PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trial registration and time to publication in a retrospective cohort of publicly funded randomised controlled trials in New Zealand 1999-2017
AUTHORS	Jull, Andrew; Walker, N

VERSION 1 – REVIEW

REVIEWER	Decullier, Evelyne Hospices Civils de Lyon, pole santé publique
REVIEW RETURNED	30-Jun-2022

GENERAL COMMENTS	The article is interesting, some points could be more explicit. Especially, I would replace “trials” by “RCT” and I think the paragraph on search strategy should be rewritten. The authors should also discuss the good performance of New Zealand.Below are the detailed comments. 1) Page 3 line 47 to line 54: difficult to read and to understand. Maybe skip the history of the multiple requests, and explain that you get one clean list and that before 2010 you had to search within text. The reader does not understand why certain grants were not in the search (for example emerging researcher). Who is maintining the database on figshare? Why might it contain new information since the excel file seem exhaustive from 2010? This chapter is really confusing and should be simplified. Maybe a flow chart could be useful. 2) From the search strategy we understand that only RCT were included. If so, it should be clear and maybe the authors should add the information in the title and at each time where they specify the objective (for instance page3 line28-29, page 4 line 54,. Page5 line 55, page 7 line 17, page 9 line 7….) 3) Not sure to understand how a grant for post-graduate degree could fund a RCT? 4) Page 4 line 26: what do you mean by reported results? Do you mean the results available in the article? Or did you get all the final reports from the HRC? 5) On table 1, maybe the authors should add the year of the grant. 6) Page 5 line 55; to my understanding the authors did not have a clear, defined list of funded RCT for the first years. The assertion that only 6 grants were awarded in 1999 seems to be misleading. If the authors could not ascertain that they found all funded RCT, they have to modify the sentence to intergrate incertainty

	7) Page 6 –table 2: “protocol published”: the figure is rather high: nearly a half were published, since thus practice is not well developed, I wonder what the author mean by this. Is it really the publication of the procotol as an article in a journal? 8) Page 6 table 2: I am surprised that there are no multiple supports for publication. How is it possible to have 6 with results posted and only 1 with “posted on trials register”? 9) Page 6 line 9: why is it 95.7% whereas the table mentions 84.8? 10) P4 line 44: the authors mentioned dissemination metrics without details and then the figures are presented in the results. It would be useful to provide at least a small definition for each indicator (citations: how are they computed? And altmetric score) Overall, the RCT funded by HRC performed well in terms of registration, publication and publication bias compared to other cohorts. It would be interesting that the authors try to provide an explanation: is one part of the funding conditional to the registration? Close monitoring by the agency? Typo Page8 line 56 teh □the Page 6 line 4: “in the period to 2009”, a word is missing? Page 4 line 12 seperate --separate

REVIEWER	Souverein, Patrick Utrecht University, Pharmacoepidemiology and Clinical Pharmacology
REVIEW RETURNED	20-Jul-2022

GENERAL COMMENTS	The authors describe an overview of the fate of clinical trial in New Zealand that were funded by the Health Research Council since 1999 with the aim to assess trial registration, publication status and whether publication was influenced by trial result. The study is clearly presented and of interest in the light of research integrity and research waste. Couple of minor questions: 1 Can the authors say something about non-HRC-funded trials? What is the proportion of trials funded by the HRC in that region and what would be the expected if studies were funded differently? 2 The clinical trial domain is rather broad, with the majority focusing on procedures or drugs. Did the authors stratify by type of intervention and see whether there were any differences. Prior work by Van den Bogert et al on drug trials in The Netherlands found that for instance phase 1 trials, non-registration of trials or single center trials were associated with a higher risk of non-publication. Are the authors able to replicate such findings in there cohort?

REVIEWER	Jakobsen, Rune

	University of Oslo, Department of Health Management and Health Economics
REVIEW RETURNED	09-Aug-2022

GENERAL COMMENTS	Peer-review Trial registration and time to publication in a retrospective cohort of publicly funded trials in New Zealand 1999-2017 General comments This paper examines trials funded by the Health Research Council of New Zealand over almost two decades starting when registration in trial registers were first discussed and later became the norm and mandatory. Funded trials were identified in a thorough and systematic manner and then explored with regards to registration (before or after they were started), design, completion and publication or other ways of dissemination. The manuscript is very well-written. Methods and results are clearly presented and adequately discussed. I find the paper to be a valuable contribution to the literature reassuringly finding most trials in recent years to be both registered and published with no apparent publication bias between trials with positive findings as compared to negative trials. I have only a few minor comments that the authors might consider: 1. A figure with a flow chart of the identification, inclusion and dissemination could be considered as a quick way for readers to get an overview. 2. The authors state in the methods that they verified 10% of the identified trials for accuracy, but do not provide any results or comments regading this in results. 3. In the last paragraph on p8 there are a few typos (informatione.g. / teh).

