Author’s response to reviews

Title: Identifying important barriers to recruitment of patients in randomised clinical studies using a questionnaire for study personnel

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Identifying important barriers to recruitment of patients in randomised clinical studies using a questionnaire for study personnel
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Answer to the Editor and Reviewers: Manuscript Rev 1. Date 05 Aug 2019

Dear Editor

We thank the Editor and the Reviewers for their careful reading and their constructive suggestion to our manuscript. We have taken the comments on board to improve and clarify the manuscript. Please find our responses to the Editorial and Reviewers’ comments below (in italics, with changes to the manuscript in bold/underlined, we could not to bolded and underlined text here but you will find it in the manuscript). To answer the reviewers, we have taken the liberty to number some of the questions.

Reviewer reports:

Reviewer #1: General
The barriers and facilitators to recruitment in trials is certainly an important element for consideration and investigation, however I feel that your use of limited and dated evidence to support your study e.g. difficulties with recruitment, work assessing barriers and facilitators to recruitment, does not accurately reflect the current status, and work previously conducted. I suggest it would be useful to review the full literature in relation to this, and to make clear how your work differs from, and adds to previous studies...
or reports.
Throughout the discussion you make some valid points with regards barriers, their impacts and potential importance for consideration, but you fail to explain why they are important or a key issue. You also appear to note elements as important which I struggled to find in your results. It may be these are there but are inconsistently labelled or equally it may be worth revisiting this section to provide supporting evidence from your results.
The manuscript would also benefit from a full proof read to ensure tense is appropriate and consistent, typo's corrected where required, and % values provided consistently.

Answer:
Thank you. We have added the following in the Introduction: The study subjects consent to participate in a trial to help answer an important health question when, in fact, the question is not answered due to insufficient power.

We added one sentence and two references [10, 11] in the Introduction: Workshop and in-depth interview studies have investigated barriers to and opportunities for recruitment in clinical studies and found that it is still a challenge; new recruitment interventions are needed.

We added one sentence and one reference in the Discussion: These factors were also found in a similar study, a survey to a pediatric trial in acute setting by Kaur et al [25].

In Table 1. Baseline characteristics of the participants we changed the word Rehabilitation centre to Neurorehabilitation unit.

We have corrected to % instead of per cent in all tables and for N (numbers) we changed to n in the tables and in the text in the manuscript.

Specific Methods
1. You note work completed previously by Kaur et al. Was this used in any way to form the basis of your survey? If so what was similar/different, if not why not?
2. Construction of Questionnaire; Page 5: It was difficult to follow what 5 free response alternatives were, and how these were changed. Some clarity here would help the reader.
3. Main Phase: You note mailing to 148 staff. Did this include those who had previously participated in your pilot? You note 'additional 10 reminders' how were these sent?

Answers to Reviewer #1

1. Although we carried out a literature search before the construction of the questionnaire, we were not aware of Kaur et al before we created the questionnaire. We did an additional search when we wrote our manuscript and found the reference and noted that Kaur et al and our ideas of what is important in the construction of a questionnaire are in overall agreement.
2. By using free-response questions we wanted the participants to respond in their own words to tell us what they think. We realised that it was difficult to come up with five alternatives so therefore we changed the option to two.

Changes in the manuscript (Methods):
it appeared to be difficult for the participants to formulate 5 free-response alternatives indicating significant barriers and factors important for inclusion, so we reduced the number of alternatives to 2.

Yes, the 148 persons included had previously participated in the pilot. So, it was largely the same group of people with the addition of a few who became active in the study after the pilot phase and a removal of a few since they stopped working in the study before the final version of the questionnaire was sent out.
We have clarified this in the manuscript (Methods):

The questionnaire was sent electronically by SurveyMonkey [16] to all physicians and nurses who were active, listed in the delegation log at the time (n=136) in Efficacy of Fluoxetine – a randomised Controlled Trial in Stroke (EFFECTS) [17], an ongoing RCT in Sweden.

3. We sent the questionnaire both for the pilot study and the final survey to all staff who were on our delegation list in the EFFECTS study at the time.
The additional 10 reminders were sent only to those who did not respond to the questionnaire by email using the SurveyMonkey system.

Results
1. Table1: Were the experience definitions included in the questionnaire or applied later?

Answer:
The experience definitions were included in the questionnaire. The respondents answered what their experiences were based on given options.

2. To Succeed with Inclusions: What is meant by 'involvement in the trial is fun'?

Answer:
Intentionally, we did not specify what fun was. Each participant had to interpret the question based on their experience. As a trialist, participating in many trials, we do believe that it must be fun to do research.

3. To Succeed with Inclusions: You note co-authorship/proposing studies as important. Are these what is meant by 'academic driven' in Table 2? It may help the reader to use consistent terms here.

