Author's response to reviews

Title: Recruitment challenges in clinical research including cancer patients and their caregivers A randomized controlled trial study and lessons learned

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Author's response to reviews: see over
Dear editors in chief; Doug Altman, Curt Furberg and Jeremy Grimshaw, Trials journal

We thank the referees and editors for the constructive and thoughtful criticism, we have considered all the comments, and have changed the manuscript according to these suggestions.

Please find a revised version of our manuscript entitled “Manuscript Recruitment challenges in clinical research. A case study and lessons learned” enclosed. These changes are explained in the manuscript file “Manuscript-changes with tracks”, while the revised manuscript (without “track changes”) is the file “Manuscript-changes with no tracks”. All the changes are marked with yellow in the manuscript, changes with tracks.

We hope that we have addressed all comments satisfactorily and made the manuscript acceptable for publishing.

Thank you again for the review!

Sincerely, on behalf of the authors,

Safora Johansen
Corresponding author

LIST OF CHANGES AND CONSIDERATIONS:

REFEREE #1:

Reviewer: Angela Craigie
Reviewer's report: Major Compulsory Revisions
Minor Essential Revisions

Abstract
It would be useful to have a little more explanation as to the definitions of the two opt-out strategies, which aren’t necessary self-explanatory.
Recruitment methods:
P5 Para 1 – the numbers are quite confusing here. On one hand it is stated that ‘560 eligible patients.. were recruited’, then that the target was 280 patients paired with a caregiver, however the experiences of only 370 of the patients were included. This reads as if more than twice as many as the target were recruited (why?), and that the experiences of only a proportion of these are being reported (why and on what basis were they selected?).

Reply: The text is revised to make it clear, page 5, 1st para: “The recruitment took place mainly at the Department for Cancer Treatment, Section for Radiotherapy, from November 2012 until July 2014. The recruitment target for the study was 280 cancer patients each paired with a caregiver (280), a total of 560 participants. However, this paper describes only recruitment experiences and data related to 370 of the 560 patients and caregiver participants (180 pairs) recruited in February 2013 until July 2014, as the detailed documentation of the remaining respondents (160) were not available.”

P5 line 1 of ‘Recruitment approaches’ – What was the ‘original recruitment strategy’, and have the results for it been included in the results?

Reply: To address this, we have added the following to the manuscript, page 6, last para;”The original recruitment strategy was the researcher, cancer nurses or the radiation technologist to contact the cancer patient and their caregiver at the radiotherapy department where they received their daily radiation treatment and informed about the project or gave them the leaflet. Because of low success with the original recruitment strategy,……”

P7 ‘Recruitment at a rehabilitation centre’ – this seems to have been considered an ‘opt in’ approach whereas, if I interpret the description correctly, you could argue that they may still have ‘opted out’ at this stage – it was just the staff member rather than the researcher that they gave their decision to. This could be picked up in the discussion.

Reply: The participants recruited at the rehabilitation center were contacted by the staff members just as cancer nurses, radiation technologists or the researcher did. Therefore, the challenges and experiences related to this recruitment method was identical to the on-site recruitment as mentioned and discussed in discussion, page 15, 2nd para. Please see discussion, page 15, 2nd para, last line; ”When using on-site recruitment……. The same challenges were observed for recruitment at the rehabilitation center.”
Results

P9 Para 1 – While the figure is much clearer, the wording of this paragraph could be improved. For example, by ‘assessment for study participation’, do you really mean that they were ‘invited to take part and assessed for eligibility’? How was the ‘assessment’ done and what was the eligibility criteria? This would hopefully make the chain of events clearer.

Reply: To make this para more understandable, we have changed it into (page 11);

“As shown in Figure 1, a total of 1562 potential participants were invited to take part and assessed for eligibility using all the described recruitment methods in this study. The eligibility of the contacted candidate could only be assessed after the initial contact by the recruiter. Therefore, three hundred and fifty-three (22.6%) of the contacted candidates showed to be ineligible on initial contact. Of the remaining 1209 potential participants, 885 (84.7% of eligible candidates and 65.6% of all candidates contacted) declined to participate in the study when on-site and user-adapted recruitment methods were employed.”

