Author's response to reviews

Title: Clinical drug trials in general practice: a ten-year overview of protocols

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Author's response to reviews: see over
Dear Editor,

Thank you for considering the manuscript *Clinical drug trials in general practice: a ten-year overview of protocols* for publication and for allowing a thorough review. We appreciate the comments and helpful suggestions made by the reviewers, and are thankful for the opportunity to revise the paper. A revised manuscript is enclosed highlighting all changes with “track changes”.

In the following we give point-by-point response to the comments and concerns raised by the four reviewers. We hope you find our responses and alterations of the manuscript satisfactory.

Yours sincerely,
Anja Maria Brænd, Kaspar Buus Jensen, Atle Klovning, Jørund Straand
Oslo, 8th of February 2013

**Reviewer’s report 1. Reviewer: Jens Sondergaard**

*This is a relevant and interesting paper. However, the authors should elaborate on the following aspects:*

1. **Why are trials from hospital populations not generalizable to general practice?**
   We see that this statement was standing unfounded in the text and have elaborated further on this in the manuscript including comments on differences in severeness of disease and how selected patients may impair external validity of trials.

2. **What were the criteria for having a drug trial approved by the Norwegian National Medicines Agency?**
   The Norwegian Medicines Agency considers whether the drug trials are planned according to current regulations, which have been revised in the ten-year period we have studied. We have included a sentence in the Methods section to clarify this.

3. **Have the authors investigated whether the results of the trials were published in peer reviewed medical journals?**
   We have not investigated this issue yet, except for the case study. However, we intend to, as this is an interesting and important question. The current study may be considered as a “baseline study” for further research, which will include exploring the studies’ relevance, scientific quality and publication output. This will require a comprehensive new data collection. We have made a statement regarding this in the Discussion section.

4. **This paper could be substantially improved, if the authors more in depth explore the design of the trials? Is that possible from the present data?**
   Please, refer to the comment given above. Our aim here is to establish a descriptive basis for future research, which also will address study design and other methodological issues. Plans for future investigations in this field have been made more explicit in the Discussion section.

5. **The discussion is rather speculative and should to a higher extent be based on published literature on relationships between the pharmaceutical industry and physicians**
We have restructured the discussion to address this comment and added references on the relationship mentioned above.

**Reviewer’s report 2. Reviewer:** Noreen D Mdege

This is a 10 year retrospective study of protocols of general practice (GP) clinical drug trials submitted to the Norwegian national medicine agency. The authors conclude that majority of clinical drug trials in GP settings were industry initiated. The manuscript is generally well written. However it requires major revisions to improve it and get it more focused. Here are my suggestions:

**Background:** Major compulsory revisions

1. After reading the background section I was still not clear what the aim and objectives of this study were; and I was not convinced about the novelty of this study? The authors state that the aim of the study was to gain systematic knowledge regarding clinical drug trials in Norwegian general practice. What does this exactly mean? They also state that they describe all clinical trials planned to be carried out in general practice. Why just describe the trials, and how does this add new knowledge considering they reference 5 references who have already described similar trials before? They say none of these reports highlighted studies in general practice. However it is not enough to do something because it has not been done before because maybe the reason it has not been done is other people tried it and it was not worth doing. Not to say what you did here was not worth doing, but what I am trying to say is you have to build a stronger case of why this was worth doing.

We acknowledge this remark, and we have tried to clarify the aims of the study in the manuscript, also considering related comments made by reviewer 4. We believe it is important to highlight what kind of drug research GPs and their patients are involved in, especially since most drug prescriptions are made in general practice. All other research in Norwegian general practice is conducted by or in collaboration with the academic departments and the college. For drug research, this is the opposite, and concerns have been voiced regarding the extent, appropriateness and relevance of general practice drug trials. There has been a decline in clinical trials in general in Europe, and we wanted to explore if this was the case also for general practice. Many commentary articles have discussed general practice trials, and we believe a data based complete national overview is an important contribution to the literature in this field. We appreciate reviewer 3 commenting that “the research question is relevant”.

2. The second sentence of the first paragraph implies that trials in hospital settings are not always generalisable to general practice. However there is no reason or explanation given as to why this might be so.

Please, refer to the corresponding comment #1 by reviewer 1.

3. The second paragraph of the background section starts by referencing a study that judged GP trials initiated by pharmaceutical companies as having a low scientifically valid and clinically relevant results. This is an interesting point, but unfortunately the issue is not explored further. For example I would have wanted to know in what way? In-fact to me this could have formed the basis of a more interesting paper rather than description of the studies- i.e. exploring if, judging from the study designs proposed in the protocols and the subjects under investigation, the studies would contribute scientifically valid and clinically relevant results. This is also related to the fact that the authors highlight that industry has largely bypassed the voluntary quality and
relevance checks by the subcommittee of the Norwegian College of General Practitioners.

We have tried to elaborate further on this issue in the Background section. The acquired data material does not allow an in-depth discussion of study design except for the case study. Please, also refer to the similar question (#4) raised by reviewer 1.

