Author's response to reviews

Title: Comparison of Serious Adverse Events Posted at ClinicalTrials.gov and Published in Corresponding Journal Articles

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Author's response to reviews: see over
Paris, June 16 2015

Dear Dr D’Souza,

Please find enclosed the revised version of the manuscript entitled “Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles” by Eve Tang, Philippe Ravaud, Carolina Riveros, Elodie Perrodeau and Agnes Dechartres, that we wish to submit for publication consideration in *BMC Medicine*.

We thank you for your interest in our manuscript and we thank the reviewers for their helpful comments. We answered all comments point by point at the end of this letter and we modified the manuscript accordingly. We hope that the manuscript is now more suitable for publication.

This manuscript has not been submitted and is not under consideration for publication elsewhere. All named authors have read the manuscript and agreed to its submission. I certify that potential conflicts about this manuscript do not exist. I certify that I have no relevant financial interests in this manuscript. I had full access to all the data in the study, and I take responsibility for the integrity of the data and the accuracy of the data analysis. I had final responsibility for the decision to submit for publication.

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With best wishes,

Dr Agnes Dechartres
Editorial requests

1. Provide email addresses for all authors.
Response: as recommended, we provided email addresses for all authors in the Title page.

2. Include an abbreviation section based on the following instructions:
Response: As recommended, we included an abbreviation section based on the instructions at the end of the manuscript.

3. For author contribution please indicate a statement that all authors read and approved final manuscript.
Response: As recommended, we indicated a statement that all authors read and approved the final manuscript at the end of the section “authors’ contribution”.

Response to reviewers

Reviewer 1

Major compulsory revision

1. The purpose of the paper is unclear, which is related to objectives not being clearly identified in the abstract. Is the purpose to examine the effect of the legal requirements in 2009, or is it to examine compliance with those legal requirements to publish SAEs on ClinicalTrials.gov since 2009? Or perhaps some other purpose is intended? It is difficult to judge the paper without understanding what was the intended purpose.

Response: We apologize that the purpose of this study is insufficiently clear. Our purpose was not to assess the effect of the legal requirements or to examine compliance with those legal requirements, which was assessed in previous methodological studies[1-5]. In this study, our objective was to assess the consistency between SAEs posted at ClinicalTrials.gov and published in journals. To do so, we identified studies with SAEs posted at ClinicalTrials.gov and we searched for corresponding publications reporting SAEs. For trials with both results posted and published, we compared SAEs posted at ClinicalTrials.gov and published in corresponding journal articles. As recommended, we clarified the objectives both in the abstract and at the end of the introduction.

Modification in the manuscript, abstract section, page 2:
“Objective: For trials with serious adverse events (SAEs) posted at ClinicalTrials.gov, we assessed the consistency between SAEs posted at ClinicalTrials.gov and published in corresponding journal articles.”

2. The conclusion at the end of the paper differs somewhat from that in the abstract and suggests that part of the solution to under-reporting is to advocate for mandatory
posting of results to all countries. However, that does not seem to have worked in the US and thus why should it have an effect elsewhere?

Response: Although compliance with the legal requirement is low [1-5], it has an important impact, with more information available concerning trial results. In a previous article, we showed that half of trials with results posted at ClinicalTrials.gov were not yet published at the time we performed the search and for trials with both results posted and published, results were more completely reported at ClinicalTrials.gov than in corresponding published articles[6]. ClinicalTrials.gov provides information that is not easily available elsewhere for many trials. This information can help patients and their physicians make well-informed decisions and systematic reviewers have a more comprehensible evaluation of available evidence.

Nevertheless, we acknowledge that our conclusion regarding the extension of mandatory posting of trial results in other countries may be too strong and we removed it. We also further discussed that the compliance to the legal requirement was low.

Modification in the manuscript, Abstract section, page 2:

“Conclusions: Many trials with SAEs posted at ClinicalTrials.gov are not yet published, omit the reporting of these SAEs in corresponding publications or report a discrepant number of SAEs as compared with ClinicalTrials.gov. These results underline the need to consult ClinicalTrials.gov for more information on serious harms.”