This was also added to page 7:

“The recruiter used a checklist to assess the eligibility of the candidates. The eligibility criteria were; the cancer patient was ≥ 18 years old, had a caregiver willing to take part in the study, had access to the internet and had both a bank ID.”

P9 Para 2 and Table 1 tend to suggest that just 885 declined to participate whereas I’d suggest that it should be acknowledged that the 139 who accepted orally but did not return consent forms also ‘declined to participate’. It is quite possible that when contacting the researcher for more information, some may feel obliged to say yes, even though they didn’t really want to take part, or that when reading more about the study they changed their minds.

Reply: Table 1 is revised according to the referee’s suggestion. The related text in the whole manuscript and Table text are also changed.

P9/10 Bullet points. To verify the accuracy of the quotes, I’d recommend that the method for how they were ‘documented’ is described in the methods – did they complete a form or were the comments given verbally (and recorded / transcribed)?

Reply: To take this comment into consideration, the following is now added to the Method at page 7;
“Documentation of the reasons for non-participation.

The reasons for non-participation using seven recruitment strategies were given to the researcher orally by the contacted candidates. These reasons were consecutively documented by the researcher and categorized into 8 groups as described earlier.”

Discussion
The discussion does address the impact of illness / treatment stage on the decision of patients to take part, but it would be helpful to know whether all participants were invited at the same stage or varying stages of treatment as this could add some complexity to the interpretation of the results.

Reply: To take this comment into consideration, the following is added to the Methods, 1st paragraph, page 5; “Two hundred and eighty eligible cancer patients receiving curative cancer treatment, each paired with a caregiver, were recruited for a research study at a tertiary university hospital.......”

Willingness of staff to introduce studies can be a challenge, particularly when recruiting patients at a sensitive time. If any feedback from the health care providers was collected it would be interesting to report this.

Reply: Unfortunately, we do not know this, as we did not interview the staff to collect and document data on that regard.

Discretionary Revisions
Abstract
A very minor wording issue, but participants were recruited as dyads so it isn’t clear without reading the paper whether the 1562 were half patients half caregivers, or all patients with another 1562 caregivers on top.

Reply: The following is added to the Methods in the abstract: “We used five opt-in and two opt-out recruitment strategies from February 2013 until July 2014 to contact 1562 cancer patients candidates for participation in research. For each of these cancer patients there was also caregivers.”

Recruitment method
P5 Para 3: Minor wording issue - the first sentence of ‘recruitment approaches’ (referring to low recruitment) initially seems contradictory to the last line of the previous paragraph (which states that the recruitment target was achieved).
Reply: This sentence is changed to: "The full number of participants specified in the study description was achieved."

In the numbered sections, I’d suggest adding ‘opt out’ or ‘opt in’ to the section headings.

Reply: Opt in and opt out is added to the numbered sections in the methods.

Results
The reasons for non-participation in Table 1 are useful, but understandably only refer to those from the two recruitment methods you could collect this data from. Given that there will have been others from the other methods who, for example saw the adverts / flyers but decided not to respond, I wonder whether there is any way in which the number of patients who may have been eligible during this period of time could be estimated. This would give a better reflection of what proportion of the target population who actually volunteered to take part.

Reply: To estimate the number of cancer patients getting to know about our study through adverts/flyers was unfortunately impossible for us. This is now added in the first paragraph page 10. With these methods, it is however, difficult to know how many people actually saw this information.

Referee #2:

Major compulsory revisions
1. Additional data – Do the authors have information about the cost of each recruitment strategy (including the cost of researchers’ time)? The paper would be much more useful if it included cost-effectiveness data (i.e. cost per recruited participant for each recruitment strategy). The yield of each recruitment strategy will depend strongly on resourcing (e.g. the amount of time researchers spent recruiting people on-site), so without this information, I don’t think the recruitment strategies can be meaningfully compared. Inclusion of retention data (i.e. the number/proportion of participants retained for the duration of the trial, by recruitment strategy) would also increase the value of the paper. If participants feel coerced into participating (e.g. for the on-site researcher strategy), recruitment rates may be high but retention rates may be low. Without retention data we do not have a complete picture and cannot confidently recommend opt-out strategies.

