Reviewer's report

Title: Funding and Infrastructure among Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey

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Reviewer: Athina Tatsioni

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Major Compulsory Revisions

Abstract: authors may consider change part of the Results and Conclusion according to the changes in the rest of the manuscript

Methods, page 7: “A true endpoint was defined as...”. To my knowledge, there is no such thing as a “true endpoint”. However, if authors have a reference for this term, they should include it in the article. Obviously, authors refer to “cardiovascular endpoints” according to the title they have in their survey questionnaire. I would recommend that authors define the endpoints as “cardiovascular endpoints” and keep the clarification they have already added for the outcomes they included.

Methods, page 7: Please change “…except sponsors that we did not have access to.” to “…except for sponsors that we did not have access to.”

Methods, page 7: After the last sentence, please add how the description of variables was presented (median and IQR for continuous variables; absolute numbers and percentages for binary and categorical variables), the groups that were used for comparison, the statistical test that were used for the comparisons between the groups, the statistical software that was used for the analyses, and the P-value that was considered as statistical significant.

Results, page 8: Please change “We calculated the numbers of large-scale clinical trials, divided by different types...” to “We calculated the numbers of large-scale clinical trials per funding source...”

Results, page 9: Please change “Of the 25 trials that were funded by foundations, all trials except those where funding was unknown...” to “Of the 25 trials that were funded by foundations, all trials except for those where funding was unknown...”

Results, page 9: “In an additional question, we asked details of the cost to the sponsors of 20 trials.” Why the authors did not address that question to all 63 participants? What were the responses of the 12 participants who replied to that question? What type of funding supported these trials (public, private, combined, unknown)? Also, in Methods, authors should clarify the number of participants the addressed each part of the questionnaire.
Results, page 10: “Regarding the infrastructure required for conducting large-scale clinical trials, we investigated the situations surrounding the support of human resources and material resources in 37 trials whose sponsors reported foundations or private organizations as funding sources.” Why the authors did not address that question to all 63 participants? Also, in Methods, authors should clarify the number of participants the addressed each questionnaire.

Discussion, page 12: “The results revealed significant differences in total trial costs between studies involving different types of funding sources (p<0.0001).” The description of the comparisons between funding sources including the P-values should be describe in Results. What should be left for Discussion is the conclusion of all these comparisons without P-values.

Discussion, page 12: “Some sponsors commented that a lack of available time of external and internal staff at the trial sites was one of the major reasons for delays in subject enrollment.” Please move this phase to Results.

Discussion, page 14: In the limitation paragraph the authors also consider including the following:
- Another limitation of this study was that it did not clarify where the money was allocated in each study. Therefore, this survey does not allow for conclusions on whether expensive trials requested the additional amount of support to recruit more staff, use more sophisticated methods and high technology resources, or they had just to pay extra money for honorariums and travel expenses, which probably does not contribute much to the improvement of the validity of an RCT.
- In addition, the infrastructure questionnaire was addressed only to the private funded trial sponsors, and therefore a comparison with the infrastructure of public funded trials cannot be completed.

To further decrease the Discussion, authors may consider the following suggestions:
1) Include the following paragraphs to one brief paragraph: “Our examination of the funding… unaware of their responsibilities in managing and/or financing the costs of large-scale clinical trials.” AND “Regarding the infrastructure… room for improvement, although these frequencies are relatively high.” In that first paragraph, the authors may also add the conclusion on the limited registration that these trials reported to have in clinical trial registries.

2) In a second brief paragraph, authors may include other information that is related to their conclusion, i.e., “Sample size numbers of participants are were similar to those reported in a review of clinical trials in Western countries between 2000 and 2005 [45], where the mean and median numbers of participants were 560-4,239 and 421-1,486, respectively, although the number of participants was found to vary between trials with different funding sources.” AND “Approximately one third of the responding trials were registered by the UMIN and clinicaltrials.gov, respectively. These sites for registration were both recommended for clinical trial registry by the International Committee of Medical
Journal Editors (ICMJE) [16].”; “Our findings suggest that some sponsors are not aware of the importance of clinical trial registration. ICMJE in 2004 [12], the Declaration of Helsinki revised in 2008 [17] and the CONSORT declaration in 2010 [18] request the disclosure of trial protocol summaries and results by sponsors of clinical trials to avoid publication biases. Considering the purpose of clinical trial registration, we wish to emphasize that sponsors should be aware an important responsibility of sponsors is to minimize publication bias, thus improving the quality of evidence produced by large-scale clinical trials.”

3) In a third paragraph, authors may include their comments on transparency. In addition, at the end of the paragraph “Considering the purpose of clinical trial registration, we wish to emphasize that sponsors should be aware an important responsibility of sponsors is to minimize publication bias, thus improving the quality of evidence produced by large-scale clinical trials.” authors need to add references related to the association of clinical trial registration and publication bias.

4) Finally, in a 4th paragraph, author can summarize the limitations of their study Conclusions, page 14: “The results of the current study revealed that many sponsors face difficulties in obtaining adequate funding and human resources for conducting appropriate large- scale clinical trials. In the years covered in our study period, the situation did not substantially change.” I think that this was not the primary outcome of the study and I cannot see how the survey revealed that. In my opinion, the authors captured very well, through their survey, the idea that the more expensive a large scale RCT with cardiovascular endpoints is, the more likely it is that the trial was sponsored by private funding. However, whether private funding is associated with a better infrastructure remains unclear. Moreover, it would be interesting to investigate whether the additional cost in private funded trials corresponds to expenses that may improve the validity of these trials.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests