Author’s response to reviews

Title: Current Problems with Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey

Authors:

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Version: 2 Date: 25 April 2011

Author’s response to reviews: see over
Dear Editors of the BMC Medical Research Methodology

MS: 4443021134896368

Title: Current Problems with Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey

Thank you for your e-mail of March 30, 2011, regarding our manuscript, “Current Problems with Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey”, and the valuable comments of the four reviewers. I attach here our revised manuscript with track changes, and I a point-by-point response to reviewers' comments. We hope that the revised version of our paper is now suitable for publication in the BMC Medical Research Methodology and we look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Comment #0
Native check of English
Response:
The native English writer in ASCA Corporation has conducted the native checking of English.
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Comments by reviewer 1
(Title)
Comment #1:1
The authors may consider change the title to “Funding and Infrastructure among Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey.
Response:
We changed the title to “Funding and Infrastructure among Large-scale Clinical Trials Examining Cardiovascular Diseases in Japan: Evidence from a Questionnaire Survey.”

(Background)
Comment #1-2
The authors may consider delete: “A large number of non-clinical and clinical investigations are required to obtain adequate evidence to improve medical treatment. Additional evidence could be beneficial for the medical practice of many health care providers. Clinical evidence can be used to inform clinical practice guidelines, and can benefit patients by providing a rationale for determining the most appropriate treatment.”
Response:
We deleted these sentences.

Comment #1-3
The authors may consider delete: “Clinical trials must be conducted to obtain adequate clinical evidence. Large-scale clinical trials involving thousands of participants are particularly important in interventional clinical trials of cardiovascular diseases to evaluate the risk reductions of cardiac events and/or deaths, because of the need to evaluate the incidence of cardiovascular events with relatively low incidence. Such clinical trials provide evidence regarding the most appropriate treatment regimen for preventing cardiovascular and metabolic diseases.”
Response:
We deleted these sentences.

Comment #1-4
The authors may consider delete: “This study was a double-blinded randomized parallel-group controlled trial carried out across 48 institutions from 1993 to 2000. The primary end point was a combined measure of cardiac events, defined as cardiac or non-cardiac death, recurrent non-fatal myocardial infarction, coronary revascularization, and hospitalization because of worsening angina or congestive heart failure. In total, 888 of 1,163 participants with acute myocardial infarction (AMI) were
eligible for the full analysis set (FAS). Participants were randomly divided into two groups; 422 participants received angiotensin-converting enzyme (ACE) inhibitors and 466 did not receive ACE inhibitors. The mean follow-up period was 5.8 years.”

Response:
We deleted these sentences.

Comment #1-5
Where does the following paragraph refer? “After the JAMP study, we found a number of issues surrounding large-scale clinical trials. In particular, the funding sources and infrastructure of clinical trials were found to be major issues. Our results indicated that financial and infrastructural resources must be maintained to adequately conduct clinical trials. However, a substantial cost is involved, and obtaining funding is thus essential for clinical trials. The infrastructural environment surrounding clinical trials is currently inadequate, although this situation is improving.” Does it refer to the present or an authors’ previous study? If it refers to the present study, it should be removed from the Introduction and placed in the Results section. If it refers to a previous study, authors should mention a reference.

Response:
It is our previous study which was accepted after submission of this article. We added the reference regarding our manuscript.

Comment #1-6
Please change “…Considering the current situation surrounding the medical and pharmaceutical industries as well as the researchers, it is impossible to completely avoid conflicts of interest of researchers…” to “…Considering the current situation surrounding the medical and pharmaceutical industries as well as the researchers, it would be unlikely for researchers not to have conflicts of interest…”

Response:
We changed the sentence to “Considering the current situation surrounding the medical and pharmaceutical industries as well as the researchers, it would be unlikely for researchers to avoid conflicts of interest completely.”

“Conflict of interest” is not a behavior but an appearance. Therefore, we left “to avoid conflicts of interest” here as it is.

Comment #1-7
The authors may consider avoid using numbers to report the purpose of the study.
Instead, authors may consider the following phrase: “In this study, we conducted a survey among trial sponsors to clarify the current funding and infrastructural environment surrounding large-scale clinical trials in cardiovascular and metabolism diseases in Japan.”

Response:
We changed the sentence to “We conducted a survey among trial sponsors using questionnaires to elucidate the current funding and infrastructural environment surrounding large-scale clinical trials investigating cardiovascular diseases in Japan.”

Comment #1-8
It is unclear how the survey would help “To find ways of improving the environment surrounding clinical trials in Japan more generally”. It may help identify certain issues in research infrastructure. Therefore, the authors may consider clarify or remove the previous phrase.
Response:
We deleted this sentence, because this may not be achieved only by conducting this study.

Comment #1-9
The authors may consider delete: “To this end, we surveyed the current situation using questionnaires. In this article, we report the results of our survey regarding relevant issues surrounding large-scale clinical trials for cardiovascular diseases in Japan.”
Response:
Based on the changes regarding comment #1-7, we deleted the sentence “To this end, we surveyed the current situation using questionnaires.”, because it is duplicated.