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Dr. Evelyne Decullier

1. I would replace “trials” by “RCT”. *We used the word “trials” for the sake of consistency. If we replaced “trials” with “RCT”, there would be occasions where the language would be cumbersome with repetitive use of “RCT” and we would still have to use the term “trials” with respect to registers. Thus we have retained the word “trials” rather than replace it with “RCT”. However, we have clarified in the title and the abstract that the focus of the study was on randomised controlled trials and added (trials) after randomised controlled trials in the opening sentence of the paper to indicate trials should be read as an abbreviated term for randomised controlled trials. Further, we have added the following sentence to the methods section: “Only studies described as randomised controlled trials were included in thi study.”*

2. The authors should also discuss the good performance of New Zealand. *See point 14 below.*

3. Page 3 line 47 to line 54: difficult to read and to understand. Maybe skip the history of the multiple requests, and explain that you get one clean list and that before 2010 you had to search within text. *We have revised the text, but have retained description of the different lists and the search processes including the supplementary sources.*

4. The reader does not understand why certain grants were not in the search (for example emerging researcher). *The original request did not include career development awards, but some were included in the 1999-2010 list anyway. Hence our scrutinising of supplemental sources for such grants.*

5. Who is maintaining the database on figshare? Why might it contain new information since the excel file seem exhaustive from 2010? This chapter is really confusing and should be simplified. Maybe a flow chart could be useful. *The dataset on Figshare was created by Emma Tumilty and she stated it "represents a list of all awarded grants" as shown on the HRC's website for the period between 2006 and 2013 inclusive. This information is available from the website listed in reference 11. The dataset is not maintained. This dataset was used to cross-check searches of the datasets obtained from the HRC and our own searches of the HRC's online repository. We have simplified the section on the search strategy and supplemented it with a flow diagram (figure 1).*

6. From the search strategy we understand that only RCT were included. If so, it should be clear and maybe the authors should add the information in the title and at each time where they specify the objective (for instance page3 line28-29, page 4 line 54,. Page5 line 55, page 7 line 17, page 9 line 7….). *Please see our response to point 1 above.*

7. Not sure to understand how a grant for post-graduate degree could fund a RCT? *The HRC supports RCTs through various funding mechanisms. Supporting the salary of a doctoral student or early career researcher who is conducting an RCT is one of those means. Funding an RCT does not necessarily mean the HRC has solely funded the entirety of a trial. It may have only part-funded the trial or supported staff associated with the trial.*

8. Page 4 line 26: what do you mean by reported results? Do you mean the results available in the article? Or did you get all the final reports from the HRC? *Good point. The source of findings could be from a published report, the trials register, some other form of dissemination, or the final report to the HRC. We have deleted the word "reported".*

9. On table 1, maybe the authors should add the year of the grant. *To do so would be to add 18 rows to the table and duplicate information in figure 1. Rather than add to Table 1, we have added the exact numbers to Figure 1.*

10. Page 5 line 55; to my understanding the authors did not have a clear, defined list of funded RCT for the first years. The assertion that only 6 grants were awarded in 1999 seems to be misleading. If the authors could not ascertain that they found all funded RCT, they have to modify the sentence to integrate uncertainty. *We have retained the number of trials on page 5 given that was the number found from our searches, but we have added the following limitation addressing the issue of uncertainty around the numbers in the early years: "Secondly, our original request to the HRC did not seek career development awards that may have supported a trial. A small number of such awards were included in the supplied list of studies for 1999-2010, which we supplemented with searching two other datasets from 2006 for such awards. However, we cannnot be certain that all career development awards from 1999-2006 were identified and thus we may have underestimated of the number of trials supported by the HRC."*

11. Page 6 table 2: "protocol published": the figure is rather high: nearly a half were published, since this practice is not well developed, I wonder what the author mean by this. Is it really the publication of the protocol as an article in a journal? *A protocol was considered published if*

the complete protocol was published separately or if the complete protocol was available as a supplement to the main results being published. The numbers reported are correct.