Modification in the manuscript, Discussion section, page 13:

“Nevertheless, compliance with the legal requirement in the United States is low[16,29-33] despite civil monetary penalties (up to $10 000 a day) and, for federally funded studies, the withholding of grant funds in cases of non-compliance[14]. So compliance must be improved. A recent article showed that sending emails to responsible parties of completed trials that do not comply with the FDAAA legal requirement to post results significantly improved the posting rate at 6 months[34].”

Modification in the manuscript, Conclusion section, page 13:

“Our results reveal that many trials with SAEs posted at ClinicalTrials.gov are not yet published, omit the reporting of these SAEs in corresponding publications or report a discrepant number of SAEs as compared with ClinicalTrials.gov. Consulting safety results posted at ClinicalTrials.gov, when available, is crucial for more information on serious harms.”

Minor essential revisions

1. In figure 1, it would make more sense to report the number not phase 3/4 trials before those with no serious adverse events reported. That way the reader could understand the number of phase 3/4 trials that did not post SAE data.

Response: As recommended, we now report the number of non-phase 3/4 trials before those with no serious adverse events reported.

Modification in the manuscript, Figure 1:

“2. In the random sample there were still 30 out of 202 trials (figure 3) that did not post SAEs, despite these supposedly being screened out in earlier screening processes - how did that occur?”
Response: In fact, all 202 trials had SAEs posted at ClinicalTrials.gov, but 30 of these 202 trials with at least one SAE posted at ClinicalTrials.gov did not mention or reported 0 serious adverse event in the corresponding published article. We clarified that point in Figure 3. We believe that this is an important result highlighting the poor quality of reporting serious harms in published articles.

Modification in the manuscript, Figure 3:

“3. It is not clear why 300 was the selected sample size for the random sample”
Response: Because we could not search for corresponding publications and extract data from them for the identified 1580 trials, we selected a random convenience sample of 300 trials. This number corresponds to about 20% of the identified trials.

Modification in the manuscript, methods section, page 5:
“Of all eligible trials (N=1580), we selected a random convenience sample of 300 trials to search for corresponding publications in journals.”

“4. It would be useful to indicate why trials comparing a drug to a device were excluded and to report that exclusion in figure 1.”
Response: This was a mistake in the manuscript text and we apologize for it. We did not exclude these trials. We removed this part of the sentence.
Modification in the manuscript, Methods section, page 5:
“We excluded trials with only one group, trials with ≥ 4 groups, and phase I, I/II, II, II/III trials.”

5. Might it be useful to describe the 33 trials that had posted the same number of SAEs on ClinicalTrials.gov and their papers on selected characteristics? Ie phase, funding source, discipline.
Response: As suggested, we now provide a description of the 33 trials adequately reporting SAEs in published articles. As shown below, the characteristics of the 33 trials did not differ greatly from that of the 202 trials with results both posted and published.

Modification in the manuscript, Results section, page 10-11:
“The characteristics of these 33 trials are presented in Table 3. In brief, 88% of these trials were phase III trials, 82% had a private funding source, 73% had at least one site in the United States and 73% were published in a specialty journal.”

Modification in the manuscript, Table 2 page 22:
Table 2: Characteristics of the 33 trials with adequate reporting of serious adverse events.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=33</td>
</tr>
<tr>
<td>Study phase</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>29 (88)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
</tr>
<tr>
<td>Parallel groups</td>
<td>31 (94)</td>
</tr>
<tr>
<td>Cross-over</td>
<td>2 (6)</td>
</tr>
<tr>
<td>No. of intervention groups</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30 (91)</td>
</tr>
<tr>
<td>3</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>
Primary funding source

<table>
<thead>
<tr>
<th>Source</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>27 (82)</td>
</tr>
<tr>
<td>US National Institutes of Health</td>
<td>2 (6)</td>
</tr>
<tr>
<td>US federal funding</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Medical condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinology</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Gynecology</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Neurology</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (24)</td>
</tr>
</tbody>
</table>

Study location

<table>
<thead>
<tr>
<th>Location</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one site in the United States</td>
<td>24 (73)</td>
</tr>
<tr>
<td>No site in the United States</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>

Type of journal

<table>
<thead>
<tr>
<th>Type</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialty</td>
<td>27 (73)</td>
</tr>
<tr>
<td>General</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov NCT reported in article

<table>
<thead>
<tr>
<th>Reported</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>27 (82)</td>
</tr>
<tr>
<td>No</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

Data are no. (%).

