Author's response to reviews

Title: Participants' understanding of randomized controlled trial (RCT) through informed consent procedures in the RCT for breast cancer screening, J-START

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Doug Altman, Curt Furberg, Jeremy Grimshaw,
Editors-in-Chief,
Trials, BioMed Central Journals

Re: MS: 1716350196129001 Participants’ understanding of a randomized controlled trial (RCT) through informed consent procedures in the RCT for breast cancer screening, J-START

Dear Dr. Altman, Dr. Furberg, and Dr. Grimshaw:

We appreciated your giving us the opportunity for further revision of our manuscript. We have carefully addressed the comments of the editors and reviewers and have amended the manuscript according to the suggestions. Below, please find our itemized replies to the comments and the changes we have made to the manuscript.

Yours sincerely,

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Editor comments:

1. A previous version of the paper indicated that 1308 questionnaires were distributed; this version of the paper indicates that 719 questionnaire were distributed. Obviously this difference has a substantial impact on the response rate. Can the authors explain?

Dr. Zheng’s calculation of 1308 participants was based on the total number of participants who were recruited at the collaborating medical centres during the originally planned period of Nov. 15, 2010 through March 31, 2011. However, that number includes participants who were contacted during the course of mobile screening by bus or in other buildings of the same centre, and that number included persons who were not given a questionnaire by any of the personnel associated with this study. For this study, questionnaires were to be distributed to J-START participants who had been newly recruited at the collaborating medical centres by the investigators at each centre. In our manuscript, we report on 719 new participants who were managed by the investigators in the collaborating medical centres. We greatly appreciate that you pointed out the discrepancy in the numbers to us. As a result, we were able to obtain more detailed information from the collaborating medical centres. We learned that, because the system was up and running early at the collaborating medical centres, that distribution of the questionnaires was started on Nov. 10, 2010 and completed on Jan. 31, 2011. We learned that the questionnaires were distributed to 745 participants in this period. We have taken this opportunity to more accurately report the questionnaire distribution period and the target number of participants in our revised manuscript. Dr. Zheng agrees with the revision of the number of participants to whom a questionnaire was distributed.

2. More detail on the process of adapting the American instrument would be useful. Was it merely translated? Were other changes made? How was the translation checked?

Before translating the QuIC into Japanese, we deleted questions that pertained only to Phase I clinical studies of cancer. We then had one Japanese and one Chinese healthcare workers who use English and Japanese on a daily basis translate the remaining questions into Japanese, and then back-translate the Japanese into English. We have added an explanation of this to our revised manuscript.

P9, last paragraph, line 1

“The J-START is an RCT that enrolled healthy volunteers as the participants for breast cancer screening. For that reason, the QuIC questions that pertained only to Phase I clinical studies were deleted (in the original QuIC full version: questions A6, A7, A8, and A10). We then had one Japanese and one Chinese healthcare workers who use English and Japanese on a daily basis translate the remaining questions into Japanese sentences that would be readily understandable in the context of current Japanese culture. Next, we had
back-translated that Japanese into English by a different person who used English and Japanese on a daily basis. Finally, that back-translated version was checked by a person whose native language was English. The comprehensibility of the technical terms and expressions in not only the Japanese QuIC, but also the full questionnaire including original items, was checked by having a medical ethics specialist and medical staffers complete the entire questionnaire. We then made revisions to the materials based on their replies. To ensure the validity of the full questionnaire, we evaluated the materials’ reliability by test-retest as following. We asked the new participants in J-START, which has the same conditions as the present study, to answer the full questionnaire, including Japanese version of QuIC and other items, two times, at a two-week interval. Twenty-one participants answered all the questions in the questionnaire two times. Weighted kappa statistics for QuIC ranged from 0.32 (objective risks) to 0.67 (subjective experimental nature of study), respectively. Cronbach’s alpha values for QuIC for internal consistency were 0.57 and 0.89 for Parts A and B, respectively.”

3. The manuscript requires thorough editing before it is resubmitted.

After making the necessary changes to our manuscript, we have had it edited by a native English speaker. During through the editing procedure, we also corrected typographic error in Table5. The correction included subheadings of “Yes/No” and “Quite disagree/totally agree.” These corrections did not change the discussion and conclusion.

Editorial requests:

1. Please include a list of abbreviations used and their meanings, after your Conclusions.
   
   We have included a list of abbreviations (RCT, IC, J-START, QuIC).
Reviewer 1,

Dr. Helena Länsimies-Antikainen

1. Major Compulsory Revisions (Comments are expressed in order they turn up in the manuscript): Main question: What is the novelty value of this study?

There have been no reports of studies conducted in Japan that used a validated international scale to evaluate the level of understanding of healthy women with regard to participation in RCTs. Our study aims to provide information that will lead to improvement in the process of obtaining IC and the conduct of RCTs that include healthy ordinary women. We think that our findings have novel value in this regard, at least in Japan. We have added comments in this regard to the Discussion.

