Author's response to reviews

Title: Quality of reporting of non-inferiority and equivalence randomised trials - update and extension

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Author's response to reviews: see over
Dear editor and dear reviewers,

thank you for your positive reception of our manuscript “Quality of reporting of non-inferiority and equivalence randomised trials - update and extension” (MS: 1018657128755518). We are grateful for the overall agreement with the importance of our evaluation. Especially, we highly appreciate the thorough review and the helpful comments that gave us the opportunity to improve the manuscript.

Below we explain point-by-point how we addressed the comments during our thorough revision of the manuscript.

(1) Response to Reviewer 1: Emilia Bagiella

Thank you very much for your helpful comments that gave us the opportunity to improve the manuscript. Following your justified recommendations, we reorganised the manuscript, reanalysed our data and rewrote parts of the manuscript. Below we explain point-by-point how we addressed your concerns and the comments.

This is an interesting manuscript exploring the quality of reporting of equivalency or non-inferiority trials in medical journals. The authors performed a reviews of articles published in 2009 and investigated to what extend the CONSORT guidelines were followed. In addition the authors attempt a comparison of their results with results of a similar review conducted in 2003-2004. The manuscript is interesting, although not very well organized. A couple of important issues should be addressed.

1. The rationale for conducting the review is not completely clear in the manuscript. While the attempt to determine whether the CONSORT guidelines had any impact on the quality of equivalence and non-inferiority trials published, the focus seems more on comparing the current review with the review previously conducted in 2003-4. Some of the CONSORT criteria were reported in that first review, however, it seems that the comparison in predicated only on 4 criteria.

Response: We thoroughly revised the manuscript, restructured the RESULT section (including Table 4 following Table 3) with the aim to better work out the main focus of the rational. The main focus is on the evaluation whether the CONSORT guidelines have an impact on the reporting and methodological quality of non-inferiority and equivalence trials (BACKGROUND, page 5 line 2-7). The comparison with the previous study should still be a part of the manuscript, but now it is presented as a
secondary part in the RESULT section (page 13, subtitle “Changes in trial characteristics and quality of reporting”) with the aim to get our main results in line. As described below (point 2), we now included a comparison stratified by the impact factor of journals to enhance the informative value of our work. We also refer now to a wider range of criteria related to the reporting quality in the discussion (page 16ff).

2. Unfortunately, only major medical journals require compliance to the CONSORT guideline for publication (e.g. JAMA or the NEJM). Many other journals, while recommend the guidelines, do not enforce them and completely rely on the reviewers to request a more rigorous approach. Given this, the analysis should be stratified by whether or not the journal in which the article were published did or did not require adherence to the guidelines. The change between before and after the guidelines were published may merely be due to an increased number of papers published in specific journals rather than a change in adherence to the guidelines.

Response: Thank you for this very helpful and relevant contribution. We share your opinion that it is important to differentiate the overall results we presented and to separate in some way between the potential impact of the guidelines and a change that might only be a consequence of an increased number of reports published in specific journals. Unfortunately, already at the beginning of our review-work it was not possible to separate between CONSORT endorsing and non-endorsement journals, because this would have meant to collect the information on CONSORT endorsement of journals for the years 2008 and 2007 (which is the time the peer-review-process of the reports might have been). This information was not available for us. Today, an increased number of journals joined the list, which did not endorse CONSORT in the period relevant for our review. Using this list for a reanalysis would have been even more improper. Since the major high-impact factor medical journals required compliance to the CONSORT guidelines already at an early stage, we decided to stratify by impact-factors and type of journal. Thus, we contrast the results for reports published in high-impact general medical journals (JAMA, NEJM, The Lancet, BMJ) with those of reports published in low-impact general medical journals (all other general journals) and in specialty journals. We reanalyzed our data and rewrote the main part of our discussion including this important additional information (page 16ff). The newly prepared table together with the figure is now added as supplementary material to the manuscript.

3. The manuscript should be reorganized. The comparison between the current and the previous review is presented in the discussion. It should be presented in the result section instead (again it should be more clear, what the main scope of the paper is...).
Response: As already stated above in point 1 and 2 we reorganized the manuscript according to your recommendation. Now, the comparison with the previous study is a part of the results section (page 13f).

4. The discussion should address many different issues around the results reported. To begin with, are the results the author report consistent with results on other trials? Again, if the aim here is to determine whether the CONSORT guidelines were effective, a comparison with other types of trials (e.g. superiority) should be made.

Response: We completely agree to address more issues in the discussion and not to focus only on the comparison with one previous study. Now, we discuss a wider range of criteria related to the reporting quality, included results stratified by the impact factors and type of the journals, and compare our results with those of others. A comparison with other types of trials might have further upgraded our work, but we decided that a review of additional reports published in the same period (e.g. superiority trials in 2009) is not feasible to be done in an adequate time. However, we hope that the way we addressed your concerns is appropriate.