6. A key finding surely from figure 2 is that fewer than 10% of trials published their results on ClinicalTrials.gov within the required 12 month timeframe (although that may be influenced by when the trial was conducted ie pre-2007)

Response: Yes, the median time for having SAEs posted at ClinicalTrials.gov was 22 months in our sample and fewer than 10% of trials with SAEs posted have their SAEs posted within a year. However, the investigators could have submitted their results earlier to ClinicalTrials.gov because we assessed the date when SAEs were first publicly available at ClinicalTrials.gov and not the date when results were submitted by investigators. The difference between these 2 dates is related to production by ClinicalTrials.gov and vetting of the results by the US National Institutes of Health, which can take up to several months. Also, as noted by the second reviewer, the efficacy results may have been posted first and SAEs later, and in this study, we focused on the date when SAEs were posted and not results for the primary outcomes.

Reviewer 2
Thank you for giving me the opportunity to review this interesting work. I have a number of comments.

Response: We thank the reviewer for the positive comment.

Major Compulsory Revisions

1) The documents on clinical trials.gov sometimes undergo repeated updates or additions of data. How then would you be able to judge when the SAE data were posted? It may be that the efficacy data were put up first soon after trial completion, and the
SAE data may only have been put up later. Hence the analysis on time to availability of SAE may be unreliable.

Response: We were able to judge when the SAEs data were posted at ClinicalTrials.gov because of the archival storage of all modifications made at ClinicalTrials.gov with the details of the modifications made and the date when these modifications were made. This information is available in the field “ClinicalTrials.gov archive site” in the history of changes. So, in this study, for each trial, we systematically looked at the archive record to determine when SAE were posted. We clarified that point in the Methods section of the manuscript.

Modification in the manuscript, Methods section, page 6:
“SAEs: total number of SAEs, number of SAEs per group, types of SAEs, number of SAEs per type per group, and number of participants at risk per group. We recorded the date when SAEs were first posted from the archive record.”

Modification in the manuscript, Methods section, page 7:
“Descriptive data are reported with numbers (percentages) and median (quartile 1–3 [Q1–3]). We compared time between primary completion date as reported at ClinicalTrials.gov and date of the SAEs first publicly posted at ClinicalTrials.gov or the date of the first online publication in journals reporting the number of SAEs per group by the Kaplan and Meier method.”

2) It wasn’t clear to me if the Groups of SAEs on clinicaltrials.gov actually matched those for the published articles. Sometime, the groups are constructed by organ system, or by threshold (e.g., >1%), or by causality (judged related). It is only possible to compare the matching numbers only if similar Groups are reported.

Response: All serious adverse events should be reported whatever the type, threshold and causality. At ClinicalTrials.gov, the total number of patients with serious adverse events per arm was reported for all trials as well as the number of patients with each type of serious adverse event. In the Results and in Figure 3, we described all potential reasons for incomplete reporting of SAEs in publications. In our sample, we found 10 trials reporting only the number of drug-related SAEs or specific SAEs of interest in the journal articles.

3) Similarly, what were the denominators used? It could be that the two datasets analysed SAE at different cut-off points e.g., at end of randomized treatment period, or within 30 days after end of trial. Again, this could have led to discrepancies in numbers of SAEs.

Response: As indicated in the methods section, if several publications were identified for the same trial, we extracted safety results from all corresponding publications having the same time-frame as reported at ClinicalTrials.gov. For trials with multiple phases (e.g., lead-in or induction, double-blind randomized treatment, and follow-up or extension) reported at both ClinicalTrials.gov and in published articles, we extracted SAE data only for the double-blind randomized treatment period.