P15, line 6

“…Until the present study, there have been no reports on either the understanding of an RCT targeting the general population of healthy women or reports concerning evaluations using international and validated scales in Japan. The present study has demonstrated hints of improvement in the IC process in an RCT that targeted the general population of healthy people.”

2. The aim of this study is described a little differently in abstract, background and discussion. Based on the results the description in background is more precise.

Thank you for this comment. We have made clear in both the Abstract and Background that the objective of this research was to investigate the level of understanding of the informed consent process among healthy volunteers participating in RCTs and the factors involved in that understanding.

3. The pilot test of the questionnaire translation is described quite cursory. In addition, at page 10 (line 1 and 2) is a confusing amount of participants (21 and 7). There is need to know how and where these participants were selected? Was the only result test-retest reliability? etc.

This was also pointed out by the Editor (point 2 of Handling editor comments).

We have added statements to the revised manuscript with regard to the method for preparing the Japanese version of the QuIC, the method for translation, and the method for including participants in the pilot test of the questionnaire. Please see page 9, last paragraph, line 1. We have also added statistical values regarding the reproducibility and internal consistency. We carried out a pilot study not only with regard to the QuIC, but also with regard to all questionnaires. The participants who participated in the pilot study also participated anew in J-START, which had the same conditions as the present study. The validity was examined only by test-retest.
4. The ‘Factors associated with low objective understanding’ results (page 13-14) are written quite inaccurate. It would be nice to read easily how these associations are interpreted (directions).

As pointed out by several reviewers, we investigated the addition of ‘A9. Benefit to self’ to Table 5 as an item that is not adequately understood. We had the manuscript proofread by a native English speaker so that it would be concise.

P14, line4

“The medical centre showed a correlation with two questions: Question A8 on “Potential risks or discomforts” (P=0.009) and Question A13 on “Compensation” (P<0.0001). The existence of prior knowledge of the RCT or J-START itself was statistically significant only for Question A4 on “Experimental nature of study,” (RCT, P=0.002; J-START, P=0.003). The educational video showed a correlation with the two questions of A8 on “Potential risks or discomforts” (P=0.003) and A13 on “Compensation” (P=0.001). Sufficient opportunity to ask a question showed correlations with Question A8 on “Potential risks or discomforts” (P=0.025), Question A9 on “Benefit to self” (P=0.023), and Question A13 on “Compensation” (P=0.049), while enough time to achieve understanding showed correlations with Question A8 on “Potential risks or discomforts” (P=0.007) and Question A13 on “Compensation” (P=0.013). The atmosphere at the venue when the decision to participate was made showed correlations with Question A9 on “Benefit to self” (P=0.001) and Question A13 on “Compensation” (P=0.043), but for each case there was a low percentage of participants who felt the atmosphere made it hard to refuse to participate. No statistically significant correlation was found between the degree of understanding and the following factors: education level, marital status, work status, informational leaflet, whether the research staff confirmed whether the participant understood, or whether the participant wanted to ask further questions at the time of IC.”

5. The authors state in discussion (page 15) that ‘Our study will provide degrees of objective and subjective understanding of the IC process among RCT’. Is this really so?

As we explained in our reply in question 1 above, in the 1st paragraph of page15, we have stated that the objective of this study was to evaluate the level of understanding of healthy volunteers in RCTs and the factors involved, and that, to date, no studies such as ours have been reported in Japan. We also note that this is an evaluation of ordinary participants’ understanding by using a
standardized international scale, and that the findings should lead to improvements in general participatory RCTs and the IC process.

6. The authors’ have mentioned some limitations of this study. The quite low amount of participant in this accompanying research is a limitation especially when the main group is so huge (over 75 000 women). The discussion of study reliability and validity is missing.

As you have pointed out, the participants in this study are not fully representative of the participants in the RCT. We have added to the Discussion a statement that the reliability and validity of the questionnaire were secured.

P19, 2nd paragraph, line1
“A limitation of the present study was that not all of the J-START study sites were included. However, the validity of the QuIC was evaluated and the reliability of the questionnaire was tested….”

Minor Essential Revisions:
Table 5: p-value is missing at A4 title column.

This was our error. Thank you for pointing it out. We have corrected it.
Reviewer2.
Dr. Julia Wade

1) The aim of the study needs describing more accurately in both the abstract (page 3) and the text (page 6) - current description of the study question is potentially misleading in the abstract, allowing the reader to misinterpret this as an RCT of informed consent within the J-START RCT whereas in fact this is a survey study of the quality of informed consent given by participants of an RCT.