5. The difference between equivalence and non-inferiority trials is not usually clear and well understood. The authors should give a definition in their introduction.

Response: We added a sub-clause in the BACKGROUND section to give a definition (page 4, line 8-10).

6. The paper should be reviewed for English language. The punctuation is often inappropriate and there are a couple of awkward sentences.

Response: We carefully looked through the whole paper and re-edited many parts of it to make the text more easily comprehensible. Moreover, the revised version was thoroughly reviewed and edited by a medical statistician who is a British English native speaker.

(2) Response to Reviewer 2: Jordi Ocana

We would like to thank the reviewer very much for his helpful comments that gave us the opportunity to improve the manuscript. Below we explain point-by-point how we addressed the comments during our thorough revision of the manuscript.
Major Compulsory Revisions:
The paper is interesting and well written, but possibly it suffers from an initial bias in the election of the population of citations under study. This bias should be corrected, or clearly justified and reflected in the paper. In my opinion, the bias comes from the exclusion of bioequivalence (BE) trials. They are equivalence randomized trials whose primary goal is research in healthcare.

I can’t see any reason to exclude BE trials. They are fully in the scope of the paper, and CONSORT statement fully applies to them. If BE trials were considered, the main consequence would be a significant increase in the proportion of crossover trials. In my opinion, the authors should follow one of the following two strategies in order to clarify the question posed in the paper, to provide sufficient details and to make data sound and well controlled: 1) To include BE trials. Then obviously many the figures and tables would need some correction, although the main conclusions will remain essentially the same. Admittedly, this is more a problem of CONSORT incompleteness than a problem of the paper, but the discussion should be completed with some consideration for the need of an extension of the CONSORT statement to crossover trials, a significant proportion of equivalence trials (if BE trials were included). The main issues to be considered would be washout periods between treatments and the related problem of carryover. The possibility of carryover (even the major design error of not including any washout period at all) is pointed as a main problem of many crossover trials (e.g. in similar revisions like Mills EJ, Chan A-W, Wu P, Vail A, Guyatt GH, Altman DG “Design, analysis, and presentation of crossover trials”, Trials 2009; 10:27 and Diaz-Uriarte R “Incorrect analysis of crossover trials in animal behaviour research” Animal Behaviour 2002; 63:815–822).

2) Alternatively, the authors should reflect in the title and the abstract that an important part of randomized equivalence trials are not included in the study. This exclusion should be justified in the introductory section, perhaps in terms of comparability with preceding studies, which is one of the main goals of the paper.

Response: We decided to follow strategy 2) and now describe in detail the reason for doing so in the BACKGROUND section (page 4, line 8-17). Furthermore, we changed the title to “Quality of reporting of clinical non-inferiority and equivalence randomized trials - update and extension” thus reflecting that our review restricts to clinical non-inferiority and equivalence trials.

Discretionary Revisions
Even under the second possibility above, some consideration to the
particularities of crossover trials (not fully absent in the paper) and the need of its consideration in CONSORT, and some reference to how the conclusions may be different if BE trials were included, would be very valuable.

Response: We intensively thought about how to implement these comments in the manuscript. Our review addresses a huge number of aspects concerning planning, conduct, analysis and reporting of randomised clinical trials, some, but not all of them given in the comprehensive Tables 1 to 4. Cross-over trials are mentioned only once in the manuscript on page 11, line 2. Here it is stated that “Five reports described trials with a cross-over design (2%)”. This means that the cross-over design plays a very minor role for the clinical trials considered in our review. Giving particular attention to this extremely specific aspect seemed to be quite artificial and inappropriate to us, especially in view of the many other aspects that might be discussed and that play an important role for the interpretation of the results. Accordingly, speculating on how the conclusions may be different if bioequivalence trials were included seemed to be not very helpful in our view. We did not find any reference of an investigation on the quality of reporting of bioequivalence trials. Therefore, statements on what could be expected would be completely theoretical and could not be substantiated. Furthermore, we now point out in the Introduction that bioequivalence trials differ from clinical equivalence trials in a number of important characteristics that will also affect reporting. For this reason, we feel that an investigation on the reporting of bioequivalence trials should not be mixed up with clinical equivalence trials and that speculative statements such as “how the conclusions may be different if bioequivalence trials were included” were not appropriate. We therefore finally decided not to include these very specific comments in the revised version of our manuscript.

(3) Editorial requests
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.
We included an acknowledgement section and also gave information on funding (no funding received). The permission to acknowledge from all those who were mentioned is also included.

Thanks again for your constructive remarks. We now have the impression, that our rewritten manuscript and in particular the discussion is indeed upgraded as compared to the first version. Hopefully, we also could fulfill your expectations and address your recommendations in an appropriate manner. We would be very pleased by a second positive reception of this revised version of our manuscript.

Yours sincerely,

Petra Schiller