Author's response to reviews

Title: Sponsor's participation in conduct and reporting of industry trials: a descriptive study

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

We would like to thank the reviewers for their helpful and insightful comments. We have revised the paper in line with the comments and have responded as outlined below.

We thank for the opportunity to revise the paper.

Yours sincerely

Andreas Lundh, Lasse T. Krogsbøll and Peter C. Gøtzsche

Reviewer #1

Q1: Major Compulsory Revisions, Page 6, second paragraph: Why were these 7 trials published in Lancet if Lancet didn’t have the full protocols. My understanding is that Lancet does not publish trials in the absence of having the protocols.

We have described this in the text. Two of the seven protocols were submitted via email outside the editorial system. Unfortunately the editors had deleted the attached protocols in these emails. The other five protocols were not full trial protocols, but three synopses, a copy from www.clinicaltrials.gov and a protocol with amendments. Based on our correspondence with The Lancet editors, at the time we conducted our study there were no minimum requirements for what information a protocol should contain and the submitted protocols were deemed acceptable.

Q2: Page 8, first paragraph: I’m not sure what the authors mean by “disagreements” - who disagreed or where were the disagreements found?

We have added the sentence “information in” to emphasize that the disagreements concerns whether information in protocols differed from information in the published papers. In addition we have now used the word ‘discrepancy’ instead of ‘disagreement’ throughout the paper.

Q3: Page 10, Discussion: If Lancet had the protocols then what are the implications for the editorial process at Lancet that the contents of the publications differed from what was in the protocols?

We have added the sentence:

“Journals should allocate editorial resources to ensure that what appears in publications corresponds to statements written in protocols, which was not always the case in our study.”
Q4: Page 12, last paragraph: Fewer industry sponsored trials being published could have negative financial implications for journals due to lower sales of reprints. The authors should discuss this point.

*We have added the sentence, after advocating independent data analysis like JAMA does:*

> “Such policies might therefore be difficult to implement, as they will likely result in loss of revenue from reprint sales of industry trials [2].”

Q5: Page 13, last paragraph: Not only should journals require these elements but they should be put on a publicly available web site.

*We have added the sentence:*

> “and preferably make such data available at public websites”.

Q6: Minor Essential Revisions Page 6, first paragraph: When the authors say that two protocols were similar to other included trials is one implication that these were instances of duplicate publication?

*Two trials had similar protocols. One protocol described a trial with a 2x2 factorial design that was published as separate papers for each drug. The other protocol described three trials, one published separately and two published in the same paper. We paired each protocol with the first identified paper and excluded the other papers to avoid clustering in our analysis.*

Q7: Page 6, last paragraph: When the authors say “in 35 trials (51%), it was not described how the clinical data were processed” do they mean that the trials didn’t describe who did the processing?

*We have rewritten the results section based on recommendations by peer reviewer 2, and have shortened the paragraph about data processing and clarified it to:*

> “In only two of these trials, it was described how data were processed, i.e. interpreted for categorisation purposes, and in those two trials, all safety data were processed by sponsor staff”.

Q8: Page 7, third paragraph: When the authors say “in 2 (3%) via membership in the Data and Safety Monitoring Board” do they mean that in 2 trials the sponsor had access via the DSMB?

*To clarify the sentence we have changed it to:*

> “in 2 (3%) the sponsor had access via membership of the Data and Safety Monitoring Board”.

Q9: Page 9, second paragraph: What statements are the authors referring to when they say “overriding statements”? 
To clarify matters we have changed the sentence to:

“overriding statements concerning reporting of results or data ownership in the protocol”.

Q10: Page 10, second line: Delete “about” at the start of this line.

Based on recommendations by reviewer 2, we have rewritten the results section and now deleted the sentence.

Tables 1 and 2:
The heading for these tables should say whether the data comes from the protocols or the publications.

We have added the sentence:

“based on information in protocols and publications”.

Reviewer #2

Q1: Is the question posed by the authors new and well defined? The question is not new, but it is interesting that the authors tried to show the participation of industry to important phases of studies elaboration. Unfortunately, they don’t describe the participation of industry in the elaboration of studies’ protocols. Also, the authors insist on the comparison between protocols and published papers. With the exception of the data analysis part, no other comparison is clearly shown.

We thank the reviewer for this point. We had initially extracted information on who wrote the protocol, but had not included it. In the last paragraph about publication of results we have now added the sentence:

“Sixty-eight of the 69 protocols (99%) seemed written by the sponsor, for example by including the company logo, and one protocol contained no information indicating who had written it.”

And also described it in the paragraph about independently conducted trials:

“...the sponsor nevertheless appeared to have written the protocol ...”

and in the discussion:

“or appeared to have written the protocol”

Concerning the discussion of the use of “comparison” we agree with the reviewer’s suggestion, in his question five, on changing the title. We have changed the title of our paper to:

“Sponsor’s participation in conduct and reporting of industry trials: a descriptive study”

and additionally changed it throughout the manuscript.
Q2: Are the methods appropriate? Methodology is simple, acceptable but not new. I don’t understand what the authors mean by “…were not part of the planned trials (e.g. secondary analyses).” (Methods, paragraph 1). They mean duplicated studies or studies that violated their original protocols?

