Author's response to reviews

Title: An international survey of physicians regarding clinical trials: A comparison between Kyoto University Hospital and Seoul National University Hospital

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Dear Dr. Arlene Pura:

MS: 5530140157735501
An international survey of physicians and dentists regarding clinical trials: A comparison between Kyoto University Hospital and Seoul National University Hospital
Toshiko Ito-Ihara, Jeong-Hwa Hong, Ock-Joo Kim, Eriko Sumi, Soo-Youn Kim, Shiro Tanaka, Keiichi Narita, Taichi Hatta, Eun-Kyung Choi, Kyu-Jin Choi, Takuya Miyagawa, Manabu Minami, Toshinori Murayama and Masayuki Yokode

It is my pleasure to resubmit the revised version of our manuscript for *BMC Medical Research Methodology*. We have addressed the concerns and the constructive comments from the reviewers, which has helped strengthen our claims and improve the manuscript.

Our responses to the reviewer’s suggestions and concerns (in bold) are as follows.

**Reviewer's report 1:**
This is an interesting study documenting the attitudes of physicians towards clinical trials and their feasibility. The statistics are straightforward and appropriate. The study is largely descriptive in nature.

**Minor essential revision**

While this is an important study, the conclusions might be a bit too strong. The authors seem to take much of what is stated at face value, which could lead to incorrect conclusions. For example, a physician who is not active in clinical trials research might simply not be interested in running clinical trials at all. However, there might be social and professional pressure to be active in clinical trials. Such pressure might lead physicians to respond to a survey in socially desirable ways that indicate a false willingness to participate in clinical trial research, but also to cite spurious reasons why they do not engage in the process (for example, lack of infrastructure). It is possible that anonymous surveys would not overcome this process. If the underlying problem is a lack of desire to participate, then building an infrastructure will not solve the problem, and could even be an expensive waste of time. As the English saying goes, a man (or woman) can lead a horse to water, but he (or she) cannot make the horse drink the water. It could be that closely tying salary increases to clinical trial accrual could have a bigger impact on physician behavior than building an infrastructure. Hence, while the survey certainly contains hypothesis generating results, future research is needed to understand if interventions to address some of the stated concerns truly change physician behavior and participation in clinical trials research. Ideally, such interventions, such as an intervention to improve clinical trial infrastructure, would start as small targeted pilot programs to test feasibility and efficacy. Once feasibility and efficacy were demonstrated, more widespread implementation of programs could be implemented.

Response:
Thank you very much for your suggestion. We have described this limitation in the Discussion section (the forth limitation, page 28, line 18-21).

Reviewer’s report 2:
This article reports findings from a comparative survey of Japanese and South Korean ‘physicians and dentists’ on their attitudes to clinical trials; the work is set in the context of ‘insufficient’ clinical trial activity in Japan compared to higher levels in South Korea. This is an interesting and useful study. However, there are several problems with the reporting which are detailed below. Additionally, the paper reports on findings of a questionnaire survey while the remit of the journal is methodology. I could not see any aspects in this paper that would contribute to or advance the methodological body of knowledge.

Response:
Thank you very much for your suggestion. We have described our possible contribution on the methodological body of knowledge in the Discussion section (page 28, line 1-8).

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1) The aim of the survey is given as: understanding how the different clinical trial environments (in the two countries) influence physicians’ attitude to trials. I find this formulation a little odd. Physicians’ attitudes may indeed be influenced by the environment and levels of trial activity but the reverse may also be true, i.e. attitudes may be one factor that explains the different levels of trial activity. The authors may want to reflect on and incorporate this duality in their statement of objective.
2) The language would benefit from some revision, to eliminate some clumsy syntax.

Response:
Thank you very much for your suggestion. We have modified our objective in the Introduction section (page 7, line 12-15). “We designed a uniform questionnaire survey to explore how individual physicians conceive the issues surrounding clinical trials in two university hospitals in Japan and South Korea: Kyoto University Hospital and Seoul National University Hospital.”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

3) The title and abstract state that the survey was sent to physicians and ‘dentists.’ However, the demographic data refer to ‘dental surgeons.’ If these were medically trained surgeons, then it would be more appropriate not to make a distinction between physicians and dentists as dental surgeons would be classified as physicians.

