PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Time to publication for publicly funded clinical trials in Australia: An observational study
AUTHORS	Strand, Linn Beate; Clarke, Philip; Graves, Nicholas; Barnett, Adrian

VERSION 1 - REVIEW

REVIEWER	Michael Köhler Institute for Quality and Efficiency in Health Care, Germany
REVIEW RETURNED	06-May-2016

GENERAL COMMENTS	Topic: The authors show the rate of publication in publicly funded randomised controlled trials in Australia with respect to publication of both trial protocols and trial results. They also give data about time to publication and possible predictors for publication and time to publication. Their results demonstrate a surprising time lag from funding to publication of study protocols, and insufficient publication of these studies overall. The manuscript is overall well written and to the largest part comprehensible to the non-Australian reader, given that the authors refer to a national Australian system which foreign readers might not be familiar with. Their results are in line with a growing body of evidence on publication bias for clinical studies. The authors report a median time to publication of a protocol paper of 6.4 years after funding was granted, and 7.2 years to the publication of the main results paper. Especially the time lag from granting of funds to publication of a protocol paper is highly interesting and not easy to explain. The subject of protocol publication at an early time point in the course of a clinical study, and the lack thereof, deserves attention and is covered by the authors in a compelling way. Issues: Introduction, page 4, lines 3-5: The authors state that one of their objectives was to investigate whether the “timely publication of a protocol paper was associated with a timely publication of the main paper”. However, the authors give no definition on what is to be considered as “timely” with respect to the publication. In the course of the manuscript it becomes clear that the publication rates and time to publication are not referenced to any “gold standards”. Instead, the time to publication of the protocol paper is used as a predictor for the time to publication of the main results paper. Suggestion: The formulation of this objective might be revised accordingly.

	Methods, page 4-5, section “Data collection”: The authors may want to consider shifting the background information on the NHMRC funding system into the introduction. To understand the significance of the results, it is important to know whether there has to be at least a preliminary study protocol to be submitted to the NHMRA to receive funding. In the results section, the authors mention that only “one protocol was published before funding”. The median time to publication of the protocol paper was 6.4 years after funding. The lack of a final trial protocol at time of funding does not seem to be a sufficient explanation for a time lag this long between funding and publication. However, information on the required status of the trial protocol at time of application and funding could be useful to judge what might be a reasonable time between funding and publication. Suggestion: Addition of a short explanation of the application process for NHMRC grants, including requirements on the trial protocol. Methods, page 5, section “search strategy”: The authors state that they identified RCTs by searching for the Words “RCT”, “randomised” and “trial” in publicly available NHMRC documents. The search terms used appear to be sufficient to obtain a sample of funded RCTs. However, the authors do not mention which NHMRC documents were searched. This would be useful especially for non-Australian readers and researchers, as the NHMRC website does not seem to be self-explanatory in this respect. Furthermore, the authors do not give an account of the identified RCTs and the corresponding documents beside the numbers in Figure 1. Suggestion: Addition of the searched document types. Also, a list of the identified RCTs should be provided as a supplement, preferably including links to the corresponding trial registry entries and references to the protocol papers and main results papers, if applicable. Figure 1: The numbers of the RCTs identified in three different study registries add to 73, which corresponds to the 77 RCTs identified in the NHMRC documents minus four studies for which no registry entries were found. Thus, the findings in clinicaltrials.gov, ANZCTR and ISRCTN appear to be mutually exclusive, which is surprising. I would expect at least some studies to be registered in more than one registry. The authors should provide an explanation for this pattern. Figure 3: Minor issue: The numbers on the arrows are redundant, as they are also shown in the boxes. Methods, page 6, line 15-24: The authors wanted to investigate whether funding amount, number of investigators or participant numbers were associated with time to publication and if publishing a protocol paper influenced the time to publication of the main results. The authors did not include the outcome of the trial as a predictor for time to publication, or publication at all. A body of evidence gathered by several authors