Answer:
By using the term “academic driven” we mean that the study is initiated, led and conducted by investigators from universities or hospitals, and that no pharmaceutical company is involved in the trial. This has been clarified in the manuscript in the Method section: Academic driven studies are initiated, led and conducted by investigators from universities or hospitals, and no pharmaceutical company is involved in the trial.
With “co-authorship/proposing studies” we refer to both academic and industry-initiated studies. This has been clarified by adding in both academic and industry-initiated studies in the manuscript (Methods).

4. What do you mean by inclusions rate - is this inclusion of a centre as a recruiting site or
conversion of screened patients into recruited participants?

Answer:
Yes, by inclusion rate we mean numbers of screened patients converted into randomised patients for the trial. But mainly it relates to how co-authorship could affect the investigators dedication to the trial and that could increase the numbers of randomised patients.

We clarified by rewording in the manuscript (Results):

Fifty percent agreed that it was relevant in some way to have co-authorship in a scientific article and that it would influence their dedication to the trial.

5. Patient barriers: What do you mean by 'language problems'. As you provide a table for all other results sections it would be good to be consistent and provide one here too.

Answer:
By speech difficulties we included aphasia as well as severe dysarthria. We do believe that speech difficulties are a broader term than just aphasia, and – at least in a Swedish context – not all study personnel can distinguish between aphasia and dysarthria. Hence, we used the term speech difficulties. We clarified this in the manuscript by adding: aphasia/dysarthria and added a table (3) for this section too.

6. Study barriers: You note a study wide website as being an important factor - for what? Offering financial compensations is noted as being important - who is the compensation for, the study team or the patient?

Answer:
A study wide website is of importance to provide information about the study, provide with essential documents and give access to study specific tools such as the randomisation system or other databases of importance for the study. A study website can also be a good place to draw attention to people who have made a good effort in the study.

The financial compensation that we meant was for the study team and it can be used at the clinic for education/training, congresses and similar things. In EFFECTS, no economic compensation was given to the patients or next of kin.

Discussion
1. You mention work by Donovan et al here, I suggest it would be useful to include this in the introduction too.

Answer:
We included a sentence and a reference in the Introduction about this: It is considered important that already in the early phase of planning a study try to predict which problems that will arise when it comes to recruitment of patients [7].

2. You note that problems should be addressed as they arise. Is it not important to also consider potential problems, as you have described in your paper, from the outset?
Answer:
Yes, it is very important to consider potential problems when you are planning a study. We have rephrased the text in the manuscript (Discussion) as follows:

When planning a study, it is important to understand what the recruitment difficulties can be and then address the problems as they arise, irrespective of whether the problem arise early or late in the study.

3. You note that the findings could be generalised outside of stroke trials, which elements could be, are there bits which don't generalise?
4. Your strengths and limitations sections would benefit from some further clarity as to why the points you note are strengths or what the impact was if a limitation, and whether these were mitigated in any way.

Answer:
We do believe that many things are similar between studies: A relevant research question, a simple protocol and that it is easy to implement the study in the daily clinical routine. Conversely, stroke affects the brain and entails specific problems such as aphasia and fatigue. Another disease, e.g. terminal pancreatic cancer, has its own recruitment problems that our survey certainly does not cover. The questionnaire, however, is tested on a stroke population and therefore we do not want to draw too far-reaching conclusions.
In the Discussion we have added: We believe a relevant research question, a simple protocol and that it is easy to implement research in the daily clinical routine applies for all studies. Conversely stroke affects the brain and entails specific problems such as aphasia and fatigue. Another disease, e.g. terminal pancreatic cancer, has its own recruitment problems that our survey certainly does not cover.

We have also added one sentence and a reference in the limitation section: Further, if we had combined a mixed model design we would probably have gained deeper knowledge [33].

Reviewer #2: Congratulations to the authors, this is an interesting article and it is could to see this type of research written for publication. Overall the message in the paper is clear and with some minor revisions will be ready to go. the research team should be commended for such a high update of study personnel completing the WIMSS-q.

Answer:
Thank you!

Abstract - no issues

Trial registration (page 3) - pleased to see that this SWAT is registered on the SWAT repository

Introduction - (Page 3) line 40/41 consider the use of 'WILL' prolong the trial - would this be applicable in all cases? Perhaps could be replaced with MAY

Answer:
Thank you, we have replaced the word WILL with may as you suggested
Introduction - (Page 3) line 55 - The authors mention the previous work by Kaur et al and I was left looking for some justification as to how this research is different or similar. Perhaps another paragraph with this information.

Answer:
Although we carried out a literature search before the construction of the questionnaire, we were not aware of Kaur et al before we created the questionnaire. We did an additional search when we wrote our manuscript and found the reference and noted that Kaur et al and our ideas of what is important in the construction of a questionnaire are in overall agreement.