Response:
Thank you very much for your suggestion. We agree with this point and have classified them all as physicians.

Major Compulsory Revisions (which the author must respond to before a decision on publication
can be reached)

Methods:

4) The authors do not say how they define ‘clinical trial’ – whether they are referring to randomised trials only or both randomised and non-randomised designs. Equally, they do not specify whether the study concerns publicly funded or industry-sponsored trials or both.

Response:
Thank you very much for your suggestion.
We have added the sentence below in the Method section (page 9, line 16-19).
“The term “clinical trial” used in this survey was not categorized by study design or funding body and thus, the definition of “clinical trial” in this survey included all randomized controlled trials, non-randomized trials, pharmaceutical-sponsored trials, and investigator-initiated trials.”

5) The authors do not make clear how the questionnaire was developed. The questionnaire was a modified version of a previous one designed with the involvement of one of the authors (Sumi et al, 2009) which, in turn, was a modified version of an earlier questionnaire (Yanagawa et al, 2006). This is not adequate to explain to the reader how the questions were developed (based on what – literature review?), tested and piloted. The explanation on each question in the methods section is unnecessary.

Response:
Thank you very much for your suggestion.
Yanagawa et al. surveyed 89 doctors in 2000 and 62 doctors in 2004 at Tokushima University Hospital, Japan. This information has been added in the revised manuscript and introduced in the Introduction section (page 7, line 2-3) and the Methods section (page 9, line 10-11) as reference No.14.

6) I do not have statistical expertise, therefore cannot judge the appropriateness and adequacy of the statistical analyses conducted; however, the brief reporting gives the impression that these were very basic and may be inadequate.

Response:
Statistical analysis of this study was performed by Shiro Tanaka, Ph.D. biostatistician, one of co-authors. We believe that the statistical methods are basic but adequate since this is a descriptive study.

Results/Discussion:

7) In terms of the sample, can the authors clarify which two KUHP departments refused participation and any reasons given. The absence of two KUHP departments from the sample means that the responding physicians at KUHP represented 27.5% of the total number of staff there while the same figure for SNUH was 45%. The quoting of the KUHP response rate as 64% without this information is misleading.

Response:
Thank you very much for your comment.
This is described in the results section (page 11, line 9-14).

“34 out of 36 departments in KUHP and 18 out of 18 departments in SNUH consented to participate in this survey. We were not able to obtain a response from the director of the Department of Endocrinology
and Metabolism at KUHP by the deadline despite two requests for participation. The department consisted of 10 faculty members and 8 staff doctors at the time of the survey. Consent from the director of Department of Medical Informatics, who was the only the medical doctor in the department at the time of the survey was not obtained for unknown reasons.

8) The meaning of some of the questions is unclear/overlapping. For example, what are ‘infrastructure’ related problems and how do they differ from ‘systemic support from hospital?’ Similarly, how do problems with ‘enrolment of subjects’ (incidentally, the preferred term these days is ‘participants’) differ from problems with ‘obtaining informed consent?’ What were the problems/merits identified in the ‘others’ option in these sections?

Response:
Thank you very much for your valuable comments.
- We have replaced ‘subjects’ with ‘participants’.
- In our paper ‘systemic support’ reflects personnel support such as research nurses, supporting entities and the general support environment provided to doctors not only for clinical trials but also day-to-day clinical practice. On the other hand, we imagined ‘infrastructure’ to imply specialized support system during clinical trials involving trained clinical trial professionals.
- Enrollment of trial participants is sometimes difficult due to eligibility related to safety concerns. So, even if a patient wishes to participate in a new and promising trial, he or she could be excluded if they do not fall strictly within the inclusion criteria. On the other hand, difficulties in obtaining informed consent may influence patient/doctor relationship. So, we distinguished the questions of ‘enrolment of trial participants’ and ‘problem with obtaining informed consent’ in item #7 and #8 in the question #10.
- We described the results of ‘other’ option provided in the questions #8, 10 and 16 in the Results section (page 13, line 10-11 and line 23-24; page 14, line 4-5 and 17-18; page 15 line 24 -page 16 line 1 and page 16, line 11-13).