Minor essential revisions
1) I think this sentence may be an exaggeration "Our results highlight that ClinicalTrials.gov provides complete and clear information on serious harms,...". Actually, we do not know that it does; the only way to find out is to compare against the original company study report to see if the clinical trials.gov version is clear or complete (or neither).
Response: We acknowledge that this sentence overstates our findings and that we have no gold standard. Our results concerning discrepancies highlight problems but do not allow for concluding that information is more accurate at ClinicalTrials.gov than in the published articles. We modified our sentence and checked the manuscript to avoid over-interpretation of findings.

Modification in the manuscript, Abstract section, page 2:
“Conclusions: Many trials with SAEs posted at ClinicalTrials.gov are not yet published, omit the reporting of these SAEs in corresponding publications or report a discrepant number of SAEs as compared with ClinicalTrials.gov. These results underline the need to consult ClinicalTrials.gov for more information on serious harms.”

2) The other big problem is that we do not know which dataset is 'true', particularly when we are trying to resolve discrepant findings between the two.
Response: We agree and further discuss this point in the discussion section of the manuscript.

Modification in the manuscript, Discussion section, page 12:
“Our results identified some trials not mentioning SAEs or reporting no SAEs in the published article, but SAEs were reported at ClinicalTrials.gov. Furthermore, when SAEs were reported in published articles, discrepancies with the number posted at ClinicalTrials.gov were common, with frequently more SAEs reported at ClinicalTrials.gov than in the published article. Although we do not know which are the “true” results, we believe that these discrepancies clearly outline problems in the reporting of SAEs.”

3) There needs to be some discussion on the implications for systematic reviewers and meta-analysts who are confronted by discrepant data – what should they include in their meta-analysis? I think the extent of publication bias here is really important.
Response: As suggested, we discussed implications for systematic reviewers and meta-analysts who are confronted with discrepant data. In case of discrepancies, we recommend systematically contacting authors for clarification and performing sensitivity analyses in case of non-response to assess to what extent these discrepancies may affect the meta-analysis result.

Modification in the manuscript, Discussion section, page 12:
“For systematic reviewers, they outline the interest of using ClinicalTrials.gov to find safety results not yet published in journals and for trials with both SAEs posted and published, to compare the rate of SAEs. In case of discrepancies, we recommend systematically contacting authors for clarification and performing sensitivity analyses in case of non-response to assess to what extent these discrepancies may affect the meta-analysis result.”

4) There needs to be more discussion on concrete proposals to solve this problem. Do you think that efforts towards mandatory posting of trial summaries is sufficient? After all, this will not solve the problem of discrepant numbers of SAEs between sources (ie. full reporting of wrong numbers in two or more datasets). Moreover, unless full and transparent format is agreed, the Summary of Results may only consiste of a few SAEs.
Response: As suggested, we expanded the discussion on that point. Several methodological studies showed that the compliance with the legal requirement is low. Therefore, compliance should be improved. As noted by the reviewer, extending mandatory posting of results and improving compliance will not solve the problems of discrepant numbers but can help in identifying problematic situations. Checking information including results, if available, at
ClinicalTrials.gov should be part of the peer-review process. In case of discrepancies, the reviewers and editors should ask investigators to clarify the discrepancies.

Modification in the manuscript, Discussion section, page 12:
“For journals, they question the peer-review process, in that the assessment of data recorded in registries including results and harms when available should be part of the process to assess if there are any discrepancies that could bias the results. In case of discrepancies, investigators should be contacted for clarification.”

Modification in the manuscript, Discussion section, page 13:
“Nevertheless, compliance with the legal requirement in the United States is low[16,29-33] despite civil monetary penalties (up to $10 000 a day), and, for federally funded studies, the withholding of grant funds in cases of non-compliance[14]. So compliance must be improved. A recent article showed that sending emails to responsible parties of completed trials that do not comply with the FDAAA legal requirement to post results significantly improved the posting rate at 6 months[34].”

References