	has shown that publication of clinical studies may depend on the outcome of the study, and that studies without statistically significant results may take longer to be published (e.g. [1, 2]). In a public funding environment, failure to publish negative results will probably lead to considerable research waste and therefore waste of research funds. In the present study, the authors identified a main results paper for only 37 out of 77 RCTs, which indicates a high relevance for the funding system. If outcome was identified as a predictor for publication of results, there might be a basis for revising guidelines in order to commit applicants to publish their results irrespective of the outcome. Results, page 7: The authors state that “31 million dollars went into studies that have not yet published the main results paper during the mean follow-up time of 6.2 years”. Furthermore, the total funding amount for 77 studies is reported to be 59 million dollars in the text. This is not in accordance with Table 1, which shows RCT characteristics by publication status of main results paper. In Table 1, a mean funding amount of 77.9 million dollars is claimed for all studies without main results paper, and 76.8 million dollars for studies with main results paper. Please explain the discrepancy. Discussion, page 10, lines 31 to 42: The Hazard Ratio for the protocol paper as a predictor for time to publication of the main results paper was 0.80. According to the authors this suggests that “publishing a protocol slows the time to the main paper”, which they speculate “could be because not having a protocol paper allows authors to focus on statistically significant results that may not have been the primary outcome, and there is a known bias towards journals accepting papers with statistically significant results”. This suggests that study authors may deliberately deviate from their study protocols in order to maximise their publication success. There may be such cases, but the idea that this might have happened in 34 out of 77 investigated studies seems unlikely. Maybe the suggested effect of the protocol paper on the publication of the main paper is just an artefact of another cause. It is possible that authors of studies with a planned short duration did simply not find it necessary to publish the protocol separately because of the presumably short interval between protocol and main publication. On the other hand, regression with a Cox proportional hazards model as performed by the authors did not show an association between project duration and publication of the protocol. Suggestion: Although their discussion of the association between protocol and main publication cannot be ruled out, the authors should discuss other possible explanations for the low Hazard Ratio. Discussion, page 10, line 50: Minor issue: Was the sentence “…that only 36% had published there results within two years…” meant to read “…published their results…”? Discussion, general remark: A relatively simple solution to insufficient protocol publication would be an obligation for study authors to submit their complete and final

	study protocols to study registries, leading to public access to the protocols via the web site of the registry. This would be the timeliest measure to make protocols available to anyone interested, and would also supersede a separate protocol publication. The authors may want to include this option in their discussion. Literature: 1. Easterbrook P.J., Berlin J.A., Gopalan R., Matthews D.R. Publication bias in clinical research. Lancet 337 (1991), pp. 867–872 2. Ioannidis, J.P.A. Effect of the Statistical Significance of Results on the Time to Completion and Publication of Randomized Efficacy Trials. JAMA 1998;279(4):281-286.

REVIEWER	Amanda Blatch-Jones (nee Young) NIHR Evaluation, Trials and Studies Coordinating Centre, Research on Research Programme
REVIEW RETURNED	11-May-2016

GENERAL COMMENTS	The paper raises an important question although it is not unique in terms of assessing time to publication. The study appears to have been conducted well and does include an interesting comparison between time to publication of the protocol with timely publication of the main results. The introduction is quite vague as to what the value of the study will add to the current literature. The authors could provide greater clarity about the current debates around timely publication of trials (in terms of trial results and study protocol) using the existing references as well as the updated Chalmers and Glasziou 2014 Lancet series. The aims of the paper could be better described by clarifying the hypotheses of the study or the specific research questions (time from funding to protocol publication and time from funding to main results publication). Although the authors provide such information it could be better described. It seems like the secondary outcome was to examine if there was an association between time to publication of the protocol and main results (funding amount, number of investigators, number of participants). This is not reported in the abstract and is only briefly mentioned at the end of introduction. If the aims were clearly clarified at the beginning it would strengthen the paper and add value to the current debates around avoidable waste in terms of publishing the protocol in a timely manner. Although, the methods section is detailed I am not sure if the study design (observational study) is appropriate for this type of study. Data extraction does not appear to be covered in the methods section, only that two investigators independently determine the publication status of each trial. How was information stored, extracted and analysed (using R?)? I would recommend checking that these points are included in the methods section. In the results section I would recommend including the IQR as well for the medians. It would be interesting to know more about the 77 included RCTs and whether any trial design factors were in fact associated to the time to publication. For example, statistically significant results, type of intervention, the disease classification etc. For the discussion, it may be useful to have/use sub headings to

	clearly separate the discussion points noted in this section. As it stands the discussion is difficult to follow although the authors raise some interesting and clearly important issues. There are a number of styling issues and typo errors which the authors need to address, such as National Institute for (not of) Health Research.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Michael Köhler

Topic:
The authors show the rate of publication in publicly funded randomised controlled trials in Australia with respect to publication of both trial protocols and trial results. They also give data about time to publication and possible predictors for publication and time to publication. Their results demonstrate a surprising time lag from funding to publication of study protocols, and insufficient publication of these studies overall.