In the revised Abstract and Background, we have stated that the objective of this study was to evaluate the level of understanding of healthy volunteers in RCTs and the factors involved, and that, to date, no studies such as ours have been reported in Japan. We also note that this is an evaluation of ordinary participants’ understanding by using a standardized international scale, and that the findings should lead to improvements in general participatory RCTs and the IC process.

2) It is not clear, how many participants were used to evaluate the Japanese translation of the QuIC, 21 or seven (page 10).

A pilot test of the questionnaire was performed in 21 participants. In addition to correcting this number, we have added details, as advised by the Editor and other reviewers. We have also included statements regarding the method for preparing the Japanese version of the QuIC, the method for translation and the method for including participants in the pilot test of the questionnaire. We have also added statistical values regarding the reproducibility and internal consistency from page 9 last paragraph to page10 the 1st paragraph. Please see also Handling editor’s point 2.

3) Questionnaires to collect data on patient characteristics and patient impressions of the consent process were presumably purpose-designed and have not been validated or tested for reliability – it would be helpful if this is made explicit (p10).

We carried out a pilot study of a questionnaire that included the questions relating to the explanatory materials and IC, as well as the Japanese version of QuIC. That pilot study was conducted in 21 volunteers who also participated in the J-START. The details are presented in our reply to question 2, from page 9 last paragraph to page 10 the 1st paragraph. Please see also Handling editor’s points 2.

4) Objective understanding of the QuIC Part A score p12 and Table 2: I was not clear why the authors did not highlight the relatively poor understanding of ‘A9 Benefits to self’ as this was only 1.6% higher than score for A13 and why this question was left out of the analysis shown in Table 5. ‘Therapeutic misconception’ arises frequently during the process of taking informed
consent for trial participation (e.g. see Flory & Emmanuel 2004).

Thank you for this comment. We have added analysis including with regard to the ‘A9 Benefits to self’ item, and we have modified the entire text. We added the result for ‘A9 Benefits to self’ to the explanation regarding the QuIC Part A items with a low score in Table 2 in the Results. In that connection, we analysed factors associated with the QuIC Part A items with a low score in Table 5, and added a presentation of the results with addition of ‘A9 Benefits to self’ to the original 3 items. We also stated the results in the Discussion. Please see Reviewer 1; Points 4.

P12, 2nd paragraph, line 4

“…Specifically, there were accuracy rates of 14.6% for Question A4 on the “Experimental nature of study,” 14.1% for Question A8 on “Potential risks or discomforts,” 34.6% for Question A9 on “Benefit to self,” and 33.0% for Question A13 on “Compensation”.

P17, 3rd paragraph, line 8

“…This demonstrates that the explanatory materials were perceived to be sufficiently easy to understand. Table 5 indicates that prior knowledge influenced “Experimental nature of the study,” but prior knowledge had not always been given by our leaflet, and the educational video did not help correct misconceptions. …”

5) Page 13 states that ‘92% reported that their understanding had been confirmed by the research coordinator at the end of the oral description during the IC process’. I’m not clear what is meant by ‘confirm’ here. Does it mean the researcher asked the participant if they had understood. Are the authors assuming that if a patient answers ‘yes’ (or fails to ask further questions at this point) that they do understand? The authors’ own findings in this paper indicate differences between participants’ subjective (perceived) and objective (actual) understanding, so the latter assumption would not be supported by the evidence.

Dr. Julia Wade brought to our attention the manuscript of Flory J, Emanuel E: Interventions to improve research participants’ understanding in informed consent for research: a systematic review. JAMA 2004, 292(13):1593-1601. Our use of ‘confirm’ can be said to mean the process that was the impetus for the ‘extended discussion’ that those authors recommended in order to improve understanding. However, for our study, we unfortunately did not investigate whether a question was asked immediately after confirmation, whether that was confused with the question item ‘whether there was a chance to ask a question’, what the content of the question was, or whether the participant was convinced by answers. With regard to a possible gap between subjective and objective understanding, we have stated in the discussion that this is an issue that warrants further study.

P13, 2nd paragraph, line 5 from bottom

“…It would be expected that, at the time of that interaction, the research coordinator
would become cognizant of the participant’s questions and points of confusion, but we do not know what sort of communication took place later in this study.”

P15, line13

” …The results of the present study revealed a tendency for the degree of subjective understanding to be higher than the degree of objective understanding, which is similar to the findings of earlier studies. The higher degree of subjective understanding can be thought to be related to the ease of understanding the IC and/or a feeling of satisfaction with the amount of information, but the reason of discrepancy with the degree of objective understanding warrants further study.”

6) Page 13 Findings highlighted in the text p13 reflect data in Table 5 however, the text needs rewording to make the message clearer, e.g. the association is between responses to questions and evaluations made by the patient about information provision.

Please see also Reviewer 1; Point 4, P14, line4

We had the revision performed by a native English speaker so that it would be concise. We investigated the addition of ‘A9. Benefit to self’ to Table 5 as an item that was not adequately understood.