Reply: We agree that it would be interesting to have cost-effectiveness data for each recruitment strategy but this was beyond the scope of this study. However, the success rate for each strategy, that is the percentage recruited gives and indicator of effectiveness. The higher the recruitment, the more effective. Except for the online and flyer strategies all strategies required considerable researcher time.
The goal of this study is share the experiences and challenges we had during a recruitment which took 1.5 years. Our goal was to inform others about the different recruitment approaches we
employed, how time consuming each approach was and what we learned from it. We believe that sharing this kind of experience with others may smooth the recruitment process and make it easier for others.

The main goal of this study is to describe the employed recruitment approaches, response data and recruitment challenges we experienced. Therefore, we have chosen not to include the retention data. The retention data and some other data are under analysis and is planned to be presented in our another study in near future.

2. Recruitment materials – It would be very helpful if the authors could provide the recruitment materials (newspaper and internet advertisements, flyers, brochures, ‘information-note’, ‘reply-note’, researcher’s recruitment script etc.) that they used as “additional files”. This is because the success of each recruitment strategy may be influenced by the content and quality of these materials.

Reply: Unfortunately, these adverts/flyers and brochures were written in Norwegian.

3. Limitations – The authors should discuss the study limitations. Limitations include the lack of appropriate comparator groups to control for confounding factors and co-interventions (so opt-in strategies cannot be directly compared with opt-out strategies, for example), and the lack of information about the number of people ‘reached’ by each method, because hospital care and rehab providers did not document how many people they gave information to, etc. The authors may find reference 13 (a Cochrane risk of bias tool for non-randomised studies) useful for thinking about the possible biases in this study.

Reply: We agree with the referee and grateful to the referee for suggesting a reference. To take this comment into consideration, we have added a paragraph to the discussion about the limitation of the study: “A limitation for this study can be the lack of appropriate comparator groups to control for confounding factors and co-interventions making the direct comparison of opt-out and opt-in strategies challenging. Another limitation for this study is the lack of information about the number of people reached by each recruitment approach since the total number of contacted candidates were not documented by all the health staff involved in the recruitment. The third limitation for this study is lack of quality assurance and documentation of how the information has been given to the patients by the health staff involved in the recruitment. It is also not possible for the study to describe or include the possible ethical implications; i.e. it is not possible to document what the contacted candidates may have felt, having impact on their choice of participation in the study.”

4. Background - I’m not sure I agree that there is a ‘lack of studies describing the challenges of recruitment in clinical research’. I have come across many, including some systematic reviews (references 6-12 below). It would be helpful if the authors could explain why their study is original/important.
Reply: We have also changed the sentence in page 4 from “lack of studies” into “few studies”. Thank you for the references that are now included in the paper.

5. Please describe in the Methods section how you collected the information presented in Table 2. For example, did you ask all respondents how they found out about the study? If so, why weren’t you able to collect information about the flyers strategy?

Reply: To take this comment into consideration, the following is now added to the Method at page 7:

“Documentation of the reasons for non-participation
The reasons for non-participation of the eligible candidates is documented and presented in this study. The reasons for non-participation were given to the researcher orally by the contacted candidates. These reasons were documented consecutively by the researcher.”

Please also see our reply to the last comment of referee #1.

6. Discussion and lessons learned, 5th paragraph – ‘we highly recommend that the researcher do as much as possible to facilitate participation i.e. have the responsibility for the contact, reminders, etc. This will reduce the burden for participants.’ For me this is too strong a recommendation, given the limitations of the study, the current lack of cost-effectiveness and retention data, and possible ethical implications. Some participants might find the opt-out approach more burdensome because they have less control over how and when they contact the research team, and may feel more pressure to make a potentially difficult decision. Instead, the authors could recommend that further research be done to address some of these issues.

Reply: We agree with the referee and have changed this paragraph, page 18, into:

“Employment of methods to reduce the burden for potential participants is important. However, it is difficult to be sure whether the researcher doing as much as possible to facilitate participation by i.e. having the responsibility for the contact, reminders to facilitate participation, etc will contribute to reduce the burden or not. Therefore, there is a need for further investigation in this area.”

Minor essential revisions
1. Abstract conclusion – I think this should read ‘In this study, opt-out recruitment strategies appeared to be the most effective.’ Given that the recruitment strategies were unique to this study and may work very differently in other contexts, I don’t think conclusions can be drawn about other studies, even within the same clinical topic area.

Reply: The conclusion is changed according to the referee’s comment: “In this study, opt-out recruitment strategies appeared to be the most effective.”
2. Recruitment method, 1st paragraph – ‘...two researchers in 50% positions were in charge of recruitment.’ I don’t know what ‘50% positions’ means – please could you clarify?

Reply: This sentence is changed into: “In total, two researchers dedicated 50% of their full time position (FTP) to recruitment.”

3. Recruitment method, 2nd paragraph – ‘The participants were randomized into four different groups.’ – What were these four different ‘treatments’? I think this is important contextual information because it could affect recruitment rates.

Reply: We have added the following to this paragraph to take the comment into consideration:
“The participants were randomized into four different groups based on access to a specific intervention (access to a web based support system); i) only cancer patients received intervention, ii) Only caregivers received intervention, iii) Both cancer patients and their caregivers received interventions, and iv) none of cancer patients or caregivers received intervention.”

4. Recruitment approaches, 1st paragraph – ‘An opt-out technique means that potential participants have the option to decline being contacted about a study...’ Do you mean decline being contacted directly by researchers? Presumably if they were contacted/approached by their clinician on behalf of the researchers this wouldn’t count as ‘opt-out’?

Reply: We mean opt-out when the potential participant decline being approached by research team and other health staff contributing to recruitment. This is added to the manuscript, page 6; “An opt-out technique means that potential participants have the option to decline being contacted about a study [9] by the research team and other health staff contributing to recruitment, i.e. they could opt out.”

5. Recruitment approaches, 1st paragraph – ‘The reasons for declining were grouped into seven categories...’ Were these categories determined before or after the data were collected? How were they decided and by whom?

Reply: The following is added to the method section page 7: “Documentation of the reasons for non-participation
The reasons for non-participation using seven recruitment strategies were given to the researcher orally by the contacted candidates. These reasons were consecutively documented by the researcher and categorized into 8 groups as described earlier.”

6. Recruitment approach (2) – ‘Cancer patients were provided with information from hospital staff about the Connect study by flyer/brochure/reply note...’ – did they give all 3 of these to the patients simultaneously, or did they choose one and how?
The hospital staff gave the patients a brochure and reply note when patients meet at the hospital for their daily treatment. The flyers and brochure were also available in the waiting rooms at the hospital. This sentence is now added to the manuscript page 8, first para.

7. Recruitment approach (2) - ‘The study recruitment team was contacted by the interested cancer patients or their caregiver or through the hospital staff asking for more information...’ This is unclear – did the patients ask the hospital staff to ask the researchers for more information? Or did the researchers contact the patients directly with permission from the hospital staff?

Reply: “The study recruitment team was contacted by the interested cancer patients or their caregiver or through the hospital staff by asking to be contacted by the researcher to get more information .......”. The hospital staff would then refer the patient to the researcher, as explained in the same paragraph line 3.

8. Recruitment approach (3) - ‘Advertising’ – I think it would be helpful to rename this strategy something like ‘Newspaper advertisements’, since other strategies (e.g. internet and social media) are also forms of advertising. What kind of information did the adverts contain?

Reply: The title is changed into “newspaper advertisement”. They informed about the connect study and web based support system, inclusion criteria, and the research team contact information. The latter is added to this para in page 8, 2nd line. “A recruitment newspaper advertisement informing the readers about the study, criteria for participation and research team contact information was inserted in the Saturday edition of....”

9. Recruitment approach (3) & (4) – Potential participants could ‘contact’ the study recruitment team for further information – how were they able to contact the team i.e. what options were they given?

Reply: Please see the added para in page 9 and also our reply to previous comment.

10. Recruitment approach (4) – What kind of information was included in internet and social media adverts? Was it more/less information than in the newspaper adverts?

Reply: This is added to the page 8, 2nd para: “Information about the study, criteria for participation and contact information for the researchers was published on Facebook and Twitter sites of the Norwegian Cancer Society and several user organizations.” The content was the same as in the flyers. Please see also the added para at page 9 and 10.

