Author's response to reviews

Title: Surgical trials and trial registers: A cross-sectional study of randomized controlled trials published in journals requiring trial registration in their author instructions

Authors:

Julia LS Hardt (julia.hardt@googlemail.com)
Maria-Inti Metzendorf (maria-inti.metzendorf@medma.uni-heidelberg.de)
Joerg J Meerpohl (meerpohl@cochrane.de)

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Author's response to reviews: see over
Revised manuscript - Surgical trials and trial registers: A cross-sectional study of randomized controlled trials published in journals requiring trial registration in their author instructions

Dear Madam, dear Sir,

please find attached our revised manuscript entitled „Surgical trials and trial registers: A cross-sectional study of randomized controlled trials published in journals requiring trial registration in their author instructions“.

We would like to thank you and the reviewers for their valuable and helpful comments and suggestions. Please find below a point-to-point response. We feel that it help very much to improve our manuscript. We would be delighted if it could be now considered for publication in Trials.

I hereby confirm on behalf of all named authors that:

(i) all named authors agree to the submission of the revised manuscript to TRIALS;
(ii) all authors who contributed to the design and writing of the study have been named on the article;
(iii) the work in the article is original;
(iv) the article has not been previously published.

Joerg J. Meerpohl, M.D.
Corresponding author

Yours sincerely (on behalf of the co-authors),

Joerg Meerpohl
Reviewer #1 (Ludovic Reveiz):

Major Compulsory Revisions

The authors should report and analyze data on prospective and retrospective registration. Many trials available in the ICTRP were retrospectively registered. This has an important implication for evaluating the implementation of the initiative.

Thank you. We really appreciate this suggestion. Thus, we extracted “study start date” and “study registration date” (“study first received” in CT.gov) in order to analyze whether a study was registered prospectively or retrospectively. Moreover, we now present these new data stratified by start of patient recruitment in a revised version of table 2 (please see supplementary file (Excel file), methods – last paragraph, results/trial registration – first paragraph).

Results reporting findings should be analyzed according to the context of the Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) requirement: for “applicable clinical trials” (compliance to “applicable clinical trials”). A key finding is non compliance of result reporting. This should be highlighted in the results section and analyze in more detail. The current version of the manuscript focus on descriptive data (i.e. list of registries of the ICTRP; this information could be described in a Table 4 as footnote) and the reader may loose the focus on key issues

We apologize for our apparently confusing comments on “applicable clinical trials” (ACTs) with regard to the included RCTs in the previous version of our manuscript. As we clarify in the methods, results, and discussion sections, we did not explicitly analyze if the included RCTs were all ACTs and thus legally obliged to submit summary data to the Results Database (please see methods – last paragraph and sentence, results/reporting results – second paragraph, discussion – first paragraph). We also added a list of registries of the ICTRP in table 4 as a footnote.

The limitations of the study should be described in more detail.
We described the limitations of our study in much more detail (please see discussion – last paragraph).

Key references are lacking in the discussion section; some of which are:
Thank you very much for suggesting these important and highly relevant references. We added both of them in the discussion.

Minor essential revisions

The authors should justify in some way why they selected 10 highest ranked journals and the implications for external validity
We added a justification for our choice (please see methods – first paragraph) and we also discussed the implications of our choice with regard to the generalizability of our results (please see discussion – last paragraph (limitations of our study)).

Including other relevant references on trial registration and result reporting compliance in the discussion section to compare their findings.
We added three new references to our discussion.

The authors could explore the process by which these 10 journals ensure trial registration (i.e. field in the system of submission, only in authors instructions etc) and discuss strategies of journal editors for ensuring good publication practice.
We agree that it would be interesting to investigate details of the editorial process, but this was not our focus for this paper. Since this ideally would have also entailed a survey of editors, we decided to not further explore how the included journals are ensuring trial registration.

Table 1: I suggest to include the journal's country. This issue as well as the specific topic of the journal (i.e. transplantation) is also a limitation for generalizability. We changed this as suggested (please see table 1).