9) A distinction is made between barriers/problems associated with ‘trials’ and industry-sponsored multinational trials with different answer options (Q 10 and Q16). What was the rationale for this? Many of the factors could apply to both kinds of trials. Quality of (multinational) trials was seen as a bigger problem at KUHP than at SNUH; as it is unlikely that there is a big difference in the quality of trials that two hospitals are exposed to, this may need explaining: is it, for example, that the expectations of KUHP doctors are higher?

Response:
Thank you very much for your suggestion.
We added the sentence below in the Method section (page 9, line 16-23).

The term “clinical trial” used in this survey was not categorized by study design or funding body and thus, the definition of “clinical trial” in this survey included all randomized controlled trials, non-randomized trials, pharmaceutical-sponsored trials, and investigator-initiated trials.

Question #6 referred to previous experience in any kind of clinical trial while Question #10 was about major obstacles in conducting any kind of clinical trial. Previous experience specifically in global trials sponsored by pharmaceutical company and major obstacles in participating in such trials were asked in Question #16.
10) Q17 was for free-text ‘comments.’ The results for this question are not reported. Is this because this question was left blank?

Response:
Thank you very much for your valuable suggestion.
We analyzed the free-text comments and have described in the Methods (page 10, line 9-16) and the Results section (Table 2; page 18 line 6 - page 20 line 7). In addition, we discussed the results in the Discussion section (page 22 line 19-20; page 23 line 2-4 and line 18-21; and page 26 line 12-14).

11) There is a general problem with the reporting of the results and their discussion: many of the interesting responses shown in the tables are not flagged up in the text and/or contextualised, with the result that the reporting appears unbalanced and fails to reflect the whole study:

Response:
Thank you very much for your suggestion.
We have changed the whole Discussion section according to your comments.

11.1 The designation by SNUH physicians of board certification as a major benefit of trial participation is important, both on its own, but also in comparison with the insignificance of this for KUHP physicians. This may go a long way in accounting for the greater enthusiasm of SNUH physicians for trial participation. This is not acknowledged or flagged up.

Response:
Thank you very much for your suggestion.
We have added the sentence below in the Results section (page 13, line 19-21).
“There was a significant difference between KUHP and SNUH in their opinions on performing clinical trials to obtain board certification, as this was least important determinant for doctors at KUHP (p<0.01).”
We have also discussed the issue in the Discussion section (page 25, line 5-10).

11.2 There is a striking difference between the two sites in terms of opportunities for and sources of information on trials. It seems that there is little information provided at SNUH, compared to KUHP. And yet, there is more trial activity at SNUH. Comment is needed from the authors on the possible reasons but also the implications of this. For example, is it possible that SNUH physicians are participating in trials without adequate information about them?

Response:
Thank you very much for your thoughtful suggestion.
We created the header of ‘The knowledge of doctors regarding clinical trials’ the Discussion section and have discussed the detail (page 26, line 16 – page 27, line 14).

11.3 The higher percentage of trials terminated due to adverse events at SNUH compared to KUHP (26% v 8%) may need a comment. Furthermore, the other reasons given by SNUH doctors are intriguing and troublesome and also need comment: adverse events (a higher percentage than at KUHP), sponsor’s request, protocol violation, publication of similar trial results elsewhere, unfeasible research design. Some of these appear to be avoidable shortcomings, with implications for resource use in trials.

Response:
Thank you very much for your comment.
The clinical trials in SNUH and KUHP are different in their numbers, phases, designs, diseases, and the investigational agents (drug, device, biological). The trials in SNUH are more early phase, risky than in KUHP so that higher percentage of adverse events is reasonable. We have added the percentage of phase I trial at the time of the survey in KUHP and SNUH in the Method section (page 8, line 11 and line 19).

