Author’s response to reviews

Title: When are clinical trials registered?: an analysis of prospective versus retrospective registration

Authors:

Stephanie Harriman (stephanie.harriman@biomedcentral.com)

Jigisha Patel (jigisha.patel@biomedcentral.com)

Version: 1 Date: 04 Jan 2016

Author’s response to reviews:

Reviewer #2: This is a descriptive study about registration of studies after enrollment of the first patient in a sample of related journals with a straightforward methodology. I have the following suggestions.

1. The results of this study stroke me and made me somewhat depressed. Of course, I was aware of retrospectively registered studies, but in this sample the percentage of retrospective registration is large. This may be due to the sample that has been drawn from a series of related journals that may have a joint policy (which they obviously have in view of the large number of studies that reported their trial registration ID). The authors could elaborate more on this potential source of bias (or 'non-representativeness').

Thank you. We have expanded on this in the limitations section of the manuscript.

2. I agree that not publishing results may be a bad idea, but the authors seem to deal quite lightheartedly with this challenge. As a systematic reviewer I check whether the study was registered and if yes, whether the authors have done what they promised to do in order to assess possible selective publication, secondary outcomes becoming primary, etc. With these journals' (and others') policy it means that we should also look carefully at the date or timing of registration.

To be honest: I'm quite annoyed by this policy. We put lots of effort and resources in (prospective) trial registration, but registration has become useless if it was after the first
enrollment, and one cannot trust the retrospectively registered data. To me, retrospective registration can only be allowed if there are clear indications that authors had not realized that there 'trial' should also have been registered (which may, indeed, apply predominantly to authors of non-RCTs).

I propose the authors discuss the various options in more detail. One can either not ask for retrospective registration and just publish the results (with the danger that this will cause a drop in registrations). Another and maybe better option could be to flag studies that were retrospectively registered. This may also cause a drop in registrations, but such a flag at least may warn the end-user, may give a somewhat negative image to the study and alerts people to carefully consider the credibility of the results.

We thank the reviewer for these comments – this is now addressed in detail in the discussion section. We have discussed the various options available to journals regarding consideration of clinical trials that have not been registered prospectively. We have also discussed in more detail the options available to journals to flag to end-users that a trial was not registered prospectively. We are also reviewing BioMed Central’s policy regarding flagging of retrospective studies to end users.

3. Study selection was based on the word 'trial'. I tend to avoid the use of 'trial' and use 'study' instead. Could that have led to having missed studies? If so, I don't expect a major risk of bias, though.

We have added this as a limitation in our discussion.

4. Would it be possible to present also some potential determinants (or associations) of retrospective registration: distribution of registration types amongst

- studies that were done by authors who may have an interest in the results (compared to independent authors).
As a proxy for authors potentially having an interest in the result, we have recorded whether financial competing interests were declared in the manuscript. Of the 108 articles included, financial competing interests were declared in 16 (15%). Of these, 8 were registered prospectively, and 8 were registered retrospectively (all before submission to the BMC series journal in which they were published. For the 92 where authors declared they had no financial competing interests, three did not include a TRN, 25 were registered prospectively, and 64 were registered retrospectively. We have added details of this this to the methods, results and discussion. We have also added this as absolute numbers to table 2. Our sample size was too small to determine whether presence of financial competing interests was associated with prospective versus retrospective registration.

- RCTs and non-RCTs

We have added a new table (table 2) which shows the distribution of prospective and retrospectively registered studies by different characteristics, including study designs; however the numbers for some of the study designs are too small to allow further analysis.

- the various trial registers

Table 2 also includes distribution of prospective and retrospectively registered studies by trial register.

There may be other factors of interest.

Table 2 also includes distribution of prospective and retrospectively registered studies by trial register.