11. Recruitment approach (5) – ‘Patients and caregivers were informed about the study by the staff members’ – how did this happen i.e. what did the staff members do or give in terms of information? ‘Eligible cancer patients who were positive about participating responded to staff members...’ – again, what happened here i.e. how could they contact staff members?
When cancer patients came to the rehabilitation center before/after their daily radiation treatment or consultation with cancer nurses, they were informed about this study verbally and the possibility of participation. If the patients were interested, the research team was informed about it by the hospital staff or the patient contacted the research team directly (usually by phone) for more and detailed information about the study and participation. The conversation between the researcher and the interested candidate when the information was given verbally to the candidates, took place in a private room at the hospital.

12. Recruitment approach (6) – ‘Flyers’ – There is no mention of what potential participants had to do if they were interested in taking part. Were they given the same instructions as in newspaper and internet adverts? How did the flyer differ from information in the newspaper and internet adverts?

Reply: The content of the flyers was as the same as the newspapers. The following is added to this para: “Flyers/brochures containing information about the study with contact information of research team, were placed in areas that were frequented visited by cancer patients, such as waiting rooms in Norwegian hospitals other than the university hospital and at the Norwegian Cancer Society offices throughout the country. Information was also presented on an interactive screen at the Department of Cancer Treatment. The flyers contained the same information as the brochure and advertisements.” Interested patients and candidates could ask the hospital staff to be contacted by the research team or they could phone the research team directly.

13. Recruitment approach (7) – ‘User-adapted recruitment strategy’ – I think this is a confusing term as it sounds to me as if service users were involved in designing the recruitment strategy. Could you call it something else that distinguishes it from the other strategies? (e.g. “opt-out with routine care letters”?) Also, please report when this strategy was being used – was it at the same time as on-site researcher recruitment? If so, how did the research team avoid duplicate invitations?

Reply: The name is changed and the following is added to page 10: “7) OPT OUT WITH ROUTINE CARE LETTERS (USER ADAPTED)

This strategy was employed at the same time as on-site researcher recruitment was going on. To avoid recruitment duplication, an existing updated recruitment list filled out by the on-site recruitment researcher was checked out before contacting the potential participants in the opt out with routine letters strategy.”

14. Recruitment approach (7) – ‘The patients who did not opt out were contacted a few days later by the researchers.’ – How? By telephone?

Reply: Yes. This is added to the same para, page 10: “The patients who did not opt out were contacted by telephone a few days later by the researchers.”
15. Figure 1 – I think this figure would be easier to understand if the main downward flow showed people remaining at each stage (i.e. Total number contacted □ Eligible on initial contact □ accepted orally □ Randomised into study), with arrows to the right indicating drop-out at each stage (i.e. Ineligible on initial contact, Refused on initial contact, and Did not return consent forms). Also, do the numbers indicate number of people or number of dyads? – please clarify and use the same unit (people/dyads) throughout.

Reply: This figure is revised (please see the revised Figure 1 in the manuscript).

16. Results and insights, 3rd paragraph – ‘The collected reasons for not fulfilling the enrolment are categorized into four items’ – How many and what percentage of people did each item apply to?

Reply: The percentage of people are mentioned in the same paragraph at the end of each category and the numbers are now shown in Table 1.

17. Table 1 – Please include percentages alongside all absolute numbers.

Reply: The percentage are included in Table 1 - Please see Table 1

18. Table 2 and throughout paper – I don’t think ‘response rate’ is an appropriate descriptor of these data (although it currently appears throughout the paper) because for most of the strategies there is no denominator; it is simply the ‘response’ or ‘number of respondents/dyads’.

Reply: The Table and text is changed according to this suggestion.

19. Recruitment method, 1st paragraph - ‘...this paper describes only recruitment experiences and data related to 370 of the 560 included participants...' However, Table 2 shows 186 ‘enrolled into the study’ - I assume this is because Table 2 shows the number of dyads rather than the number of individuals? If so please make this clear.

Reply: Table text #2 is changed into; " Number of respondents (dyads) of each ....."