Discretionary Revisions
The inclusion of other relevant information such as the type of intervention (i.e. drugs, procedures), analysing difference in date of registration (i.e. recent trials were more frequently prospectively registered?) Please see also above under Major Compulsory Revisions. We extracted “study start date” and study registration date (“study first received” in CT.gov) in order to analyze whether a study was registered prospectively or retrospectively. Moreover, we now present these data stratified by start of patient recruitment in a revised version of table 2 (please see supplementary file (Excel file), methods – last paragraph, results/trial registration – first paragraph). We did not explicitly analyze the type of intervention, but the titles/topics of the RCTs are listed in the supplementary excel file.

Explore difference between prospectively registered versus retrospectively registered and not registered trials according to results availability. We now explore whether prospectively registered trials are more likely to post results and added this as recommended. Please see results/reporting results – first paragraph).

Reviewer #2 (Andrew Prayle):

Major Compulsory Revisions
1. Regarding the Results section, "Reporting results" subsection. The authors report that a large number of trials were "clearly" required to report results. However, I think they may have misinterpreted the FDAAA. My understanding of this legislation is that it applies to only a specific subset of all clinical trials, termed "applicable clinical trials" (ACTs) in the literature surrounding this area of the FDAAA. The authors give the correct definition of an ACT in the introduction. However, in the methods and results they do not assess whether any of the trials are ACTs.

Thank you for your very important comment. We agree with you that we cannot tell - based on our data - whether a trial was in fact legally required to submit results. Indeed, we did not analyze if the included trials were actually "applicable clinical trials" (ACTs), but we totally agree with you that the majority of the RCTs in our sample was most likely not concordant with the definition of an ACT. We have clarified this (please see methods-last paragraph, results/reporting results – second paragraph, discussion – first paragraph).

The authors haven't given us the data to look at, which makes it difficult for the reviews to make an assessment as to whether these trials were in fact ACTs. Again, we agree with you. Thus, we now submitted our primary data as supplementary files.

Our group's experience of categorising trials into ACTs or otherwise is that this area is very difficult, but it turns out that most trials within the ClinicalTrials.gov database are not in fact ACTs. Therefore I suspect that most of the trials were not ACTs and are not required to publish summary data on ClinicalTrials.gov. An assessment of whether or not the trials were ACTs is required before using such strong language in the results. If this analysis is kept in the manuscript, a discussion of the limitations of trying to determine if a trial is and ACT or otherwise with only the ClinicalTrials.gov record is required. This area requires careful analysis and very clear writing up, as if you
state that a trial is not in compliance with the relevant legislation, you are implying that a responsible party is breaking the law.

As mentioned above, we apologize for our misleading comments on “applicable clinical trials” (ACTs) with regard to the included RCTs in the previous version of our manuscript. We did not want to imply that trialists/sponsors of included RCTs without posted results break the law. As we explain and discuss in the methods, results, and discussion sections now, we did not analyze if the included RCTs were all ACTs and thus legally obliged to submit summary data to the Results Database (please see methods – last paragraph and sentence, results/reporting results – second paragraph, discussion – first paragraph). Consequently, we cannot judge on the basis of our data which trials were clearly and legally required to submit summary data to CT.gov. We are thankful for your comprehensive comment and we hope that we could clarify this important aspect.

2. I think that the raw data should be deposited in a repository. This would allow us and others from being able to review the data.

We completely agree with you and now submit our primary data as supplementary files.

3. When comparing registered versus unregistered trials the authors state in the final paragraph of the results "Trial Registration" section that sample sizes were smaller. Were any statistical tests to confirm this carried out?

We changed this as suggested and calculated the median sample size for each group. Now the reader is given the range as well as the median of sample sizes for both groups (please see results/trial registration – last paragraph and the revised version of table 3). We also weakened our statement since no statistical tests were conducted.

4. I think from several sections of the methods that 2 authors independently did the data collection and then compared the study records, and then resolved differences with a third arbitrator. Absolutely correct. But it's possible that they shared the workload of data collection from the way it is written. Please could this be clarified.