5. I would also like to see whether there's a difference between pro- and retrospectively registered studies in the percentage of studies that had significant results.
We thank the reviewer for this suggestion. We agree that it would be interesting to see whether there is a difference in percentage of studies with statistically significant results between those that were prospectively and retrospectively registered; however to obtain meaningful results, it would be necessary to look at this only for the primary outcome. This would require first determining what the primary outcome was, and whether this was the same as indicated in the trial registry record. This was not the aim of the current study and the protocol was not designed to answer this. As editors, we do not feel we have the expertise to analyse whether a primary outcome has changed. If the Editor wishes, we can assess whether studies present any statistically significant results, however from an assessment of the first ten included studies, all but one present at least one statistically significant response.

6. The authors may wish to add (row) percentages to the cells of Figure 1.

We have updated the figure so that percentages are given. Percentages are all given of the total number of included studies.

Reviewer #3: I do not feel competent enough to judge whether the study provides sufficient new insight on the topic of publication of retrospectively registered clinical trials. The authors mentioned some other studies but at first glance all seem to be rather explorative. However, my focus will be on another point which I mention in the following paragraph.

The issue of retrospective registration itself is of interest for those that study issues around registration as one cornerstone in the overarching "increasing value, reducing waste" discussion. The fact that the majority of published trials in the BMC series were not registered prospectively is certainly an interesting finding, helps raising awareness of the work to do and supports on-going efforts such as the All-Trials initiative. The fact that the authors build part of BMC is welcomed.

Before I come to my major comment I would like to highlight some minor comments:
Page 4, line 7: the authors stated that clinical trial registries address the problem of selective reporting. Maybe it is better to state that registries "aim" to address this problem and then the authors could mention some recent reviews that assessed the completeness of registries and how often summary results are published in registries, etc.

We agree and have changed this to say that clinical trial registration aims to address these issues.

Page 4, line 20 and 24: the authors should cite references for their empirical claims.

Thank you for this comment. We have clarified that the statement that journals receive submissions of manuscripts reporting clinical trials that were not registered prospectively, we have added clarification that this is based on our experience as previous editors of the BMC series.

Regarding the statement that there are few studies that have investigated the extent of retrospective registration, there is no reference for this as there are no published systematic reviews assessing this research question to identify the lack of research in this area.

Page 9, line 7: the authors mentioned that "Journals are not well placed to enforce prospective registration". Some more discussion on this topic would strengthen the claim. Although it is true that other stakeholders could be more involved in promoting prospective trial registration, editorial policies are in a strong position to influence registration efforts and contribute their part to increase value and reduce waste in research. I am fine with the argument of the authors that some journals should also publish trials that have not been registered so as to avoid the loss of trial information, but this does not mean that journals could not play an important role in enforcing prospective registration at the same time.

We have added further discussion around this point, clarifying that journals do play a role in enforcing registration but that there are other stakeholders who are placed earlier in the process and therefore may be better able to enforce it.
The discussion on the ethics of publishing retrospectively registered trials is important for this paper and should be expanded; especially, but not only, because the authors build part of BMC. The argument in favor of publication of retrospectively registered studies to prevent the potential loss of information is sound. However, it is only one argument that needs to be analyzed and balanced with regards to other equally sound arguments against publication. The authors should mention these arguments in a neutral way as well. Otherwise, the discussion section is too biased. After neutral presentation of arguments for and against publishing non registered or retrospectively registered clinical trials, the authors can then state that the BMC series decided, of all things considered, for an editorial policy that allows this type of publication.

We thank the reviewer for these comments which we have now addressed in the discussion section. We have added arguments against consideration of retrospectively registered studies and after presenting both sides of the argument, state that the BMC series has decided to allow consideration.

However, the ethical analysis should not stop at this point but should elaborate more on "what conditions should be fulfilled to make the publication of retrospectively registered trials as ethical as possible". For example, journals such as the BMC series might require authors to explicitly state in the main text that the study was registered retrospectively. This is necessary information for the reader. Otherwise, the reader might put more trust in the paper than they should. Simply because the higher credibility of results that might come with prospective registration (such as transparency about protocol deviations) do not apply for this paper. If papers only state that the study was registered without adding the relevant information that it was retrospective registered, journals consciously misinform the reader.

We have also added further discussion on how journals can make publication of retrospectively registered studies as transparent as possible by flagging to readers that a study was not registered prospectively.

