Author's response to reviews

Title: Why we need easy access to all data from all clinical trials and how to accomplish it

Authors:

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Version: 2 Date: 11 July 2011

Author's response to reviews: see over
Author's comments in italics

Reviewer's report

Title: Data sharing in clinical research is a moral imperative

Version: 1 Date: 25 June 2011

Reviewer: Elina Hemminki

Reviewer's report:

Referee comments on the paper "Data sharing in clinical research is a moral imperative"

This is a polemic and stand taking selective review of debate over openness of drug trials data. I found the paper interesting to read: it had collected into one paper discussion and cases which otherwise one has to make a special effort to find. However, even though I enjoyed reading it, for a journal article it could be made more attractive, by changing it, e.g. according to the following guidelines:

1 The nature of the paper: it is not a usual results paper, protocol, review or editorial. It could be a debate paper, but it is too long and contains too much data for such. This is something the editors should look at.

No comment needed.

2 The title refers to “clinical research”. However, the paper is almost totally on drug trials and drug research; I recommend narrowing the title.

Title changed into: “Why we need easy access to all data from all clinical trials and how to accomplish it.” This is what my paper is about; the reason the main focus is on drug trials is that this is where few people have argued for universal access to data. I have made this more clear now.

3 The paper is very long and contains many different issues. It could be made into two papers, or alternatively concentrating on the main issues. Currently the paper deals with the following issues, among others: publishing results, publishing protocols, publishing raw data.

Publishing results, publishing protocols, and publishing raw data are not separate issues; indeed, they belong together, which I also explain.

4 The text contains repetition, particularly in regard to recommendations and their argumentation. All that could be collected to the end.
I have removed repetitions and moved bits around as suggested.

5 The style is emotional and moralistic. I would abolish emotional expressions. The data are convincing enough without additional adjectives and sentences.

I agree it was a bit much and have made changes as suggested.

6 Likewise, I would separate the “should” sections (recommendations, condemnations) from the rest of the text. Following the traditional sections in a scientific paper (even though not with those subtitles) might help. A possibility is to structure the paper: 1. Introduction (the purpose of this paper and the issues to be covered), 2. Cases, 3. What are the problems and what has been made this far, 4. Future and recommendations.

Very good suggestion; I have now provided an Introduction outlining what the paper is about and what it isn’t about.

7 The data on withdrawals because of adverse effects by the decision time and speed, is interesting. However, the text on dead-lines is formulated in a difficult way; please, clarify.

Explained more clearly now what the shorter deadlines for FDA means for subsequent withdrawals of drugs from the market.

8 The problems of current secrecy and ownership rules are well presented. However, I would like to see thinking what are the unintended possible (negative) consequences if total openness to data will become mandatory, and what measures might be needed to correct such effects.

A discussion of this has been added, which means there are now two subheadings instead of one: Benefits of data sharing, and Harms of data sharing.

9 The chapters on “Necessary legislation” and “punitive measures” are weak. There are many different issues, and all suggestions are not well thought of. I would either leave these out (and say something general about that these measures are needed to amend the current situation) or make the chapters more well-thought.

I have changed this section considerably, shortened my proposals, made them more general, and avoided the term “punitive measures.”

10 References are many (needed); I did not check them but trusted they are OK.

No comment needed.
Details

1. Both trade-names and generic names are used; trade-names are not identified with R.

*Instructions to authors do not say that trade names should be followed by an R, and it is not customary in journal articles, in fact I have seen this for many years although I read a lot. The custom is to write generic names in small letters and the trade name with a capital letter, which is what I have done.*

2. Some of the sentences are long and complicated, e.g. p.6, 6th para, 1st sentence, p.7, 5th para both sentences (these are just examples, there are many more).

*Paragraphs made shorter.*

3. Citations on EU regulation is not needed (reference + summary), p 7.

*I agree and have instead described what this means, which is also shorter (the text is reprinted verbatim in my BMJ paper about access at the EMA, to which I refer).*

4. The statements in italics on p.8-13; I would delete them. Not clear why they are given as separate text.

*I have made changes to the statements and made them part of the main text, no longer in italics.*

5. On p.12 last para before “Academic interests” the author recommend excluding from meta-analyses such trials in which authors are not willing to share their data. I wonder how many trials would be left. I wonder would happen to claim to include all trials and to the interest of doing meta-analyses if such clarification is needed. In long term it may be realistic.

*I agree it is a long term goal and have modified the text accordingly.*

Comment 5, some concrete sentences which particularly bothered me:

- p. 3, 2nd para, 2nd sentence.

*I cannot know why the reviewer was bothered. I wrote: “The published analyses were mainly “per protocol analyses,” where patients who drop out of the trials, e.g. because of lack of effect or adverse effects, are not accounted for, whereas those required by law are “intention to treat analyses,” which are far more reliable, as they include these patients.” I believe what I wrote is correct.*

- p. 6, 4th para
Again, I cannot know why the reviewer was bothered. I wrote: “There are plenty of such examples, and they tell us how important it is for public health that independent researchers can get access to the full clinical trial data set at drug agencies and drug companies.” I had just explained, with examples, that published trial reports can be intensely misleading and that data available at drug agencies or companies can be very helpful for revealing the misconduct and helping us getting closer to the truth. I have a huge collection of additional examples, which is why I write as I do.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests
Reviewer's report

**Title:** Data sharing in clinical research is a moral imperative

**Version:** 1  **Date:** 5 July 2011

**Reviewer:** David Ransohoff

**Reviewer's report:**

OVERALL

While there are good ideas in this paper, it also risks being diffuse, including substantial problems in important definitions (what exactly is data sharing, for example) and implications. It might be more useful to focus on one or two specific problems and next-step reachable solutions.