**Methods**
The methods used for this study are appropriate.

**Major compulsory revisions**
1. The description of the methods could be improved by including details on the following:
   a. How many people were involved in the searching and selection of studies, and extracting data from the studies?
   b. Where there any procedures in place to minimize errors in the searching and selection of studies for inclusion; as well as in data extractions?

We have added a more detailed description of this in the Methods section. The comprehensive hand-search was performed (shelf by shelf) by one author. The last author also contributed in the planning and pilot testing of the search, selection and data extraction together with the person responsible for the archive at NoMA. Supplementary data collection and error checking was performed by another author for a total of 89 studies. No formal inter-rater reliability calculations were performed, but no major errors or discrepancies were disclosed. A random check of non-included studies in the archive did not reveal any additional general practice trials.

2. What was the rationale behind including studies that were a combination of general practice (GP) and specialist care settings? Was there any cut-off point used for inclusion of such trials? For example if only 5% of study participants were to come from general practice and the remaining 95% from specialist care settings, would the study still be eligible? Considering that these studies that were a combination of GP and non-GP settings form the bulk of the studies analysed here- how do the results then truly represent studies conducted in GP settings? Why did the authors not concentrate on the 45 that were solely in the GP setting and do a more details study of these?

The aim of this study was to give a complete picture of all drug trials conducted in general practice. We therefore also included trials with a combination of settings, without cut-off points related to numbers of GP investigators. In planned follow-up research based on this study, it will be prudent to differentiate between studies undertaken in general practice only versus those in mixed settings.

**Results: Minor essential revisions**
1. There are a number of typos and omission of some words in the first paragraph of the results section
   This paragraph has been revised.

2. Table 1- Zeros missing for some of the years under Researcher initiated column.
   This has been corrected.

3. Two table 3s and no table 2?
   This has been corrected.
Discussion and conclusions:
Discussion is well written with some very interesting points raised.

Major compulsory revision
1. I think the conclusions have to follow directly from the aims and objectives, and the results obtained from the study. This is not the case at present. The first sentence reads “it is a challenge for general practice to increase the number of clinical trials in general and non-commercial clinical drug trials in particular.” Although this sentence might be true, it is not rooted in the results of your study, nor is it related to the aims and objectives of this study (you did not set out to find how challenging it was to increase the number of clinical trials in GP settings)- so why is it the opening sentence of the conclusion? For the conclusion it would be better to limit it to your main findings and the policy and practice implications of your results.

We see that the Conclusions paragraph was rather a discussion of the implications of our findings than a concluding statement of the results in this study. We have therefore revised this paragraph and moved some of the contents to the general discussion, and made corresponding changes in the Conclusions paragraph of the Abstract.

Reviewer’s report 3. Reviewer: Louise Berendt
Reviewer’s report:
Summary
The study aims to describe selected characteristics of clinical drug trials in general practice in Norway. Methodologically the study was conducted as a cohort study of clinical drug trial applications submitted to the Norwegian Medicines Agency in the period 1998-2007. Previous studies have reported characteristics of Norwegian clinical drug trials, but not for general practice trials in particular. The major findings were that only a fraction of Norwegian clinical drug trials are conducted in general practice, of which very few are non-commercial trials. In general, the research question is relevant and the manuscript well written.

Major compulsory revisions
1. The time of collecting the data should be stated, including the time of conduct of the literature search related to the ONE trial. It should also be stated whether all of the included applications were approved by the Norwegian Medicines Agency or if any were rejected.

The time of data collection has now been stated in the Methods section. NoMA does not keep a separate register of rejected trials and in general reject very few trials each year (<5, personal communication, NoMA). During the data collection it was not apparent that any of the trials included in the study was rejected, however, we sometimes noted a comprehensive correspondence between the study initiators and NoMA regarding details or refinements to the protocol before final approval. Studies may however have been rejected by the regional ethics committees, which will be taken into account in further research. We have added a statement on this in the Discussion section.

2. A few files may easily be missing from a large archive of historical trials. However, no reasons for exclusion are given in the flow chart when selecting 196 of the 2,054
All trial protocols and applications were stored in the same paper archive at NoMA. From year 2007 on, electronic registration was introduced, but for that year paper files were still stored in the same archive. The total number of 2054 trials was calculated from publications, yearly reports and a personal communication from the Head of preclinical assessment and clinical trials at NoMA. This has been more clearly stated in the Methods section and the figure legend to the flow chart.

3. **Methods for minimising errors during data collection should be described. Is it correct that data collection was conducted by a single assessor?**

Please refer to corresponding comment (Methods comment #1a+b) by reviewer 2.

**Discretionary revisions**

3. **Background, fifth and sixth paragraph:** It is mentioned that previous studies have demonstrated a low output of scientifically valid and clinically relevant results and a low rate of randomised controlled trials in general practice. It would be interesting to know whether this also holds for clinical drug trials in Norwegian general practice. Please, refer to corresponding comment #4 made by reviewer 1. We agree that a further exploration of study design and methodological considerations would cast more light on the implications of these clinical trials, and we intend to explore this in the future. We have made a statement regarding this in the Discussion section.