As stated in the methods section, “one author (JH) screened titles and abstracts, excluded clearly irrelevant references, and downloaded full-texts of all potentially relevant citations”. ALL following steps of data extraction/collection were done by two authors (JH+MIM) independently to minimize bias. All discrepancies were resolved by rechecking and discussion with a third author (JM). Please also see methods – third paragraph. We have now clarified that all these steps were done independently by two authors.

Minor Essential Revisions
1. Table 3. In country of origin is "Korea" actually "South Korea" or "North Korea".

We changed this as suggested: in the revised version of table 3, we clearly differentiate and specify this now.

2. Table 3. The study sample size ranges are very wide. Having a measure of location (e.g. median) may be helpful in interpreting them. See also the Major revision 3 above.

We changed this as suggested and calculated the median sample size for each group. Now the reader is given the range as well as the median of sample sizes for both groups (please see results/trial registration – last paragraph and the revised version of table 3).

Discretionary Revisions
1. Table 4 is difficult to interpret at first glance. A legend or re-design may be helpful.

We changed table 4 slightly and added a list of registries included in the ICTRP as footnote as recommended by the first reviewer (Ludovic Reveiz). However, we were not able to short en the information provided in this table, since we consider all given information important to present.

Reviewer #3 (Richard McGee):
Major Compulsory Revisions

1. Please provide a list of the included trials in a supplementary file grouped by registration status.
   Thank you for your comment. Our data are now provided in two Excel tables as supplementary files. Autofilter is set, so the data can be grouped as needed (e.g. by registration status).

2. Please provide a reason why surgical trials were not searched for in other locations e.g. medical journals.
   Our approach consisted of selecting the ten highest ranked (by impact factor) journals (Journal Citations Reports, Science Ed. 2011) from the field of surgery that required trial registration. The ten journals identified are all fully indexed in MEDLINE, so from our point of view there was no need for additional hand searching. The RCTs were identified by using a validated methodological RCT filter optimized for high sensitivity that is regularly used within the Cochrane Collaboration for identifying RCTs in MEDLINE.
   There might be a tiny chance that we have missed some RCTs, because the PubMed search was performed only 6 weeks after the evaluated time period. Some citations might not yet have been fully indexed with MeSH terms in MEDLINE. However, the Cochrane RCT filter does not only use MeSH terms to identify RCTs, but also text words within the database’s title/abstract field that have been validated for identifying RCTs. Thus, the chance to have missed publications reporting an RCT not yet indexed with MeSH terms is possible, but low. The overall possibility of not having identified a RCT published in these 10 journals within the given time span is also low, because the identified citations were screened (title + abstract) to assess whether they were RCTs or not. If this could not be assessed by screening the abstract, the full text was evaluated. Please also see discussion – last paragraph (limitations of our study).

3. Please comment on the likely impact of only including trials from high impact surgical journals.
   We added our rationale for including RCTs from high impact surgery journals (please see methods – first paragraph). In addition, we discuss the implications of our choice with regard to the generalizability of our results (please see discussion – last paragraph (limitations of our study)).

4. Please clarify if there were any surgery journals you located which did not explicitly require trial registration and were thus excluded from your analysis.
   Thank you for your valuable comment. We excluded the “American Journal of Surgical Pathology” and the “Annals of Surgical Oncology” because both journals did not require trial registration in their author instructions. This is now mentioned in the manuscript (methods – first paragraph) and in table 1 as a footnote.

5. I have major issues with how you defined a trial as ‘unregistered’. Your definition of an unregistered trial is one that could not be found through key word searching of the ICTRP. There are several issues with this: 1- This may reflect a poor search strategy. 2- The trial register used by a trial may not be included in the ICTRP. 3- You looked at the actual publication to see if registration was mentioned- so why not use this as well? 4- You say you used the ‘advanced search form’ on the ICTRP for a more “precise search” when really you should have been aiming for a sensitive search. These issues need to be resolved before the paper would be acceptable.
   We agree with you. Indeed, we should have explained in more detail how we proceeded in order to find the included trials on the ICTRP. We defined a trial as unregistered if:
   1. there was no hint for trial registration within the full text of the identified publications (i.e. no registration number or identification, no sentence about trial registration)
   AND
   2. the trial could not be identified within the ICTRP.
   Our extensive ICTRP search was independently conducted by a clinician (JH) and an information specialist (MIM). We did not only search for the topic of the trial (with different key-
words from the original publication reporting the trial), but also tried to make our search more sensitive by 1. searching for the authors’ names, 2. searching for the name of any given institution in the authors’ affiliations, or 3. searching for the country or city where the trial was conducted, combined with one or two specific terms describing the trial. Only if all these efforts and search steps could not verify the registration of a trial, we declared it as unregistered.