The manuscript is overall well written and to the largest part comprehensible to the non-Australian reader, given that the authors refer to a national Australian system which foreign readers might not be familiar with. Their results are in line with a growing body of evidence on publication bias for clinical studies. The authors report a median time to publication of a protocol paper of 6.4 years after funding was granted, and 7.2 years to the publication of the main results paper. Especially the time lag from granting of funds to publication of a protocol paper is highly interesting and not easy to explain. The subject of protocol publication at an early time point in the course of a clinical study, and the lack thereof, deserves attention and is covered by the authors in a compelling way.

Issues:
Introduction, page 4, lines 3-5:
The authors state that one of their objectives was to investigate whether the “timely publication of a protocol paper was associated with a timely publication of the main paper”. However, the authors give no definition on what is to be considered as “timely” with respect to the publication. In the course of the manuscript it becomes clear that the publication rates and time to publication are not referenced to any “gold standards”. Instead, the time to publication of the protocol paper is used as a predictor for the time to publication of the main results paper.
Suggestion: The formulation of this objective might be revised accordingly.
RESPONSE: We agree and we had no prior idea of what we meant by “timely”. A recent related paper by Chen et al (2016) used two years from study completion to publication, and this influenced our target of 18 months for the protocol after funding. We have removed the word “timely”.

Methods, page 4-5, section “Data collection”:
The authors may want to consider shifting the background information on the NHMRC funding system into the introduction.
To understand the significance of the results, it is important to know whether there has to be at least a preliminary study protocol to be submitted to the NHMRA to receive funding. In the results section, the authors mention that only “one protocol was published before funding”. The median time to publication of the protocol paper was 6.4 years after funding. The lack of a final trial protocol at time of funding does not seem to be a sufficient explanation for a time lag this long between funding and publication. However, information on the required status of the trial protocol at time of application and funding could be useful to judge what might be a reasonable time between funding and publication.
Suggestion: Addition of a short explanation of the application process for NHMRC grants, including

requirements on the trial protocol.
RESPONSE: For the years covered by our search strategy (2008 to 2010) the NHMRC did not require a published protocol and the current rules do not mandate protocol publication. We have added two paragraphs on the application process and the key NHMRC policy changes to the introduction (pages 3-4). These provide important context and help international readers to understand the Australian situation.

Methods, page 5, section “search strategy”:
The authors state that they identified RCTs by searching for the Words “RCT”, “randomised” and “trial” in publicly available NHMRC documents. The search terms used appear to be sufficient to obtain a sample of funded RCTs. However, the authors do not mention which NHMRC documents were searched. This would be useful especially for non-Australian readers and researchers, as the NHMRC website does not seem to be self-explanatory in this respect. Furthermore, the authors do not give an account of the identified RCTs and the corresponding documents beside the numbers in Figure 1.
Suggestion: Addition of the searched document types. Also, a list of the identified RCTs should be provided as a supplement, preferably including links to the corresponding trial registry entries and references to the protocol papers and main results papers, if applicable.
RESPONSE: The documents searched were the published lists of funded studies in each year. We have included the full list as a supplement together with the registry links, and we will make the complete data set freely available after publication.

Whilst preparing the supplement list we went through each trial again and found two more eligible main paper publications. This has slightly changed the results, with the main change for the impact of the number of participants on the time to publication which became stronger and is still in the expected direction. The overall conclusions remain the same.

Figure 1:
The numbers of the RCTs identified in three different study registries add to 73, which corresponds to the 77 RCTs identified in the NHMRC documents minus four studies for which no registry entries were found. Thus, the findings in clinicaltrials.gov, ANZCTR and ISRCTN appear to be mutually exclusive, which is surprising. I would expect at least some studies to be registered in more than one registry. The authors should provide an explanation for this pattern.
RESPONSE: When looking for the relevant information we first searched for the projects on the ANZCTR website. If we could not find it there we searched the ISRCTN and finally ClinicalTrials.gov. So it is likely that some trials were registered more than once, but after we found the required information in one registry we did not keep looking. We have revised the methods section to better explain this (page 6).

Figure 3:
Minor issue: The numbers on the arrows are redundant, as they are also shown in the boxes.
RESPONSE: We have removed the numbers.