11.4 While the Discussion addresses the infrastructural and operational factors in limiting the number of trials in Japan, it does not address other findings. For example, the authors explain the higher tendency of KUHP physicians to refer to recruitment problems in terms of the limited availability of eligible patients to any single hospital in Japan, compared to South Korea. However, they offer no explanation for the higher percentage of Japanese physicians referring to problems in obtaining informed consent compared to those in South Korea.

Response:
Thank you very much for your valuable suggestion.
We have added the issue of obtaining informed consent in the Discussion section (page 24, line 7-15).

12) In the Discussion, the authors state that ‘financial gain’ was the second to last merit reported at KUHP and last at SNUH. Financial gain is not a category in any of the tables and is not mentioned in the results section.

Response:
Thank you very much for your comment.
We had thought that getting research grant or other rewards would be comparable to the financial gain. However, we agreed with you that would be different meaning and deleted the description about financial gain in the Discussion section.

13) The discussion is a little diffuse and repetitive. The ‘resolutions’ section repeats findings; it should focus on suggested solutions. A paragraph (or possibly bullet points) on the main recommendations to emerge from the study would be welcome. The section on ‘patients’ perspectives’ is irrelevant, uninformative and not justified, as this was not covered by the survey and should be removed.

Response:
Thank you very much for your thoughtful suggestion.
We conceptualized the topics into social and individual levels of awareness to avoid the receptiveness. Then we have changed the topic that we deleted the ‘resolutions’ section and inserted ‘The individual level of awareness of issues clinical trials’ in the Discussion section.
In addition, we completely deleted the section on ‘patients’ perspectives’ from the Discussion section according to your comment.

Limitations

14) The questionnaire was explained and handed out to staff by departmental directors. This may have compromised the independence of the research and, despite the offer of anonymity, staff may have been under the impression that participation was preferred by management. Conversely, staff may have been reluctant to respond because of this. Additionally, this method may have been less reliable than direct posting in ensuring that each potential respondent received the questionnaire.

Response:
Thank you very much for your precise suggestion.
We agreed with you and described this issue as the limitation of this survey (page 28, line 18-21: the forth limitation).

15) There was no ‘other’ option provided in many of the questions, raising the possibility that important opinions and attitudes may not have been elicited.

Response:
Thank you very much for your precise suggestion.
We have described the results of ‘other’ option provided in the questions #8,10 and 16 in the Results section (page 13, line 10-11 and line 23-24; page 14, line 4-5 and 17-18; page 15 line 24 -page 16 line 1 and page 16, line 11-13).

16) The ethics of trials was not covered by the questionnaire. While there is a knowledge test regarding the Declaration of Helsinki, there are no questions on how doctors feel about trials and possible conflicts of interest, a prominent issue in the literature especially in relation to randomised trials (Hales et al, 2001 Sackett and Hoey, 2000, Garcia et al, 2004).

Response:
Thank you very much for your important suggestion.
We agreed with you and described this issue as the limitation of this survey (page 28 line 15-17 :the third limitation).
Although our questionnaire did not specifically ask about opinions on potential conflicts of interest, 2 KUHP doctors commented on their reluctance to offer help to randomized controlled trials because of the difficulty in separating their conflicting role as a clinician versus an investigator, which might affect their patient/doctor relationship. This information has been added in the Discussion section (page 24, line 12-15).
The references No. 21 (Hales et al, 2001), No. 22 (Tomlin et al), No.30 (Sackett et al, 2000), and No. 31 (Garcia et al, 2004) were also added.

In summary, we appreciate the careful reading of our manuscript, and for providing such valuable comments and suggestions. We trust that the changes made meet the high standards required, and that you will consider the revised manuscript worthy of publication in *BMC Medical Research Methodology*.

Thank you for your consideration.

Yours sincerely,

Toshiko

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