Comment #1-10
The authors may consider delete or move the following phrase to Discussion: “These results will contribute to the future improvement of conflict-of-interest management in Japan as well as other countries.”
Response:
We moved this sentence to the last of Discussion: “These results will contribute to the future improvement of conflict-of-interest management in Japan as well as other countries.”

(Methods)
Comment #1-11
11) How “…the individual with the most responsibility…” was defined?
Response:
The individual with the most responsibility was defined based on their officially disclosed organizations. We added the sentences “according to the organizations disclosed officially” after “…with the most responsibility”.

Comment #1-12
Please clarify what “…29 newly identified…” means and how they were identified. Did authors use the same process as for the 90 trials?
Response:
They were identified using the same sources. Therefore, we changed the sentences to “In addition, 35 more trials were found using the same data sources as mentioned above on 25 July, 2009. We found addresses for sponsors of 29 of these 35 trials, and, sent questionnaires to all sponsors whose addresses could be identified between July 2009 and August 2009.”

Comment #1-13
A brief presentation of the questionnaire content, i.e., number of questions, type /categories /content of questions, time needed to fill in the questionnaire. Did authors pilot any survey before they perform the study?
Response:
Number of questions and contents of questions are shown in Additional file 1, which was additionally provided with our revised version. As for the time to fill in the questionnaire, I added “Our questionnaires consisted of categorical choices (Additional file 1). Sponsors were asked to return the questionnaires within 2 weeks, but all responses were included in our analyses, regardless of when they were returned”. No pilot survey was conducted.

Comment #1-14
What do authors mean by “true endpoints”? Do they mean “hard outcomes”?
Response:
We added the definition of “true endpoint” in methods: “A true endpoint was defined as an endpoint consisting of cardiovascular events, such as myocardial infarction, chronic heart failure, ischemic heart attack, and/or death.”
Comment #1-15
The authors may consider compare the results between studies sponsored by industry/private sector vs. studies with a public sponsor
Response:
We combined the tables and additionally compared each parameter by funding source.

(Results)
Comment #1-16
A “Additional file 1” to present the questionnaire may be informative
Response:
I added the questionnaire translated in English as Additional file 1.

Comment #1-17
A formal statistical test might be useful to compare number of participants between respondents and non-respondents in Table 1.
Response:
We compared it by funding source.

Comment #1-16(2)
Table 2 may be redundant. The information may be given only in the Results section text
Response:
We deleted the Table 2, and we added this information in the Results.

Comment #1-18
The authors may consider merge Tables 3 to 7, present results separately for studies sponsored by industry/private sector vs. studies with a public sponsor and formally compare them. For number of participants (Table 3), median with interquartile range (IQR) would suffice
Response:
We combined the tables and additionally compared each parameter by funding source. IQRs were added in Table 2 (re-numbered from Table 3).

Comment #1-19
Please clarify “self-funded” in a footnote for Table 2. Please also, clarify what “other” included in a footnote for Tables 3, and 7.
Response:
Branches of each questionnaire including “other” are shown in Additional file 1.

(Discussion)

Comment #1-20
Discussion should be shortened. The authors should not include arithmetic results in their Discussion section. These results have already been reported previously in the paper. In addition, if the authors compare the results between studies with a private sponsor vs public sponsor, the Discussion should also include comments on these results as well.
Response:
We deleted the duplicated descriptions in Discussion.

Comment #1-21
The following sentence is not related to the present study findings: “This finding indicates that unclear funding sources could potentially bias trial results.”
Response:
We changed to “... there are still many studies whose funding sources are unclear.”

Comment #1-22
What do authors mean by “true endpoints”? Do they mean “hard outcomes”?
Response:
We added the definition of “true endpoint” in methods: “A true endpoint was defined as an endpoint consisting of cardiovascular events, such as myocardial infarction, chronic heart failure, ischemic heart attack, and/or death.”

Comment #1-23
The authors may add one paragraph to comment on the limitations of their study, i.e., high non-response rate, data collected through a survey process, lack of a control group.
Response:
We added the limitations caused by the response rate. Response rate of about 60% would be considered reliable in this kind of questionnaire surveys, although we can not completely reject the possibility of biased results.

Comments by reviewer 2
Comment #2-1
In the abstract, more details on quality control, investigated population etc should be described.
Response:
We mentioned more details of our study in Method due to the limitation of word counts. We added the details of large-scale clinical trials in our previous article, which was accepted and published after the original submission of this article (added reference [4]).

Comment #2-2
Minor Essential Revision
In the fulltext, more details of the characteristic of the investigated participants such as location, year etc should be reported.
Response:
We added the details of large-scale clinical trials in our previous article, which was accepted and published after the original submission of this article (added reference [4]).

Comment #2-3
limitation of this study should be reported.
Response:
We added the limitations caused by the response rate. Response rate of about 60% would be considered reliable in this kind of questionnaire surveys, although we can not completely reject the possibility of biased results.