Methods, page 6, line 15-24:
The authors wanted to investigate whether funding amount, number of investigators or participant numbers were associated with time to publication and if publishing a protocol paper influenced the time to publication of the main results. The authors did not include the outcome of the trial as a predictor for time to publication, or publication at all. A body of evidence gathered by several authors has shown that publication of clinical studies may depend on the outcome of the study, and that studies without statistically significant results may take longer to be published (e.g. [1, 2]). In a public funding environment, failure to publish negative results will probably lead to considerable research waste and therefore waste of research funds. In the present study, the authors identified a main

results paper for only 37 out of 77 RCTs, which indicates a high relevance for the funding system. If outcome was identified as a predictor for publication of results, there might be a basis for revising guidelines in order to commit applicants to publish their results irrespective of the outcome.
RESPONSE: We agree and mentioned this bias in the discussion and cited an RCT that convincingly showed how "statistically significant" studies are more likely to be published. To properly examine outcome we would need more trials to be published. For example, the Ioannidis trial (JAMA 1998;279) had only 8 out of 109 studies that were not published. Whereas close to half of our studies were not published meaning that we cannot use the published p-value (or effect size) as a predictor. We have now cited the relevant Ioannidis paper (page 11) and now also mention other possible causes such as sponsor termination and contractual issues (page 10).

Results, page 7:
The authors state that "31 million dollars went into studies that have not yet published the main results paper during the mean follow-up time of 6.2 years". Furthermore, the total funding amount for 77 studies is reported to be 59 million dollars in the text. This is not in accordance with Table 1, which shows RCT characteristics by publication status of main results paper. In Table 1, a mean funding amount of 77.9 million dollars is claimed for all studies without main results paper, and 76.8 million dollars for studies with main results paper. Please explain the discrepancy.
RESPONSE: This was an error and has been changed. The mean funding amount in Table 1 should be $768,000 for projects with the main paper results published and $779,000 for projects without the main paper.

Discussion, page 10, lines 31 to 42:
The Hazard Ratio for the protocol paper as a predictor for time to publication of the main results paper was 0.80. According to the authors this suggests that "publishing a protocol slows the time to the main paper", which they speculate "could be because not having a protocol paper allows authors to focus on statistically significant results that may not have been the primary outcome, and there is a known bias towards journals accepting papers with statistically significant results". This suggests that study authors may deliberately deviate from their study protocols in order to maximise their publication success. There may be such cases, but the idea that this might have happened in 34 out of 77 investigated studies seems unlikely.
Maybe the suggested effect of the protocol paper on the publication of the main paper is just an artefact of another cause. It is possible that authors of studies with a planned short duration did simply not find it necessary to publish the protocol separately because of the presumably short interval between protocol and main publication. On the other hand, regression with a Cox proportional hazards model as performed by the authors did not show an association between project duration and publication of the protocol.
Suggestion: Although their discussion of the association between protocol and main publication cannot be ruled out, the authors should discuss other possible explanations for the low Hazard Ratio.
RESPONSE: We speculated on how the protocol may have a slowing effect, but the evidence is not strong that the slowing effect is real. As the reviewer suggests, clinical trials with a short time line may not have seen the need for a protocol. We are happy with the current discussion as it covers potential mechanisms but also warns that there may be no effect.

Discussion, page 10, line 50:
Minor issue: Was the sentence "…that only 36% had published there results within two years…" meant to read "…published their results…"?
RESPONSE: Agreed and changed

Discussion, general remark:
A relatively simple solution to insufficient protocol publication would be an obligation for study authors to submit their complete and final study protocols to study registries, leading to public access to the

protocols via the web site of the registry. This would be the timeliest measure to make protocols available to anyone interested, and would also supersede a separate protocol publication. The authors may want to include this option in their discussion.
RESPONSE: This is an interesting suggestion. The ANZCTR allows users to upload their protocol, but this is not mandatory. Using a clinical trial registry would also provide a free place to upload protocols, and so would remove the barrier of publication fees and avoid delays due to peer review. We have added this suggestion to the discussion (page 11).

Literature:
1. Easterbrook P.J., Berlin J.A., Gopalan R., Matthews D.R. Publication bias in clinical research. Lancet 337 (1991), pp. 867–872 2. Ioannidis, J.P.A. Effect of the Statistical Significance of Results on the Time to Completion and Publication of Randomized Efficacy Trials. JAMA 1998;279(4):281-286.

Reviewer: 2
Reviewer Name: Amanda Blatch-Jones (nee Young)

The paper raises an important question although it is not unique in terms of assessing time to publication. The study appears to have been conducted well and does include an interesting comparison between time to publication of the protocol with timely publication of the main results. The introduction is quite vague as to what the value of the study will add to the current literature. The authors could provide greater clarity about the current debates around timely publication of trials (in terms of trial results and study protocol) using the existing references as well as the updated Chalmers and Glasziou 2014 Lancet series.
RESPONSE: We agree that this is not unique, although ours is the first study to use Australian data and the first to examine the protocol paper. In response to reviewer #1 we have added more details on the Australian situation mention the Alltrials campaign.

