed. Fatigue and quality of life measures are now also deemed important and, I would argue, are also relevant to patients. These two new attributes may deserve some commentary; especially as the data registration went from 2002 to 2016.

>> We are aware of these important patient outcome developments in this field. Comments added to the discussion with some quantitative summaries of fatigue and QoL in this current cohort of trials.

The case has been well argued and the nature of this project does not necessitate patient involvement as data collection is determined by third parties passive entities (i.e. registries). I recommend the paper.

>>Thank you for your support.

Reviewer: 2

OVERALL
Major comment: To my understanding, the authors of this manuscript intended to assess if the 'outcomes' (what to measure) of the original COS RA were used in clinical trials, therefore it is important that the authors of this manuscript should refrain from using the terms 'outcome measures', 'measures' or 'instruments' (how to measure) when referring to 'outcomes'. An example of this is on page 4, line 32-33, when the authors refer to "seven measures", however, the terms following in brackets seem to refer more to 'outcomes' rather than 'outcome measures'. Besides this, the authors of this manuscript did not assess the uptake of recommended 'outcome measures'. In fact, it is possible that authors of a clinical trial include a COS core 'outcome' but without using the core 'outcome measure' recommended by the COS. I believe adding this part to this study would be too much extra work, and since I am unsure on whether the original COS RA made also recommendations on 'outcome measures', I am not suggesting to do this. However, since I strongly believe that it is fundamental to assess not only COS 'outcomes' uptake but also COS 'outcome measures' uptake, could the authors make any consideration about this?

>>Thank you for pointing out our inconsistent use of the terms 'outcomes' and 'outcome measures'. We have changed the phrasing throughout the manuscript and refer only to 'outcomes'. It would not be feasible at this stage to assess uptake of specific outcome measurement instruments as many trial registry entries do not report this level of detail.

INTRODUCTION

Minor: Page 4, line 14-18, could the authors double check if the sentence "Core outcome sets (COS) can enhance … are measured routinely" makes perfect sense and it is grammatically correct?

>> Appropriate punctuation added

METHODS
- Minor: Page 6, line 7. It should be reported when the trials registry ClinicalTrials.gov was searched.

>> Date added

- Major: Page 6, line 13-14, "The returned hits were then screened by a single reviewer". I wonder why the authors did not strive to make a double assessment considering that this manuscript aims to be an example for future similar studies on other COSs. This may be a potential limitation and that does not allow to state this manuscript had a systematic approach (which the authors correctly did not do). However, in a systematic review era, it seems a bit counterintuitive to read that the work of a reviewer was not (at least) double checked by a second one, and I wonder if this is appropriate for a very high ranking journal such as the BMJ.

>>We agree that in the current era of systematic reviews, double screening is preferential. However, the term 'screening' here, commonly associated with systematic reviews does not apply. When selecting eligible studies from trial registries we applied built in filters from ClinicalTrials.gov, exported the results to an Excel file then filtered again using the extracted design fields that are populated with a list of expected entries. No manual screening based on reviewing of free text, such as titles, abstracts and full texts was done/required. This process can be done by one reviewer and replicated.

Methodological detail updated for clarity.

- Major: Page 6, line 40-44, "The assessments were carried out by one reviewer …". This is already acknowledged as a limitation of this work in the discussion, however, taking into account also my previous comment, I wonder whether this is indeed sufficient for such a prominent work, considering that a single person basically did everything. Having two reviewers would have certainly been more appropriate.

>>A random sample of 10% of trial registry entries/publications have now been independently verified with a second author. Methodology and results sections have been updated.

- Major: Page 6, line 56-57. The authors decided to use Google and Web of Science to retrieve publications of eligible trials. The authors recognize in the discussion that this could be a limitation and that "we are likely to have missed some trial reports". I wonder why the authors limited their searches in these databases to the use of trial numbers, whereas using the names of authors (e.g. in PubMed) might have been a good strategy to miss less trial reports.

>> This was something that was considered. However, as stated in the manuscript, most trials listed on the trial registry were pharma funded which in the majority of cases meant that the listed investigator was the company rather than an actual contact person, meaning that author name could not be searched on PubMed.

Moreover, in my personal experience, Web of Science is usually the least updated of the citation database because: it takes more time for a publication to appear if compared to other citation databases (e.g. Google Scholar, Scopus), publications [epub ahead of print] are not included (whereas in Google Scholar they are), and publications in journals with low or no impact factor are not indexed (in Google Scholar they are). Therefore, I do not know if acknowledging such a limitation is sufficient to justify the methods, and if the editor believes it is sufficient, the authors may consider to provide at least some indications for future studies on how to have a more comprehensive search strategy to identify published trials.

>>Thanks for this comment and your knowledge of citation databases. In the original conclusions section of the manuscript we make a recommendation for authors on how they should assess uptake using this new trial registry approach.

We have amended our final recommendation slightly in the conclusion section of the manuscript. This recommendation does not suggest that an additional systematic search for published reports is done outside the trial registry, as this would add to the resource burden of others carrying out such an uptake evaluation.

We anticipate that the number of trial publications registered on trial registries will improve as automatic data linkage between published articles and trial registries improves.

Manuscript has been updated to clarify points above

- Minor: Page 7, line 21-23. Could you please double check the use of singulars and plurals in the sentence “Any publications… was removed”?

>> ‘Was’ changed to ‘were’

- Minor: Page 7. No reference to statistical softwares is provided. Is it because none was used?

