Author's response to reviews

Title: Legislation for trial registration and data transparency

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Version: 3 Date: 15 April 2010

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

Thanks for your comments and your suggestion about our manuscript titled with “Legislation for trial registration and data transparency” (Reference number: MS: 1489602353327790). We have revised the manuscript according the reviewers’ comments. Now we submit it to the journal for further consideration.

Best wishes

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Reviewer1

1. The topic of clinical trial registration and data transparency is important to every scientific clinical researcher. The rationale is sound, but with a better structured paper this key message could get more attention. Some arguments are repeated and therefore the key message was sometimes difficult to follow. In the current manuscript two following paragraphs are “Why can previous efforts not ensure data transparency” and “Trial registration cannot automatically result in data transparency”, while trial registration is one of the earlier mentions efforts. My suggestion would be to clearly divide the two initiatives: trial registration and data transparency. Also a more structured content, for example with the following items; the (historical) description, current state/‘players in the field’ and recommendation and implications for the future could be helpful and might improve the readability.

Reply: Thanks for this suggestion. We have revised the manuscript and separated the content as i) Introduction; ii) Registration; iii) data transparency; iv) Legislation; and v) Global network.

It is clear that trial registration alone does not automatically lead to data transparency. For me it would be interesting to include more discussion on ‘side effects’ of legislation of trial registration and data transparency (For example: What will be the effect on local research if country A has legislation on data transparency, but country B still has not. All research shift to B?). What is the opinion on this topic of other important stakeholders? Why is legislation the best option to provide data transparency? With the current version of the manuscript it is still difficult how we are we going to persuade our politicians to do this together. However, this article is definitely of importance in its field to raise awareness and provoke discussion.

Reply: Thanks for your meaningful suggestion. We have added the following points directly related with your comments in the manuscript, involving:

1) Why legislation is the best option to provide data transparency?
2) Why global efforts are needed for data transparency?

Quality of written English: Needs some language corrections before being Published.

Reply: Thanks. The language corrections have been conducted.
Reviewer 2:
Major Compulsory Revisions
1. The abstract should be re-written to remove repetition and clarify the message.
   Reply: Thanks. We have rewritten the abstract, and clarify the message.

2. The language is also repetitive in the conclusion.
   Reply: Thanks. We have revised it accordingly.

3. English grammar and text flow can be improved to better convey the authors' messages.
   Reply: Thanks. We have restructured the text, thus to hope to better convey our messages.

4. The language style carries, perhaps unintentionally, a negative tone. Researchers are making progress in work that the paper suggests is important, but not enough of this paper highlights these efforts towards harmonisation of processes. Some acknowledgement of these works in progress would be useful.
   Reply: Totally agree. We have changed it to a positive tone now.

5. The paper calls for a “global system” and then routinely refers to nations creating legislation. With individual nations creating legislation, the harmonisation of a global system will not just automatically occur. The writers should consider how this global system would be created, giving more attention to the link between national programs and a global system. There are good recommendations made for individual nations to create legislation (as is already occurring), but these efforts should not be confused with global harmonization and collaboration, although it can be acknowledged as a first step towards it in situations where no local legislation occurs.
   Reply: Agree with this strong point. Global efforts should be based on the efforts from individual country; and also even each country does a good effort, it does not mean the certainly global success. Thus we added the points to clarify why and how the global system be established.

6. Throughout the piece the authors make broad sweeping statements that generalize clinical trial practices – these absolutes are not always correct and examples that stray from their sweeping generalizations are easily found.
7. Publication bias, in general, should be discussed within the section of the piece using sensationalized examples to show why data transparency is so important. The concept of publication bias and the realization of its existence became the motivating imperative behind the 2004 call for a central registry.
Reply: Thanks for your suggestion. With the limitation of words, we briefly introduced this concern in the revised manuscript accordingly, but have not using a sensational example.

8. This paper correctly calls for a global commitment to clinical trial registration legislation, but is written with a strong US focused perspective. If this perspective is necessary, then an explanation of that need is in order. Legislation in other countries or regions should be explored. Some nations have successfully legislated that all trials be registered and are finding this a great success for monitoring trial activity in their country (the example of India comes to mind). Some nations have legislation that mandates trial registration for their country, but this has been unsuccessful, or the infrastructure is not in place to sustain such measures. These comparisons are important to the global perspective.
Reply: Thanks for your suggestion. We have discussed it in the revised manuscript, thus to compare the response about legislation.