The aims of the paper could be better described by clarifying the hypotheses of the study or the specific research questions (time from funding to protocol publication and time from funding to main results publication). Although the authors provide such information it could be better described. It seems like the secondary outcome was to examine if there was an association between time to publication of the protocol and main results (funding amount, number of investigators, number of participants). This is not reported in the abstract and is only briefly mentioned at the end of introduction. If the aims were clearly clarified at the beginning it would strengthen the paper and add value to the current debates around avoidable waste in terms of publishing the protocol in a timely manner.
RESPONSE: The main aims were to look at time to publication of the main paper and protocol. The association between study characteristics and time to publication were not the main focus and so were not mentioned in the abstract. We have now described this secondary aim better in the introduction (page 4).

Although, the methods section is detailed I am not sure if the study design (observational study) is appropriate for this type of study. Data extraction does not appear to be covered in the methods section, only that two investigators independently determine the publication status of each trial. How was information stored, extracted and analysed (using R?)? I would recommend checking that these points are included in the methods section.
RESPONSE: Our study was an observational study that followed the design of related published studies. We used publicly available data extracted from web sites, and the small number of variables needed were available in the clinical trial registries. The information was stored in Excel and analysed in R, and this information is now included in the methods (pages 6 and 7).

In the results section I would recommend including the IQR as well for the medians. It would be

interesting to know more about the 77 included RCTs and whether any trial design factors were in fact associated to the time to publication. For example, statistically significant results, type of intervention, the disease classification etc.
RESPONSE: We cannot calculate the inter-quartile range as less than three-quarters of studies published their main paper or protocol. Hence the time to the third-quartile is unknown.

We think the issues apply across interventions and disease areas, and this is based on our experience of working in a variety of clinical fields (as statisticians and economists we have worked with a wide range of researchers). Reviewer #1 also mentioned "statistical significance" as a predictor, and please see our response above. We would have reduced statistical power to examine variables such as "disease classification" with many categories. Our planned analyses covered variables that are generic and continuous, such as total funding and number of investigators.

For the discussion, it may be useful to have/use sub headings to clearly separate the discussion points noted in this section. As it stands the discussion is difficult to follow although the authors raise some interesting and clearly important issues.
RESPONSE: We agree and we have now added subheadings to the Discussion.

There are a number of styling issues and typo errors which the authors need to address, such as National Institute for (not of) Health Research.
RESPONSE: We have done a thorough edit of this version.

VERSION 2 – REVIEW

REVIEWER	Michael Köhler Institute for Quality and Efficiency in Health Care, Germany
REVIEW RETURNED	15-Aug-2016

GENERAL COMMENTS	The authors adressed all of the issues I mentioned in the first review. They have adapted most of the text sections accordingly. The issues that were unclear to me in the first version are much better understandable now. Adding a full list of the studies that were included in their investigation has contributed to transparency of the results. I agree with the authors that examining statistical significance of outcomes as a predictor is difficult given the circumstances, and therefore is better left out. The authors covered this point with the inclusion of the suggested literature on the topic, which seems to be sufficient. There is one point that I missed in the first version, but needs to be changed for final publication: The abstract does not tell anything about the multi-variable analysis. This should be mentioned in the methods part of the abstract, as well as in the results. It should mention that apart from project duration and possibly protocol paper, there was no association of any factor with time to publication of protocol and main results paper, preferably with hazard ratios and confidence intervals. If this is covered, I recommend the manuscript for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Michael Köhler
Institution and Country: Institute for Quality and Efficiency in Health Care, Germany

The authors adressed all of the issues I mentioned in the first review. They have adapted most of the text sections accordingly. The issues that were unclear to me in the first version are much better understandable now. Adding a full list of the studies that were included in their investigation has contributed to transparency of the results.

There is one point that I missed in the first version, but needs to be changed for final publication: The abstract does not tell anything about the multi-variable analysis. This should be mentioned in the methods part of the abstract, as well as in the results. It should mention that apart from project duration and possibly protocol paper, there was no association of any factor with time to publication of protocol and main results paper, preferably with hazard ratios and confidence intervals.

RESPONSE: We have added our multiple variable analysis to the methods and results of the abstract.

We have also added one more recent relevant reference to the Discussion section.