>>Analysis was carried out in Microsoft Excel 2010 and R version 3.1.2 was used for the graphics. Sentence added to methods.

DISCUSSION

- Minor: Page 10, line 9-10. To which “plateau in recent years” do the authors refer? Could they be more specific? From Figure 2, I believe that from 2010 to 2016 the uptake of COS RA is constantly and slightly increasing.

>> Text amended

- Major: Page 11, line 8-13. To justify their methods, the authors state that “there is no reason to believe that the trials identified on ClinicalTrials.gov are not a representative sample of all trials in rheumatoid arthritis, given that trials entered onto the site are registered from across the world”. I believe this is not a strong argument because it does not involve any consideration about non-registered trials which are probably of lower quality and less likely to adopt an existing COS. Therefore, I believe it is not appropriate to state that a clinical trial register is representative of all trials for a given condition. The following consideration (line 14-21) also does not take into account non-registered trials but just compares different trial registries, therefore the authors should add a consideration about the representativeness of one or more trial registries for all clinical trials.

>>Thank you for this comment. Our intention was to make the suggestion that our sample was representative of all those that are registered (noting we only selected trials from one registry). Indeed our uptake method would not pick up any trial that is not registered and we acknowledge that those that are not registered may be of lower quality in general and so are probably less aware of the COS and the importance of using it.

The text has been amended in the Discussion.

TABLES AND FIGURES

- Minor: Percentages should be included in Table 2.

>> Percentages added

Reviewer: 3

Appropriate methods have been used to address the aim of the study and the conclusions are supported by the data presented. The paper could be improved by providing some further clarity in wording in:

- the section 'Assessment of the uptake of the RA-COS' - last sentence (p, lines 26-31),

>>Sentence amended – see also similar comment from reviewer 4.

- the results (p8, lines 29-34)...'Similar proportions of trials...'.

>> Proportions have been changed to percentages, %'s presented in text to improve clarity

An extension of the flowchart showing the study's main endpoints (number planned to collect COS & number of publications reporting COS) would provide a useful visual presentation of results.

>> Flow diagram has been amended. Note – Table 2 has also been deleted as this information is now incorporated in the updated flow diagram.

Reviewer: 4

1. Introduction: it would be helpful if the authors could specify the timeframe considered in the previous analysis of Cochrane systematic reviews.

>> Detail added

2. Methods: the timeframe considered for the trial registry search is not detailed in the methods (although it is mentioned in the results and the abstract). Please add this to the methods.

>>The method was to identify ALL trials meeting the eligibility criteria that were registered with CT.gov. Date range of those found is in the results section.

3. Methods (Assessment of the uptake of the RA-COS): Could the authors provide further information on how the moving average was calculated. For example, was the average proportion calculated for publications 1-10, 2-11, 3-12 etc or 1-10, 11-20 etc.

>> Detail added.

4. Methods (Assessment of the uptake of the RA-COS): "In calculating the moving average, the percentages…" – change "percentages" to "proportions" for consistency with previous sentence.

>> We plot percentage uptake of full RA COS – for consistency we prefer to change proportion to percentage throughout. Detail changed.

5. Methods (Assessment of the uptake of the RA-COS): Final sentence – this doesn't quite make sense to me – are the authors referring to the period of crossover between the

original assessment and the new one and the fact that additional studies were identified from the trial registry? This needs to be clarified. How were the proportions from the later trials amended?

>> The adjustment was made due to additional trials found in the crossover period between the 'systematic review' (previous research) and 'trial registry' (current research) approaches. Extra text added for clarity.

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6. Results: The authors present the percentage of registered trials for which a publication was identified (45%; 122/273) – would this not be more informative as the percentage of completed trials that have been published (122/167)?

>> We agree with this suggestion but would also include 'terminated' trials in the denominator as some trials that were terminated early, either had results (on the registry) or were published. The new denominator is 189.

Table and text amended.

7. Results: The authors state that "…no information on whether the trial was completed or where the data could be found was available for 63 trials (Table 1)", however Table 1 suggests that recruitment status was known for all 273 studies.

>> Amended from above.

8. Results/Discussion: In terms of comparing the original approach (searching systematic reviews) with the current one, is there added value in comparing the percentages identified as reporting the full RA COS from the two approaches in the overlapping period? Or is this period too short?

>> The original approach based on systematic reviews found 10 trials in the overlapping period, 8 (80%) of which reported the full COS. The new method based on trial registry entries found 10 trials, 9 (90%) of which reported the full COS. Result added to manuscript.

9. Results/Discussion: The authors find that within the 122 trials for which a publication was available a greater percentage reported the full RA COS in the publication than was planned according to the registry. Some discussion of why this might be the case would be valuable.

>>We suspect this is down to the poorer quality data that is recorded in trial registries. Comment added to discussion.

10. Results/Discussion: Could the others also report the percentage of trials planning to report the full RA COS amongst those that are ongoing? Given the result that 76% of the (122) trials with a publication had planned to measure the full RA COS and yet only 67% of the full 273 had, does this infer that of those trials yet to be completed and published the percentage planning to report the full RA COS may be substantially lower than 76%, hence the potential that the rate of implementation might actually now be decreasing over time?

>> Text added to the discussion

11. Figure 2/Discussion: The percentage of studies reporting the full RA COS appears to have been increasing over time prior to the publication of the RA COS (indeed at a similar rate to after 1994) – why might this be?

>> Consensus may have been developing, with the publication of the COS then formalising that. Text added to discussion

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