12. Page 6 table 2: I am surprised that there are no multiple supports for publication. How is it possible to have 6 with results posted and only 1 with "posted on trials register"? *Do you mean "multiple reports"? There were multiple reports of dissemination for some trials, but we only reported a single source of dissemination in the order listed in table 2 i.e. if dissemination included journal paper and thesis, then only journal paper was reported for dissemination. We have clarified that by adding we only counted once in the following sentence: Research dissemination could take the form of a journal publication, a publicly available thesis, a letter, a conference abstract or proceedings (but only where the final results were published), a preprint paper on MedRxiv, or the results being posted on a trials register and was only counted once in that hierarchy. With respect to information reported in the register, 89 main publications were reported, in addition to six trials also posting separate reports of results. Thedifference between six trials posting results on the register but only one being included in list of dissemination occurs because that one trial was the only trial that did not have another means of dissemination in the hierarchy. We have added the following sentence to the table legend: "Means of dissemination was only counted once in the order reported in the table."*

13. Page 6 line 9: why is it 95.7% whereas the table mentions 84.8? *The 200 published trials are 95.7% of the disseminated trials. We accept that the change in denominator can cause confusion, so have deleted that text.*

14. P4 line 44: the authors mentioned dissemination metrics without details and then the figures are presented in the results. It would be useful to provide at least a small definition for each indicator (citations: how are they computed? And altmetric score). *We did not compute the citations or altmetric scores, but obtained the citations from Google Scholar and the altmetric scores from the publication page on the journal websites as described on page 4. However, we have added the following clarification to the description on page 4: "The citation counts were obtained for each published trial from Google Scholar and other dissemination metrics (altmetric score and download counts) from each publication's page on journal websites, all on the same date."*

15. Overall, the RCT funded by HRC performed well in terms of registration, publication and publication bias compared to other cohorts. It would be interesting that the authors try to provide an explanation: is one part of the funding conditional to the registration? Close monitoring by the agency? *We cannot account for why the HRC-funded trials have performed well in comparison to other funders. Funding is not conditional on registration and HRC research contracts are only monitored through annual reports. Trial registration is possibly influenced by NZ having a national standard for ethics committees, which stipulated in 2011 that trials must be registered and thus all ethics applications request a trial registration number. However, we cannot account for the publication rates and have added much of the above comment to our discussion.*

16. Typos - Page 8 line 56 teh - the - Page 6 line 4: "in the period to 2009", a word is missing? *The current wording is correct.* Page 4 line 12 seperate – separate. *Thank you. We have corrected these errors.*

Reviewer #2 Dr Patrick Souverein

1. The study is clearly presented and of interest in the light of research integrity and research waste. *Thank you.*

2. Can the authors say something about non-HRC-funded trials? What is the proportion of trials funded by the HRC in that region and what would be the expected if studies were funded differently? *We know that an average 97 trials sought ethical approval between 1999 and 2003 and an average of 124 trials sought ethics approval in New Zealand between 2005 and 2009. We have no information about trials activity other than that. We have revised a limitation in the following way to reflect this information: Fourthly, the HRC funds many different types of research and our focus on trials means our findings should not be considered as representative of all research funded by the HRC the HRC only funds a small proportion of the number of trials conducted in New Zealand each year. Between 1999 and 2003 an average of 97 late phase trials sought ethical approval each year, while that increased to an average of 124 trial each year between 2005 and 2009.[10][26] Thus, our findings should not be considered representative of all trials conducted in New Zealand*.

3. The clinical trial domain is rather broad, with the majority focusing on procedures or drugs. Did the authors stratify by type of intervention and see whether there were any differences. Prior work by Van den Bogert et al on drug trials in The Netherlands found that for instance phase 1 trials, non-registration of trials or single center trials were associated with a higher risk of non-publication. Are the authors able to replicate such findings in there cohort? *We did not investigate any associations between trial characteristics (such as trial phase) and registration or dissemination. It is likely such an investigation would be of limited utility with our dataset given the greater proportion of trials were registered and only a very small number were not registered, meaning investigation of factors influencing registration would have quite low numbers in cells for the unregistered trials.*

Reviewer #3 Dr Rune Jakobsen

1. The manuscript is very well-written. Methods and results are clearly presented and adequately discussed. I find the paper to be a valuable contribution to the literature reassuringly finding most trials in recent years to be both registered and published with no apparent publication bias between trials with positive findings as compared to negative trials. *Thank you*

2. A figure with a flow chart of the identification, inclusion and dissemination could be considered as a quick way for readers to get an overview. *Thank you. We have now included the such a figure (figure 1).*

3. The authors state in the methods that they verified 10% of the identified trials for accuracy, but do not provide any results or comments regarding this in results. *A comment has been added to the results section with these findings.*

4. In the last paragraph on p8 there are a few typos (informatione.g. / teh). *Thank you. We have corrected these errors.*

VERSION 2 – REVIEW

REVIEWER	Souverein, Patrick Utrecht University, Pharmacoepidemiology and Clinical Pharmacology
REVIEW RETURNED	15-Sep-2022

GENERAL COMMENTS	I'm happy with revisions made.