4. **Methods, sixth paragraph:** Various methods of classifying trials as industry-initiated/industry-funded/commercial and researcher-initiated/non-commercial/academic exist. In this study, the categorisation was based on the source of funding, who wrote the study protocol, and who conducted the study. It is stated that trials funded by a pharmaceutical company was categorised as industry-initiated. Does this categorisation take into account the situation of a clinical trial partially funded by a pharmaceutical company (e.g. by receiving the study drugs free of charge), but otherwise designed and conducted under the responsibility of a GP? Furthermore, it is not clear to me how trials with unclear funding were handled (e.g. an application stating that further external funding will be applied for). This should be specified.

We did not identify any trials where the funding was unclear, but we agree to the suggestion of stating this classification more explicitly, and have made an amendment to the Methods section.

5. **In the time period 1998-2007, the European Clinical Trials Directive 2001/20/EC were enforced. With the directive came a formal definition of investigator-initiated clinical drug trials. In your opinion, would a classification of the trials in your sample according to the definition in the directive lead to different results?**

We believe our classification in practice is according to the description in the European Clinical Trials Directive 2001/20/EC of “non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry”. Since the term “sponsor” was formally defined and in use only during part of the time period from which we have included trials, but not through the whole time period, we have rather given a description of how we classified the trials.
6. Discussion, second paragraph: Three studies assessing the proportion of non-commercial clinical drug trials are cited. Similar results from Danish clinical drug trials is available: Berendt et al, BMJ 2008;336:33-35.
We thank you for making us aware of this interesting Danish study, and we have included this article in our references, as Denmark and Norway are comparable in many ways.

7. The term ‘GP academics’ should be clarified.
The term is now stated in the methods section, hopefully clearer than before.

8. It is unclear to me whether the terms “non-industry”, “non-commercial”, and “researcher-initiated” are used synonymously. Are they all to be thought of as antonyms of “industry-initiated trials” as defined in Methods, paragraph 6? If so, I would recommend the use of these terms to be streamlined as much as possible.
The terms mentioned have been used synonymously as antonyms for “industry-initiated”. We have now chosen a more consistent use of “researcher-initiated”.

Minor issues not for publication
9. Punctuation is missing in Methods, paragraph 8.
This has now been corrected.

0. Two tables are named “Table 3” and there is no “Table 2”.
This has now been corrected.

Reviewer’s report 4. Reviewer: Puvan Tharmanathan
Reviewer’s report:
This article attempts to highlight two important, linked issues to do with the conduct of clinical trials in a primary care setting. It is uses a comprehensive database over a 10-year period to source cases for discussion. However, the text needs to be re-structured slightly, and the importance of this issue outside of Norway made more explicit.

Major Compulsory Revisions
1. The description of the case study (Case: A seeding trial?) should be done in the “Results” section, and then discussed in conjunction with the other findings under “Discussion”. In relation to this, the criteria for “seeding trials” in text box 1 should be mentioned earlier in the text, possibly in the “Background”, and then referenced for discussion points.
The description of the case study has been restructured as suggested, moving facts regarding the trial to the Results section. The introduction to seeding trials in the Background section has been extended slightly with a sentence moved from the Discussion, also mentioning the criteria in Text box 1.

2. The “Methods” section should be more structured, and sub-headings identifying major steps would be useful.
The Methods section has now been restructured, and relevant sub-headings have been included for greater transparency.

3. The “Results” section should also then be structured to reflect the description in the “Methods”, including the use of sub-headings.
The Results section has been structured reflecting the sub-headings in the Methods section.

**Minor Essential Revisions**

1. There should be a statement in the “Background” section making explicit that this issue is of concern outside of Norway.

   We thank you for this suggestion, and a statement regarding the relevance of this study for international readers has been added in the Background section.

2. The last paragraph of the Background section states that the aim was to gain systematic knowledge of Norwegian trials in general practice. It would be useful for the investigators to state/re-state their purpose of gathering this information. Most of the description currently in this last paragraph can be moved to the “Methods” section.

   We acknowledge this remark, and we have tried to clarify the aim of the study, also considering the related comments (Background comment #1) made by reviewer 2.

**Discretionary revisions**

1. The language used in certain sections does not follow convention, and needs revision:
   - Result, Paragraph 1: The word “planned” before “included” is unnecessary
     The sentence has been moved in the restructuring of the whole section, and rephrased.
   - Discussion, Paragraph 2: “Over the last few years, there has been a decline in the number of clinical trials…”
     This has now been rephrased as suggested.
   - Discussion, Paragraph 2: Switch “most selling” with “most profitable” or something similar.
     This has now been corrected as suggested.
   - Discussion, Paragraph 3: Please rephrase “…more than averagely interested in clinical research”.
     This has been rephrased.
   - Discussion, Paragraph 3: Please rephrase “…by professionalising such participation and returning a not insignificant yearly income.”
     This has now been rephrased.
   - Discussion, Paragraph 4: Please correct “…most frequently researched…”
     This has now been corrected.
   - Discussion, Paragraph 4: Please replace “overweight” in “overweight of clinical trials”
     This has now been rephrased.