And the following changes are also performed:
The recruitment took place mainly at the Department for Cancer Treatment, Section for Radiotherapy, from November 2012 until July 2014. The recruitment target for the study was 280 cancer patients each paired with a caregiver (280), a total of 560 participants. However, this paper describes only recruitment experiences and data related to 370 of the 560 patients and caregiver participants (180 pairs) recruited in February 2013 until July 2014, as the detailed documentation of the remained respondents (160) were not available. In total, two researchers dedicated 50% of their full time position (FTP) to recruitment. One of these researchers was also in charge of registration of the participants and other relevant paperwork during the recruitment process.

20. Table 2 - Why did only 373 radiotherapy patients receive the information via letter, but 1181 were approached by researchers? Did the administrative staff fail to send the information to some patients? Or was the ‘user-adapted strategy’ only employed for a short time? It would help to see approximate dates for each strategy.

Reply: The user adapted strategy was used in only 6 months of the approximately 2 years recruitment period. The on-site recruitment strategy was documented in only 10 months of the 2 years recruitment time. Please also see our reply to the comment # 19. This is now specified in the manuscript page 7, 1st para.

21. Table 3 – ‘Trust between patient and researcher’ – I don’t understand this. Was the researcher already known and trusted by the patients? If not, why would the patients ‘trust’ the researcher?

Reply: We mean that the relationship of trust between patient and the researcher can also be established through the long conversation they have when the study information is giving to the patient.

22. Table 3 - ‘High cost’ of advertising in newspaper – Was this strategy really more expensive than on-site researcher recruitment? (assuming the researcher’s time was expensive) If you are going to list ‘cost’ or ‘cost-effectiveness’ as a pro or con, then comparative cost data should be provided.

Reply: We agree with the referee and remove the statement about cost from Table 3, as we do not have exact cost data for the other recruitment strategies.

23. Table 3 - What is the evidence that internet and social media was a ‘cost-effective’ strategy, especially given that it only yielded 6 participants? The amount of researcher time spent identifying and using appropriate internet platforms should be taken into account.

Reply: We agree with the referee and remove the statement from Table 3.
24. Table 3 - The internet and social media and rehab center strategies were ‘less effort for the researcher’ – wouldn’t this apply to the other opt-in strategies too?

Reply: We agree with the referee and have added this benefit to other opt-in strategy in the same table.

25. Discussion and lessons learned, 2nd paragraph - ‘Advertising on the internet was much more cost-effective’ – please provide data in the paper to support this.

Reply: The cost of advertisement is already mentioned in the same para. The cost of advertising on the internet is added: “Our data indicate that the opt-in strategy with advertisement in newspaper gave a very low yield of enrolled patients in relation to the money resources used. Advertising in two newspapers yielded 10 enrolled participants, at a cost of approximately USD 1000. However, those who actually contacted the researcher team due to the advertisement showed more interest in participating: 10 out of 13 candidates (77%) completed the enrollment, representing the highest number of enrollments among the recruitment approaches used in this study. Advertising on the internet (free of charge) was much more cost-effective, with greater potential for information reaching the target individuals.”

26. Results and insights, 4th paragraph - ‘The response rates for the approaches are not comparable due to differences in prioritized resources and time’ – please could you explain this further? What differences? For me this lack of comparability is one of the main limitations of the study and should be moved to the Discussion section. If it is possible to calculate the cost (including staff time) and therefore cost-effectiveness of each strategy, this would make them more comparable.

Reply: We agree with the referee and remove this sentence from the “Results and insights” and the manuscript. We also added the following to the limitation para in discussion page …:” A limitation for this study can be the lack of appropriate comparator groups to control for confounding factors and co-interventions making the direct comparison of opt out and opt in strategies challenging. Another limitation for this study is the lack of information about the number of people reached by each recruitment approach since the total number of contacted candidates were not documented by all the health staff involved in the recruitment. The third limitation for this study is lack of quality assurance and documentation of how the information has been given to the patients by the health staff involved in the recruitment. It is also not possible for the study to describe or include the possible ethical implications; i.e. it is not possible to document what the contacted candidates may have felt, having impact on their choice of participation in the study.”