*By secondary analysis we mean for example when the trial data is used as a cohort study to explore predictors and outcome (e.g. heart rate as a predictor for cardiovascular mortality in a trial of an anti-arrhythmic drug). We have added the following sentences to Figure 1.*

“Secondary analysis refers to when the trial data were used in an exploratory fashion. For example the placebo group was analysed as a separate cohort study to investigate heart rate as a predictor for cardiovascular mortality in a trial of an anti-arrhythmic drug.”

Q3: Data control and deposition. Data are presented in a descriptive way and comparisons are not clearly shown. The result section should be extensively revised, if the authors want to emphasize on comparisons. Otherwise, the words comparison, compared etc, should be replaced by the words describe, descriptive etc. Moreover, the result section, which I really found difficult to follow, describes in exhaustive details the two tables provided by the authors plus additional data. Focusing on the most important points of the tables will help the reader better understand the manuscript.

*We thank the reviewer for this point and have rewritten and shortened the results section, emphasising relevant data from tables. In addition, we have added a Table 3 to better describe our data for the ‘independently’ conducted trials.*

Q4: Are the discussion and conclusions well balanced and adequately supported by the data? The discussion is better written than the result section, in my opinion. Nevertheless, the authors didn’t avoid to arrive to hypotheses that may reflect their opinion, but are not justified by the results: (Result section, paragraph 6, “…This continuous access to accumulating data could potentially have led to premature stopping of the trial.”) and (Discussion section, paragraph 2, “…We find it likely that tasks not described were handled by the sponsor because the protocols were written by the sponsor. It was therefore implicit that what had been left out would be managed by the sponsor. The role of the sponsor may therefore be even more extensive than our results indicate.”). The above phrases should be rephrased, so that they better correspond to the results or even omitted.

*Concerning the sentence “This continuous access to accumulating data could potentially have led to premature stopping of the trial”, we originally included it in order to explain that ‘access to accumulating data’ together with ‘statements concerning sponsor’s right to stop the trial prematurely’ may risk trials being stopped prematurely. We agree that it might be viewed as an opinion and have removed it from the results section.*

*Concerning the sentence “We find it likely that tasks not described were handled by the sponsor because the protocols were written by the sponsor. It was therefore implicit that what had been left out would be managed by the sponsor. The role of the sponsor may therefore be even more extensive than our results indicate”, we have rephrased it to:*
“We find it likely that tasks not described were handled by the sponsor because the protocols in all except one case, were most likely written by the sponsor. The role of the sponsor may therefore be even more extensive than our results indicate.”

In general we believe that our discussion and conclusion are justified by our results and we believe that we as authors are entitled to discuss and theorize about our data. One of us (Peter C. Gøtzsche) has worked intensively with trial protocols, both as a researcher and as a former employee of a drug company and is very familiar with what it means when companies include and omit information.

Q5: Do the title and abstract convey what has been found? I propose the title “‘Sponsor’s participation on conduct and reporting of industry trials: a descriptive study” that is closer to the message given to the reader by the result section. In general, the abstract convey the authors’ ideas, but the result section of the abstract should be better written. I couldn’t correspond the numbers of the following phrases from the result section of the abstract to the results reported on the tables or the manuscript: “One trial had independent data analysis and two reporting of results.”, and “In another 10 trials it was not possible to tell who analyzed the data based on the published paper alone.”

We agree with the reviewer’s suggestion for change of title, see response to his question one.

Concerning the sentence “One trial had independent data analysis and two reporting of results” we thank the reviewer for spotting the error. The numbers should be reversed in line with data in the paper, so:

“Two trials had independent data analysis and one reporting of results”.

We have deleted the sentence “in another 10 trials it was not possible to tell who analysed the data based on the published paper alone”. While the information is correct the focus on what appear in publications alone is confusing as the other sentences focus on information in both protocols and papers.

Q6: General comments The authors’ main objective, that was to show that the sponsors’ ownership of studies’ data leads to manipulated studies, can only be hypothesized and is not explicitly shown. Another disadvantage, also mentioned by the authors, is the fact that the trials were retrieved only by Lancet and the study focused only on industry sponsored trials. The paper could be considerably improved if the authors included clinical trials from other peer reviewed journals and non industry sponsored trials.

We agree with the reviewer that our study would be better if we had had access to protocols of trials in other journals. Unfortunately, The Lancet is the only one of the BIG 5 journals requiring submission of protocols as a prerequisite for publishing the trial. As pointed out by reviewer 1:

“While the findings from the authors are limited to what happens at Lancet, if there are problems at a high-impact journal then in all likelihood the problems are even more severe
at other journals without the resources and prestige of Lancet. Therefore, despite the authors noting that their results are not necessarily generalizable I view the results of this present study as very important.”

We have added the following sentence to the discussion:

“However, The Lancet’s access to protocols and editorial resources might indicate that the sponsor’s role is greater in trials published in other journals.”

In addition, trials published in The Lancet have major clinical impact and are important for medical decision-making. Lastly if we want to investigate the sponsors’ influence on conduct and reporting of trials we do not believe that including non-industry sponsored trials would add much information.

Q7: A reference list with the analysed studies is missing and should be added.

Based on the description of data from individual trials in the paper, particularly the independent trials, it is possible to identify individual trials if the references are listed. Due to the promised anonymity to authors and our agreement with The Lancet we are not at liberty to share this information.