27-Mar-2017

Dear Dr. Kirkham

Manuscript ID BMJ.2017.037434 entitled "An assessment of the uptake of core outcome sets using ClinicalTrials.gov"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (Chair), Julie Morris (Statistics advisor), Sophie Cook, Kristina Fišter, Elizabeth Loder, José Merino, Rubin Minhas, Georg Röggla, Amy Price, Tiago Villanueva, Wim Weber.

Decision: Put points

Detailed comments from the meeting:

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.

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

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)?

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

Recommendation:

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.

As a patient and as an OMERACT patient-researcher the matters raised in the paper are relevant and important as the outcome of drug trials impact patients directly. The research demonstrates that rheumatoid arthritis core set of outcomes has continued to rise over time in trials based on examining trial registry entries. This is good news from a patient perspective.

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.

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.

Additional Questions:
Please enter your name: Michael Gill

Job Title: Patient

Institution: None

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: Patient-researcher for OMERACT

Reviewer: 2

Recommendation:

Comments:
This is a very well written manuscript that presents the uptake of a core outcome set (COS) for pharmacological interventions in rheumatoid arthritis (RA) clinical trials, using the data presented in ClinicalTrials.gov. As claimed by the authors, this work provides good evidence of the increased uptake of the COS RA over time and, indirectly, on the usefulness of developing COSs for various health conditions. Moreover, (at least part of) its methods can provide a good basis for future studies aiming at assessing the uptake of other COSs. However, I have a list of major and minor comments mainly regarding the methods and the discussion to be considered by the editor and the authors.
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?
ABSTRACT
It is well written and very clear, and it presents all key information in a concise way.
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?
METHODS
- Minor: Page 6, line 7. It should be reported when the trials registry ClinicalTrials.gov was searched.
- 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.
- 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.
- 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. 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.
- Minor: Page 7, line 21-23. Could you please double check the use of singulars and plurals in the sentence "Any publications… was removed"?
- Minor: Page 7. No reference to statistical softwares is provided. Is it because none was used?
RESULTS
I find this section very well, clearly and consistently written.
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.
- 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.
TABLES AND FIGURES
- Minor: Percentages should be included in Table 2.

Additional Questions:
Please enter your name: Alessandro Chiarotto

Job Title: Research Fellow

Institution: Department of Epidemiology and Biostatistics, VU University Medical Centers, Amsterdam, Netherlands

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
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Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: For full disclosure, I was an invited speaker at the 2014 COMET meeting (Rome, Italy) which was organized by the COMET management group to which two authors of this manuscript belong. For that conference, I received a reimbursement for my travel expenses from the COMET initiative, but no fee for speaking. I do not have any other competing interest regarding the content of this manuscript.

Reviewer: 3

Recommendation:

Comments:
Thank you for the opportunity to review this insightful paper assessing the uptake of core outcome sets (COS) using the ClinicalTrials.gov database. It is original in its identification of an effective and pragmatic method to assess COS uptake. It is important work and will have impact for clinical trials groups in showing that this method can be useful more widely in assessing uptake of COS in other fields. The paper build upon previous work showing that the uptake of this particular COS has increased over time, albeit slowly in this case. However it highlights that adherence to COS reporting and acceleration of COS uptake can be influenced by including links to the COS in registering trials. This information will benefit COS developers from other fields.

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

Additional Questions:
Please enter your name: Bronagh Blackwood

Job Title: Senior Lecturer

Institution: Queens University Belfast

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
This paper reports a novel method to assess the uptake of a core outcome set (COS) for rheumatoid arthritis in randomized trials, undertaking a review of outcomes recorded in trials identified on ClinicalTrials.gov. There are currently many groups developing COS in different clinical areas; however, if these are not implemented in future trials they are of little value. Measuring the degree of implementation is not easy and this paper presents a feasible and potentially efficient approach.

The paper is well written, however there are a few areas where I think further clarification or discussion would improve the paper.

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

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.

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.

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.

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?

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)?

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.

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?

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.

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?

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?

Additional Questions:
Please enter your name: Dr Sara T Brookes

Job Title: Senior Lecturer in Health Services Research

Institution: University of Bristol

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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