27. Discussion and lessons learned, 4th paragraph – ‘…only 6.7% were enrolled into the study and it was therefore not a cost-effective approach.’ Again, this would be much more convincing with some cost figures/comparison.
Reply: We agree with the referee and added the following to the Methods section page 7: “It is estimated approximately 540 and 140 hours spent when using on-site and user-adapted methods, respectively.”

28. Discussion and lessons learned, 4th paragraph – ‘...in addition to introducing bias.’ I am not sure what kind of bias you mean – please clarify.

Reply: This statement is changed to sampling bias, where subjects are not representative of the study population.

29. Discussion and lessons learned, 4th paragraph – ‘the user adapted approach caused no disturbance for the candidates’ – what do you mean by ‘no disturbance’ and how do you know?

Reply: We agree, we do not know whether the patients experienced being asked about participation in the study before / after daily treatment as disturbance. Therefore, we change this sentence in page 16 from “the user-adapted approach caused no disturbance for the candidates,” into “By user-adapted approach, patients were contacted when they were at home by phone in a more relaxed environment and not before or after their daily treatment.”

30. Discussion and lessons learned, 6th paragraph – ‘...which resulted in recruitment of different groups of people and populations’ – please could you provide data to support this statement, or make it a suggestion rather than a statement of fact? If you do have information about the relative characteristics of participants recruited via the different strategies, this would be extremely useful.

31. Discussion and lessons learned, 6th paragraph – ‘...and thus introduced a confounding variable’. I am not sure I understand this – please could you rephrase?
32. Discussion and lessons learned, 6th paragraph – ‘...the sample will represent considerable variability that affects the possibility to detect significant results’. I don’t understand this sentence – what results are you referring to? There was no test of statistical significance so ‘significant’ is a confusing word.
33. Discussion and lessons learned, 6th paragraph – ‘That will reduce the biases of the study.’ Please be more specific – which biases?

Reply: The following is taken out: “In the current study, different approaches were used to recruit patients and their caregiver, which resulted in recruitment of cancer patients receiving their cancer treatment in other hospitals than OUIH, and thus introduced a confounding variable. Because it was not possible to rely on one strategy during the whole recruitment process to achieve a sufficient sample size, the sample will represent considerable variability that affects the possibility to compare the response rate detect significant results. That will reduce the biases of the study. Therefore, it is worth investing in a solid planning phase of the recruitment and conducting a thorough pilot.”
34. Conclusion - ‘...the opt-out recruitment techniques were the most effective recruitment strategies to use in clinical research’ – It would be worth clarifying that by ‘effective’ you mean ‘yielded the highest number of participants’, since this is a very crude measure of effectiveness. Also, as mentioned before I don’t agree that these conclusions can be generalized to all clinical research; please keep the conclusion specific to this study.

Reply: We agree with the referee. This sentence is changed into; “In our study we tested seven different recruitment strategies, and concluded that the opt-out recruitment techniques yielded the highest number of participants in clinical research.”

35. Conclusion - ‘We also found that the stage in the course of the treatment was essential for determining when to approach the potential participants’ – Please could you provide more information about this in the results section?

Reply: We have changed this sentence in the conclusion and added to the result section.: “We experienced and took into account that the stage in the course of the treatment was essential for determining when to approach the potential participants.”

And added this para in discussion page 17-18:

“For example, head and neck cancer patients have much poorer health when they receive radiation treatment compared to prostate cancer patients. For head and neck cancer patients it was best to contact them at the beginning of the radiation treatment when radiation induced side effects have not yet been developed and they are able to talk to us.”

Discretionary revisions

1. Title – It would be helpful to readers if the title indicated the clinical topic area (cancer) and case study design (e.g. randomised controlled trial of a web-based support system?)

Reply: The suggested changes are made; “Recruitment challenges in clinical research including cancer patients and their caregivers” A randomized controlled trial study and lessons learned

2. Recruitment approach (4) – Could you name the ‘several user organizations’ and ‘Health blogs’? (the blogs could be given as references).

Reply: Norwegian Cancer Society and sister society for Norwegian Cancer Society. We have removed several user organizations and Health blogs from the manuscript.

