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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17 September 2013

Journal Editorial Office
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Dear Dr. Arlene Pura:

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

Authors: 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 reviewer, 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

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

Version: 2 Date: 25 June 2013
Reviewer: zelda tomlin

Reviewer’s report:

Major compulsory revisions

The authors have responded to the points raised in my original review and the paper is now much improved. However, a few points remain that should be fairly easy to deal with:

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.

For readers interested in the design of the original questionnaire, can the authors say whether References 14 and 15 include an explanation of design? I still think that some detail needs to be given about how the questionnaires (the original and the current one) were developed. I note that there is a reference to this in the Discussion, but there needs to be a brief explanation in the Methods too.

Response: Thank you for your careful observations. Based on your suggestions, we have now added an explanation of the survey design of the two previous studies and describe how the focus of those surveys is different from our current study. These explanations have been added to the Methods section on line 10 of page 9 and on line 9 of page 10. We also added a brief description of the structure of our survey on line 10 of page 10 and on line 3 of page 11, so the reader can understand how the questions were developed.

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?

The authors’ explanations of the difference between systemic support/infrastructure and between enrolment/informed consent are helpful but can they please add these to the paper by inserting them in brackets after each term (p 14, lines 9, 10, 13, 15).

Response: Thank you very much for your comments. We have added an explanation below on line 3-13 of page 15.
“Among the subordinate items, ‘systemic support from the hospital’ refers to personnel support such as research nurses, supporting entities and the general support environment provided to doctors not only for clinical trials but also for day-to-day clinical practice. This should be distinguished from the subordinate item ‘infrastructure’ which refers to the specialized support system during clinical trials involving trained clinical trial professionals. We also distinguished ‘enrolment of trial participants’ from ‘problem with obtaining informed consent’ in items #7 and #8 of this question. ‘Enrolment of trial participants’ refers to difficulties in patient recruitment because of safety concerns and the eligibility criteria. Difficulties in ‘obtaining informed consent’ specifically related to difficulties in the interaction between the patient and the doctor.”

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?

The authors haven’t dealt with the second point here (on quality).

Response: Thank you very much for your comments. We have now discussed the “point of the doctors’ perception on the quality of global trials” in the Discussion section on line 3-16 of page 25.

The major obstacle other than infrastructure in participation in global trials for KUHP doctors was quality of the global clinical trial. 54% of KUHP doctors stated that the quality of the clinical trial was an obstacle; on the other hand, only 25% of SNUH doctors stated this was an obstacle. Language barrier is not assumed as an obstacle for many doctors of both KUHP and SNUH. Although the actual quality of clinical trials does not differ in both countries, the differing answers regarding quality may be explained by the fact that KUHP has less infrastructure, and fewer personnel and investigators who are experienced in multinational trials than SNUH. Furthermore, KUHP investigators may be unaccustomed to the various requirements; such as the different format of documents, how to put the signature on records which would not be an issue for people with experience in global trials. Therefore it is likely that KUHP doctors may be compelled to have more rigid perception in regarding the quality of trials or might have higher expectations when participate in multinational clinical trials.

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.

The authors explain that the higher % of adverse events at SNUH may be due to the higher risk profile of the trials there. Can they please add this to the paper, with a brief explanation on p 15, after the last sentence, on line 15.

Response: Thank you very much for your comment. We have added this statement followed by an explanation after the last sentence on line 23 of page 16.

“There are many differences in the clinical trials conducted at SNUH and KUHP including their numbers, phases, designs, diseases, and the investigational agents (drug, device, biological) being tested. The higher fraction of adverse events observed at SNUH may be due to the higher risk profile of the trials there.”

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.

Can the authors provide a little more analytical comment on the issue of informed consent as they have done with some of the other points? Could the fact that South Korean doctors regard informed consent as less problematic be due, in part, to the higher proportion of Phase I trials if the participants in these are offered payment (if they are)? What may be other reasons for the difference in perceptions between the two countries?

Response: Thank you very much for your thoughtful comments. We have discussed about the issue of informed consent and added this between line 2 of page 27 and line 2 of page 28. The references No. 26 (Rousseau DM et al 1998) and No.27 (Hofstede G 1991) were also added.

“The difference might be explained in part by the higher proportion of Phase I trials at SNUH compared to KUHP, as the content of informed consent is different between Phase I trial and trials that have moved further along. There were 218 industry-sponsored trials in SNUH and ~20% of them were the Phase I trials, whereas of the 77 industry-sponsored trials at KUHP only 1 trial (1.3%) was a Phase I trial in 2008 at the time of the survey. There might be other factors as to why physicians face difficulties in obtaining informed consent of which one is “conflict of interest” [24,25]. 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. In addition to conflicts of interests, a “defensive attitude” to avoid lawsuits may contribute to lengthening the time needed for informed consent. KUHP doctors may tend to explain
everything about the clinical trial in an obsessive manner in their desire in not wanting to leave out anything unexplained. Cultural differences may also play a role in the increased time needed for obtaining informed consent. KUHP doctors may not acquire proficiency in obtaining informed consent because of the cultural gap between contractual relationships and affective trust [26, 27]. Together, we believe that multiple factors could contribute to the perception that informed consent was a major obstruction in conducting clinical trials. However, in our study, we did not address any questions in matters relating to the deep personal feelings of physicians in obtaining informed consent, and thus we are not able to throw any light on the comparison between the opinions of physicians regarding this matter in both the university hospitals.”

Limitations:
There seems to be some conflation of two different kinds of limitation (p 28, lines 9–12 and 22-24).
The point about differences between the two cohorts in the two hospitals (lines 22-24) is the limitation highlighted in lines 9-12 (differences in response rate and composition at the two hospitals). The other selection bias -more doctors interested in trials responding than those who’re not -is a different point and may apply equally at both hospitals. These points need to be separated.

Response: Thank you very much for your advice. We moved the point about differences between the two cohorts in the two hospitals to just after the second limitation. The points you suggested were separated into the third limitation on between line 20 of page 30 and line 1 of page 31.

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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