7) NOTE As a qualitative researcher I do not feel qualified to judge the statistical analysis. The statistics used, as far as I am aware, are suitable.

Thank you.

8) The discussion would benefit from being more concise. Findings reiterate previous findings that are already relatively well established in the literature (p15) so are not novel and fail to reference a key systematic review (Flory & Emmanuel 2004) which in common with Nishimura et al. 2013 found that extended discussion was the optimum method of improving understanding in informed consent for research - perhaps a reason why differences were found here between study centres?

As recommended, we have unified our modifications to the materials with the results in the papers of Flory et al. and Nishimura et al., and made the discussion more concise by deleting sentences that we decided were unnecessary. Also, with regard to the differences in the results for understanding among the medical centres, we do not have information regarding the time that was required, the contents of extended explanation, etc. For that reason, we were unable to investigate what the causes of those differences might have been.

P18, line2

”… Other studies have indicated that a simplified IC form with emphasis added by verbal
description [26], and user testing, which examines not only the wording of leaflets, but also the layout and paper thickness, in order to design interesting materials for participants to read, leads to improved explanatory materials and better understanding [27]. However, in systematic reviews of understanding of RCTs [28] and of trials and ICs [29], it was reported that multimedia informational materials were not as effective for improving participants’ understanding as test-feedback quizzes or discussion of the IC process [28,29]. The result of our survey corroborated the systematic reviews. Improving face-to-face communication would foster better understanding than improving written materials.”

P18, 3rd paragraph, line1

“Regarding the third possible reason for participants’ misunderstanding of IC, there were, unfortunately, significant gaps or inconsistencies between the IC information-providing procedures of the different medical centres (Table 5). Regrettably, we did not have the data on how IC was obtained from each of the participants. For the standardized information dissemination process in the J-START, the manual included specific procedures concerning IC and the use of materials, and held several training sessions for the research coordinators, who had previous experience working at a medical centre (e.g., nurses and public health nurses). To avoid misconceptions arising from verbal communication, explanatory materials were also integrated into the IC process. Despite this, the materials were reported by a certain number of participants as unsure about them. However, we did not have the IC process data, it was not clear that the process was lost or the participants did not read or watched. Given that explanatory materials are reported to improve participants’ understanding [8], the differences in understanding observed in the present study might be attributable to insufficient use of the materials. A previous systematic review reported that having a long discussion time with a team member and a neutral educator was effective for participants’ understanding, and it worked even over the telephone [29]. These discussions would make sure team members the IC process or better ways of communicate with participants. In J-START, this type of discussion was not programmed officially. If we could have had the opportunity to include such a discussion, IC and accompanying materials might have been delivered more effectively. In order to more effectively perform the IC process, we must create opportunities for the team members to have frequent discussions with the educator, with the topic of discussion to include better information-providing procedures.”

9) Discussion p16 – whilst it is interesting to consider how these findings may arise in this particular context, it would be even more interesting to reflect on why these same failures of understanding arise across very differing trials.
We agree that the question you pose is deeply intriguing. We can suggest that our lack of understanding regarding the scientific natures of trials and the disadvantages caused by that nature might also be a manifestation of the inadequacy of scientific education and/or confidence in health care workers. However, the data from our present study are insufficient for enabling discussion of whether or not that is actually the case.

10) The authors suggest that insufficient or variable use of information materials across study centres may explain observed differences in understanding between centres, but there seems to be no presentation of data as to whether such variation occurred between centres (p18).

We considered whether we could present pertinent data, as you suggest. However, with regard to handling of the documents, we think that this was performed in compliance with the manual. Actually, we have not compiled information regarding the handling methods at individual centres. For these reasons, we are unable to make any statements regarding the basis for the differences among the centres. Although the materials were distributed according to the manual at each centre, the participants were free to do as they liked, and we suspect the possibility that not all of them looked at or read them.

11) Moreover current evidence suggests that face to face discussion is one of the best methods of optimising quality of understanding in informed consent (Flory and Emmanuel 2004, Nishimara et al. 2013). The literature suggests that the key to improving quality of understanding lies in the interaction between recruiter and patient rather than in adjusting content or presentation of patient written or video information. The authors might like to comment on the limitations of a purely quantitative investigation as presented here and consider mixed methods approaches to future research which includes qualitative investigation of what is said during informed consent discussions.

Yes, as you point out, those two systematic reviews indicated that good understanding is promoted by a multi-pronged approach of using a research coordinator, educational materials and discussion, with prolongation of the face-to-face discussion between the research coordinator and the prospective participant. As suggested, in page18, line 2, and page19, line6, we have added a comment that, although we were unable to apply this multi-pronged approach in our RCT.

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

Following our revisions and additions to the manuscript, we have had it checked by a native English speaker.