9. In the fourth paragraph of the piece, the authors begin to discuss the development of the registry systems in place now. Key events and organizations are left out of the development and some assertion are not correct (for example “there is no significant plan to ensure that all researchers register their trial”; the ICTRP hosts 10 primary registries, not nine) .the importance of the ICTRP’s networks in this push for global trial registration should be discussed, especially the development of the Universal Trial Number system and the steps being made with various regional organizations to bring clinical trial registration, oversight and ethical approval together in a harmonised way (one example is AVAREF, but networks like these exist throughout the world and are attempting to harmonise the processes around clinical trial work).
Reply: Thanks for your suggestion. We have added this point in the revised manuscript, majorly as ‘A global network could be established through two steps, with first step to legislate, as USA FDAAA Act 2007, and second step to
establish a network involving all countries which has ability to conduct clinical trials, to ensure uniform, international consistency in policy and enforcement of trial registration and data transparency’.

a. The development of an international call for clinical trials as described by the manuscript is missing some key components
b. Call initially came from the 2004 Ministerial Summit of Health on the WHO, followed by ICMJE endorsement . . .in 2007 ICMJE updated their statement to call for prospective registration on ICMJE endorsed registry in order to publish in member journals
c. For an example of the history of development of clinical trial registration in the ICTRP see Ghersi, D and Pang, T. (2009) “From Mexico to Mali: four years in the history of clinical trial registration” JEBM 2, pp 1 - 7
d. In 2008 the Declaration of Helsinki made prospective registration mandatory in order to comply, so the paragraph focusing on the Ottawa statement and its weak call through ethical obligations to register is perjorative . . .not fully recognizing the power of ICMJE in controlling publication in member journals and the impetus to align with the Declaration of Helsinki

Reply: Thanks for your suggestion. We have added the missing components in the revised manuscript.

10. There seems to be a confusion between ethical trial oversight and registration (particularly in the abstract, but also, I think in the body) – although linked one does not necessarily mean the other. Additionally, transparency of protocols is an ethical commitment, but an ethics board does not have to approve a trial for the process and protocols to be transparent . . .linking ethics and registration should be specific to regions, depending on the region’s or people’s norms and standard ways of living as ethical concern and focus could differ according to different norms and ways of life.

Reply: Thanks for your suggestion. This is very important because different country and region have different norms and standard.

Minor Essential Revisions
1. Reference to the “inadequate situation” in the US should be explained

Reply: It is the ‘inadequate reporting’. We have revised it accordingly.

2. The suggestion at the close of the piece before the conclusion that the WHO
“organize an international committee to provide consultation for each country and help them legislate for this purpose” is already underway in the African region. There also exists a body of this kind for South America and both collaborate under the networks of WHO and PAHO.

Reply: Perfect! We changed our manuscript accordingly.

3. The statement “Trial registration alone is not enough” begs the question, for what? If the goal is data transparency then registration in a registry that demands the WHO 20-item mimimum dataset and makes the trialist responsible for updating that trial could be enough if the individual PI is responsible...this then becomes a matter of individual persons and not the infrastructure in place.

Reply: Agree. We revised it accordingly.

4. To consider: Why not suggest a network, organization or body under which this could be centralized? Individual nations and regions have been attempting to create this legislation through various networks (in Africa, networks of excellence, AVAREF, SADC) and efforts are overlapping so resources are lost in duplication. In addition to stating the obvious in suggesting individual nations get on board, I suggest you go further and develop a framework to create the “system” you refer to more than once in your piece.

Reply: Thanks for your suggestion. We added this point and revised the corresponding part in the manuscript.

Discretionary Revisions

1. The statement, “The concept of trial registration was first mentioned by Simes RJ in 1986” This statement refers to an article written by Simes RJ in that year...I am not sure it’s a true statement, but at the moment the strong language concerns me.

Reply: I have checked it again. It is correct.

Quality of written English: Needs some language corrections before being published

Reply: Thanks. We have revised the manuscript and a native English speaker, Dr. Martha Dehlen has helped us to polish it further.