Unfortunately, this important point does not appear in the discussion and even more important the authors do not present any data on how many of the retrospectively registered studies reported that fact explicitly (and not only the registration number or date). This empirical information should be added to paper. It is only in the last sentence of the conclusion where this point shows up (but again without data about the current status quo). Additionally, I also miss
any remark on whether BMC or any other journals have this explicit policy that requires (and not only recommends) an explicit statement on the date of registration or even better an explicit statement that the registration was retrospective. The latter is better because most readers will probably not check whether the data of registration was for or after enrollment of participants.

We did not specifically record whether the studies reported in the text that they were registered retrospectively, however this was not a requirement of submission to the journal so the authors are unlikely to have included this. We are also reviewing BioMed Central’s policy regarding flagging of retrospective studies more clearly to end users.

In summary, I vote for a major revision decision with regard to my major comment. If the authors present the mentioned data and comprehensively discuss their findings with an outlook on the potential changes for editorial policies, the paper would contribute highly to the field of clinical research reporting and suit well for a publication in Trials.

Reviewer #4: This is well described and discussed study looking at registration status of trials submitted to BMC journals.

It wasn't clear until the end of the manuscript that BMC doesn't require registration of clinical trials in order to be published in the journals. At the end of the introduction it is positioned that the study is looking at retrospective registration but really, it looked at registration status more generally.

Thank you for this comment. To address the first point we have added clarification to the end of the background section that the BMC series (and some other journals) will consider manuscripts reporting studies that have not been registered prospectively.

Regarding the second point that the study really looked at registration status more generally, we feel that this is covered by the study’s first aim ‘the proportion of clinical trials that were registered prospectively or retrospectively’.
I think the paper could be shortened significantly and yet still contain the essential information of the study. The discussion especially was too long and repetitive.

We have revised the discussion so that it is less repetitive; however in addressing the points raised by the other reviewers regarding additional discussion, the overall length of the manuscript has not been shortened.

Did the authors check with authors of the 4 unregistered trials whether they really didn't register the article? It could be they simply didn't report the registry number.

Thank you for this suggestion. We have now emailed the corresponding author for all four trials. One confirmed that the study had not been registered (stating that it was a small pilot study), one confirmed that the Eudra CT number that we were (and still are) unable to locate was correct, but was unable to provide any further information, and one did not reply. The corresponding author of the final article that had been classified replied to say that the study had been registered. This identified an error in classifying this article. This article has now been reclassified as ‘retrospectively registered before submission to the journal’ and the manuscript has been updated accordingly.

I found Figure 2 redundant.

We have removed figure 2 and have added the percentages to the flowchart in figure 1.

I think it was a shame, after all that work, that the authors didn't also look at selective outcome reporting. That is, look to see if for those studies that were prospectively registered whether there was a match between the registry and the article in terms of POMs. A number of studies have done that, for example: Scott, A., Rucklidge, J. J., & Mulder, R. T. (2015). Is Mandatory Prospective Trial Registration Working to Prevent Publication of Unregistered Trials and Selective Outcome Reporting? An Observational Study of Five Psychiatry Journals That Mandate Prospective Clinical Trial Registration. PloS One, 10(8), e0133718. doi: 10.1371/journal.pone.0133718. Such an investigation can be quite revealing and it would be a strength of the study if the authors went and gathered that information. As it stands, the study
simply reports on registration status which, while interesting, could be made more interesting by looking further into the registration status.

We thank the reviewer for this suggestion. The aim of our study was to determine when during the research timeline a study is registered. We feel that the question the reviewer is asking us to answer (whether the prospectively registered trials adhered to their stated primary outcomes) is a different question for which the protocol for our study was not designed to answer. Although we agree with the reviewer that the additional information might make our article more interesting, we feel this would be an entirely new study and therefore not essential to our study, especially as the reviewer states that a number of studies have already explored adherence to primary outcomes.

Furthermore, as editors rather than trialists, we do not feel we have the expertise to adequately perform such an analysis.