*That would be a completely different kind of article, but I see the point and have changed the structure and also provided an Introduction outlining what the paper is about and what it isn’t about, and what I mean by data sharing.*

As currently written, it sounds like it is calling for everything to be publicly available, including all protocols and raw data of every study. If that's the case, the argument is not well-made. If that's not the case, then details need to be specified.

*I do not agree. As explained above, results, protocols, and raw data are not separate issues; they belong together, and recent empirical studies have clearly shown that we need access to it all, if we are to grapple effectively with selective reporting.*

As an example of lack of focus, some "calls for data sharing" on page 17ff are not about sharing raw data but are about establishing clinical trials registries. The author's own interpretation of "calls for data sharing" risks looking skewed to bolster the author's argument which appears to be "always release everything."

*Again, these are nuances of the same main issue, but as I have followed the reviewer’s advice (see just above), it is no longer a problem. Further, clinical trials registries should also contain results and there are ongoing discussions about which results, in what amount of detail, how and when. This, however, is not the focus of my paper.*

MAJOR SPECIFIC POINTS

1. Definition of "data sharing"

The definition of "data sharing" is, perhaps surprisingly, not really clear. The problems identified in the first part of the manuscript are of several different sorts, including (this list is in no particular order and is not comprehensive; it is meant to
illustrate that "data sharing" includes quite different things):

a. trial registries (to reduce problems of selective reporting) [This is the subject of many of the problems listed, and is the main topic in the next to last paragraph of the Abstract.]
   b. academic authors should have access to all data/results (to avoid hiding of problems)
   c. anyone should have access to all data/results

It would seem to me that serious efforts at 1 and 2 would be hard enough, for logistic and political reasons, but may be worthwhile enough to seriously entertain as "next steps."

Again, these are nuances of the same main issue, see above. I have now changed the structure of the paper and also provided an Introduction outlining what the paper is about and what it isn’t about. It is not so much about practical or political difficulties, but about what needs to be done from a moral perspective.

As it stands, it sounds like you are recommending "release all data for every study." Couldn't that situation be chaotic, in that anyone with an agenda could selectively utilize or interpret complicated data in a way that advances a cause (e.g. as done by plaintiffs' lawyers, say, for silicone breast implants)? Currently we have institutions (academic authors, regulatory agencies like FDA, NICE, etc) with responsibility for interpreting complexity and preventing distortion. They may not be doing their jobs in the best way all the time, but would total transparency all the time (Is that what you are proposing?) really improve the situation? In contrast are there incremental ways -yet substantive -to make institutions do a better job so that we can trust them?

Very good point. A discussion of harms has been added, which means there are now two subheadings instead of one: Benefits of data sharing, and Harms of data sharing.

2. Tone

The tone of the piece ("moral imperative" and "appropriate punitive measures" in Abstract) risks being self-righteous and not the right metaphor. If you are going to treat something as a crime (punitive measures), you need to be very specific about what the crime is. In the body of the piece you list very different problems or "crimes," so it is not exactly clear what you are calling for. Your argument about "moral imperative" is undermined when, in the "call for data sharing" you list so many different kinds of things without a realistic or clear enough argument (including about others' support) for each.

I have changed this as suggested. The term “punitive measures” doesn’t appear any longer, and I have clarified what I mean. See also my reply to Hemminki. I believe that people with a background in ethics (which I have) would agree with me that
sharing our data is a moral imperative; it is something that we simply have to do, and I have explained why, also with reference to the Helsinki Declaration. And yes, I happen to believe it is a crime to let many patients die because of dishonest and selective reporting.

2 Title

"Data sharing" should be used cautiously in a title if it's not really clear what data sharing means.

Similarly, "moral imperative" should be used cautiously if it applies to multiple things.

The title is engaging, but it risks not being a fair description of the content.

*Title changed, see above.*

4. Focus

There are a number of problems reflecting lack of focus:

a) On page 3, in the top section, you discuss how the drug industry can compare new drugs with placebo rather than best-existing drugs or instead of head-to-head comparison. This may be true, but is this problem solved by "data sharing"? Much of the last 2 paragraphs of the 4-paragraph section titled "The problem" seem to be about topics note related to data-sharing.

*Good point, I have changed the text accordingly and have moved some bits to other places in the paper.*

b) On page 3, "selective reporting", first paragraph, is clearly important. Isn't this addressed by trial registries? Is the "per protocol" problem solved by "data sharing"?

*I have now explained more about these issues. Trials registries cannot solve the problem unless they end up containing all data I call for in this paper, which I think they should. Access to raw data allows intention to treat analyses.*

c) On page 6, you describe how papers are written not by academic authors but by companies. This may be a serious problem when it occurs, but is the only solution of the best solution "data sharing?"

*The best solution is access to all data, which, as noted above, will allow independent investigators to do their own analyses.*

5. Solutions

On page 12 you describe legislation, but it is not clear exactly what is being called for: -What is "protocol-related information"? What is the initial
experience with this legislation?

Clarified, apart from "protocol-related information" because this is not explained in the source I quote. My paper is not much about practical or legal difficulties, which can always be resolved if there is a willingness to resolve them. People often tell me: We cannot do this and that because the law says… and my reply is: Then change the law, please. Politicians always understand that they can change the law but people working in institutions, e.g. in drug agencies, are surprisingly rigid and cannot – or will not - see beyond what is current legal practice, or even just accept that most laws are open to interpretation, which means that their interpretation is not necessarily the correct one. Our experience with the EMA illustrates exactly this point.

-Registration of clinical trials: This seems sensible; why hasn't this been adopted in more countries?

I just don't know. Why are humans so resistant to change? It probably carries an evolutionary advantage to stick to what you once learned.

**Level of interest:** An article of importance in its field **Quality of written English:** Acceptable **Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests' below.