We used the standard search form when trying to identify a trial, not the advanced search form. In fact, the basic search allows for a more sensitive search approach. We corrected and changed this in the manuscript.

We might indeed have declared a trial erroneously as unregistered, if it was registered within a registry not included in the ICTRP search platform, unless the registration was mentioned in the publication. This is now mentioned as a limitation of our study (please see discussion – last paragraph).

6. Your second study aim was to address whether “study results of the registered RCTs were publicly available”. You need to more clearly specify that you considered a journal publication or publishing of the raw data as ‘publicly available’. Clearly publication does not always equate to ‘freely’ available. It is not clear whether you considered trials registered in trial registers that are a) not publicly available or b) do not contain sections for publication links, as ‘submitted’ i.e. your second objective.

Thank you. We agree with you and distinguish in the revised manuscript more clearly between a publication that reports a RCT and the results (aggregate summary study data) provided in the Results Database of ClinicalTrials.gov.

Minor Essential Revisions
1. Abstract- background: RCTs should be spelled out in full in the first instance before being abbreviated.
   We changed this as suggested.

2. Abstract- methods paragraph: The authors state MEDLINE was searched but PubMed was actually searched – please correct.
   We changed this as suggested.

3. Abstract- methods paragraph: Please clarify what ranking was used e.g. ‘ranked journals by impact factor’.
   We changed this as suggested.

4. Abstract- results paragraph: When starting a sentence with numbers please write in words i.e. Four-hundred and sixty.
   We changed this as suggested.

5. Abstract- results paragraph: Please insert ‘A’ at the start of the third sentence.
   We changed this as suggested.

6. Background- second paragraph- first sentence: ‘would allow’ who to track trials?
   …scientists, clinicians, and (prospective) study participants. We added this in the revised manuscript.

7. Background- third paragraph- first sentence: please insert a comma after ‘statement’.
   We changed this as suggested.

8. Background- third paragraph: please clarify what is meant by “which is also claimed by the ICMJE”.
   We changed the phrasing and inserted a reference.
9. Background- sixth paragraph- please insert your usual paragraph spacing between the sixth paragraph and the final two paragraphs of the introduction. 
We changed this as suggested.

10. Please change the phrase ‘sine qua non’ from the 5th paragraph of the discussion.
We replaced “sine qua non” by “precondition”.

11. Results- paragraph 2: Please further explain what you mean when you say “study not concordant with the WHO definition of a clinical trial”. How was the trial different? 
We further described the study and explained why it is not concordant with the WHO definition of a clinical trial. Moreover, we added a reference.

Discretionary Revisions
The paper is currently difficult to read because the focus is on the wrong areas. For example, there are eight paragraphs in the introduction covering almost two pages of text, while the discussion comes in at barely more than one page. The introduction could be made significantly shorter and the research questions more clearly highlighted. The discussion mentions plenty of relevant studies in the area, but frequently does not relate these studies back to the author’s results.
We shortened our introduction a little. Also, you will find three new references in the discussion of the revised manuscript which we now discuss in the light of our own results. We also expanded the section of limitations.

I’m not sure about calling your Figure 1 a PRISMA flowchart. The reason being PRISMA is designed for systematic reviews. This study is not a systematic review. It might be better to rename it a study flow diagram or something similar.
Thank you. We changed this as suggested.

The tables are all rather inconsistently formatted. Please fix.
We revised our tables as suggested in order to create a more consistent and uniform appearance.