Methods - (Page 4) line 26 no 's' on the end of systematic

Answer:
We have corrected the spelling, thank you!

the authors should be congratulated on the development of the questionnaire. to make it clearer to the reader I suggest you could give the questionnaires version number - for example the pilot questionnaire could be version 1 and the final questionnaire could be version 2.

Consent - not sure I am clear on the consent process for this questionnaire study?

Answer:
Thank you for asking for clarification of the consent process for the questionnaire. We informed the participant on the first page of the questionnaire as follows:

Participation in the study is, of course, entirely voluntary. Your decision whether or not to participate will not influence our contact with you. If you do not wish to take part, we would appreciate it if you state this in response to the first question. This will prevent you from being sent any reminders.

Then the first question was:
1. Do you agree to respond to this questionnaire and for the responses to be anonymously published at group level?
   • Yes, I accept the conditions
   • No

We added a sentence in the manuscript (Methods) We informed the participant on the first page of the questionnaire that it was voluntary and that their decision would not influence our contact with them, if they said no we did not send any reminders.

I am curious about if the pilot study and the main study used the same group of participants - I can’t find this information in the text.

Answer:
Yes, it was largely the same group of people with the addition of some who became active in the study after the survey in the pilot phase was sent out and some who were removed because they stopped working in the study before the final version of the questionnaire was sent out.

We have clarified this by rewording in the manuscript (Method):
The questionnaire was sent electronically by SurveyMonkey [16] to all physicians and nurses who were active, listed in the delegation log at the time (n=136) in Efficacy of Fluoxetine – a randomised Controlled Trial in Stroke (EFFECTS) [17], an ongoing RCT in Sweden.

Observation - lots of reminders were sent to participants to obtain responses - was this level of reminders detailed in the approvals?

Answer:
No, it was not detailed in the approvals. We sent as many reminders that felt appropriate at the time.

Results - Observation - large sample from Stroke Unit (84%) and classing themselves as very inexperienced in clinical trials (66%). I appreciate that this is identified as a limitation further along the paper.

(Page 12) line 42 - 'Weakly' should be 'Weekly'

Answer:
We have corrected the spelling, thank you!

Discussion - page 13 line 15 - Is it true that all studies would have a dedicated research nurse? This may be true to the host trial that this group of people work in but not all studies

Answer:
No maybe it’s not essential for all studies to have a research nurse but its important to have dedicated people who are willing to work with the study. But you have a point and we agree, it needn’t be a research nurse it could also be a research assistance.

Page 13 line 37 - Donovan et al - how does the research by this team relate to the authors research - make this clearer

Answer:
Donovan et al found it important to try to predict which problems that could arise when it comes to recruitment of patients and to do so in the early phase of planning a study.

This sentence was added to the manuscript (Discussion) With this study we have made it clearer what barriers can be of importance and when writing the protocol and planning the study this can help in predicting what is to be done early in the process.

Page 14 line 14 consider changing the MUST it would be ideal, but this is not always possible

Answer:
In Sweden, each patient must give their consent and must therefore understand the information. In
other countries it can be the physicians that gives consent and then the information of course could be adapted accordingly.
We clarified this in the manuscript (Discussion):

The informed consent process must be comprehensible, which is especially important when it is the patient or the next of kin who make the decision,

Page 14 lines 19 - 26 what are the authors trying to say in this paragraph - I think this needs reworded and the point made clearer

Answer:
We reworded this in the manuscript (Discussion):
The budget for a study, irrespective whether it is academic, or industry driven must be large enough to allow activities such as trial meetings, training in trial-specific topics and participation in congresses. It is important to have a stable budget to achieve this. Also, small things such as shortbread or a cinema voucher can encourage study staff to go the extra mile as well as prioritise time for the study.

Page 14 line 26 What are the several promising methods - the ones already discussed or others - this needs to made clearer

Answer:
We were thinking about the ones already discussed. We made this clearer in the manuscript (Discussion): As an example, the protocol and informed consent process should be simple and the study-related follow up should be coordinated with the clinical follow up. They also highlighted the importance of the availability and encouraging support of the central team in the event of questions.

Page 14 line 41 - 56 - consider rewording this paragraph to make a stronger Point

Answer:
We to believe that many things are similar between studies: A relevant research question, a simple protocol and that it is easy to implement the study in the daily clinical routine. Conversely, stroke affects the brain and entails specific problems such as aphasia and fatigue. Another disease, e.g. terminal pancreatic cancer, has its own recruitment problems that our survey certainly does not cover. The questionnaire, however, is tested on a stroke population and therefore we do not want to draw too far-reaching conclusions.
In the Discussion we have added: We believe a relevant research question, a simple protocol and that it is easy to implement research in the daily clinical routine applies for all studies. Conversely stroke affects the brain and entails specific problems such as aphasia and fatigue. Another disease, e.g. terminal pancreatic cancer, has its own recruitment problems that our survey certainly does not cover.

Good limitations section