Author's response to reviews

Title: Outcome measures in rheumatoid arthritis randomised trials over the last 50 years

Authors:

Jamie J Kirkham (jjk@liv.ac.uk)
Maarten Boers (mboers56@xs4all.nl)
Peter Tugwell (Tugwell.BB@uOttawa.ca)
Mike Clarke (m.clarke@qub.ac.uk)
Paula R Williamson (prw@liv.ac.uk)

Version: 2 Date: 19 August 2013

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

Re: Outcome measures in rheumatoid arthritis randomised trials over the last 50 years [MS Ref: 2931842395505787] (resubmission)

I would like to thank you for providing us with the opportunity to resubmit the above titled manuscript. In particular I would also like to thank the reviewers and the Associate Editor for their extremely helpful comments and suggestions, which we have thoroughly taken into account when revising the article.

In particular, we have made a number of amendments to Figure 3, so that this is less confusing to the reader. Detailed responses to each of the reviewer’s comments are provided below. All changes from the original submission have been included as track changes.

I hope that with these revisions, you will seriously consider publishing this work in Trials. Many thanks again for taking the time to consider our work for publication in your journal.

Yours faithfully,

Dr Jamie Kirkham
University of Liverpool
Reviewer 1: Kent Johnson

Major compulsory revisions: none

Minor Essential revisions
1-Figure 3: Better to use the early date, 1996, for FDA, as you did for EMA using 1998? I find Figure 3 confusing. The vertical axis is the percentage reporting the full RA COS for pharmacologic (red) and non-pharmacologic (blue) trials, and the vertical axis is also the average clinical outcomes (core and non-core), the black line, for all trials – this cannot be a percentage? This is confusing and should be clarified, using separate graphs if necessary. And how is it that the “average clinical outcomes” graph starts close to zero at the beginning time point of 1982. By the way, the color coding gets lost in black and white printings while dots, dashes, etc. do not. And could you comment why there are no non-pharmacological trials before 1992 or after 2004 – just a feature of Cochrane?

The following changes have been made to the plot:

1) The earlier date of 1996 has now been used for the FDA guideline.
2) Colour has been removed from the plot in favour of different line styles.
3) The plot has two y-axes. Y-axis 1 (left) represents the % update in the COS for both drug and non-drug trials (these are the solid thick black lines) which have now been labelled. Y-axis 2 (right) shows the average number of clinical outcomes, which is represented by the dashed line. To make this clearer which axis is being refereed to, two changes have been made. Firstly, y-axis 2 is now a dashed line, which corresponds to the dashed line on the plot. Secondly, a legend has been added to indicate what the solid black and dashed lines represent. These are co-ordinated with the line styles of each y-axis.
4) There were non-drug trials pre- 1992 and post- 2004. However the numbers of trials in these periods were sparse. A reasonable number of trials are needed in each period in order to obtain a reliable data point for plotting. The same applies for the drug trials, as there were publications in the 50-70s. The methods have been adjusted accordingly.

2-Table 1: For the novice, could you identify what the abbreviations for DMARD, SSAARD, and SMARD are at the bottom of the table?

Done

Discretionary revisions
I have only a few suggestions. Some readers long involved with RA might like more commentary regarding a number of related topics such as the following (I
realize this would expand the scope of the paper).

1-Brief mention of the methodology and rationale used to construct the ACR20, in particular, the use of the DMARD trial data sets from the Cooperative Clinics trials to adjudicate, along with expert opinion, the exact construction of the ACR20 – the choice and number of components and the algorithm for declaring success – 20% improvement in TJ and SJ plus 20% improvement in 3 of the other 5 components.

This is beyond the scope of this current study.

2-Comparisons with the DAS including uptake over time. Has anyone studied the DAS in a similar fashion? Are there examples in other disease settings of similar outcome creation using a combination of trial data and expert opinion, then subsequently studied regarding its uptake by the trialist community?

Similarly this is beyond the scope of this current study.

3-Possible intrinsic limitations of the ACR20 including the argument, albeit it made with observational, not randomized data, that ACR measures underrepresent morbidity in the long term because damage and disability are not sufficiently represented (e.g., Pincus. Clin Exp Rheumatol. 2004 Sep-Oct;22(5 Suppl 35):S50-6)

This is beyond the scope of this current study.

4-Consider calling all “trials” rather than “studies” in Figure 2

When referring to the clinical reports, we have changed the wording to read ‘trials’ throughout.

5-Web Table 4: add the word “only” before “Erythrocyte” and before “C-reactive”

Done
Reviewer 2: Robert Landewe

Major compulsory revisions: none

However, I would give the authors the suggestion to be a bit more positive regarding the usage of the core set after the publication of the core set. Admittedly, it cannot be proven that a better usage is due to the publication of the core set, and as such a better implementation is difficult to attribute to the (ACR/Omeract) initiative and the publication itself, but fact is that implementation has improved. You can see that best in the results regarding biologic treatments, whilst these cannot be compared with similar trials before the publication of the cores set, since these treatments were not available by then. This reviewer, though, has no doubt that the core set has become the standard for outcome assessment selection in modern clinical trials. Obviously, there is still room for improvement, and this should be emphasized over and over.

An additional sentence in the discussion has been added to further emphasize that the publication of the core outcome set has made an impact on the selection of outcomes for this conditions in more recent trials.

Editors Comments:

1) If applicable, please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

An acknowledgments section has now been added.