3. Table 2 - It is good to see the number of people approached/contacted for the opt-out strategies, and it would be interesting to see what proportion of the total number of eligible patients were
approached/contacted for each of these two strategies, if the authors have this information? A low proportion would suggest possible selection bias at this early stage in the recruitment process.

Reply: It is not possible for us to include this data in the study as the numbers were not documented by all the health staff included in the recruitment process. This is one of the limitation of our study as mentioned in the discussion, last para.

4. Table 3 - ‘No information about how many read the information’ in newspapers – but could you estimate this based on knowledge about readership?

Reply: We put the ad in the most popular national newspapers, but the number of readers in that time is not available for us. Although we could have provided this figure, it would still be difficult to know for sure how many have read the advertisement.

5. Table 3 - ‘User-adapted strategy’ – should pros include ‘Possible to document reasons for non-participation’ and cons include ‘time consuming’ (compared to the opt-in strategies)?

Reply: Table 3 is revised according to the referee’s comment (please see the revised Table 3).

6. Discussion and lessons learned, 4th paragraph – ‘The latter can be easily solved by sending the information in a separate letter.’ But the burden would then be radiotherapy staff to do this, so maybe not such an easy solution...?

Reply: It is a routine to send a letter containing the radiation treatment appointment to each cancer patient prior to treatment start. The only extra burden will be to also put this letter about the study in the same convolute. Radiotherapy personnel did not experience this task as an extra burden.

Referee # 3

Reviewer’s report
Title: Recruitment challenges in clinical research. A case study and lessons learned.
Version: 3
Date: 29 May 2015
Reviewer: Adwoa Hughes-Morley
Reviewer's report:
The authors report the outcome of recruitment for their clinical trial of a web support tool for people diagnosed with cancer and their carers. In terms of strengths, this paper focuses on an under-researched area, and the subject matter is interesting. This paper has the potential to add to the literature. It is useful to have a clearly documented response rate of each recruitment strategy tested in the case study, and for the authors to summarize the pros and cons of each recruitment strategy. However there are some weaknesses within this manuscript that in my opinion need addressing before it can be accepted for publication.

Case studies of recruitment experiences in cancer clinical research are not new [1-5]. The authors could have gone further to generate additional, important insights which would benefit the wider literature and those conducting similar studies in future.

Reply: We have now expanded our review of earlier studies and added more references in the manuscript.

The authors write that advertising in two newspapers cost approximately $1000, and that advertising on the internet was much more cost-effective. More detail would be useful:
- What were the relative costs of the various recruitment efforts?
- How much time resource was spent on each of the recruitment interventions?
- How much did the recruitment interventions cost per recruited participant?

Reply: This issue was also addressed by reviewer # 2. Please see our reply to the comment # 27 – referee # 2 and in the manuscript. As stated there, we do unfortunately not have data on cost per recruited participant.

The authors conclude that opt out recruitment strategies are the most effective, yet this contrasts with their own admission that “response rates for the approaches are not comparable due to differences in prioritized resources and time”. A clear economic assessment of the resource commitments of each of the strategies used would be useful, and certainly make the conclusions more meaningful.

Reply: This comment was also mentioned by the referee #2, please see our response to comment # 26 and 30-33 – referee # 2. We have revised this paragraph and changed the sentence to “the opt out recruitment strategies” resulted in a larger proportion of participants.

It is important to show reasons why people declined to participate. However, it is
perhaps more important to show whether or not decliners differed significantly from those enrolled into the study in demographic and disease related variables, to demonstrate the representatives of the final study sample.

Reply: We are unfortunately unable to connect the decline response to the disease for each contacted candidate. Our ethical review committee does not permit us to collect data on people that decline.

The McDonald and Colleagues reference is out of date and should be updated. The same study group have published an updated paper, which found that recruitment rates into clinical trials are improving, with 55% of trials meeting their original recruitment target[6]; however much remains to be done to improve recruitment into clinical trials.

Reply: The reference is updated. Please see the reference list and background in the manuscript.

More detail about the clinical research would also be useful, such as what were the four groups that participants were randomised into? The intervention arms could have had an impact on the patients and carers decisions to participate.

Reply: The reply to this comment is added to the manuscript, page 5, second para (please also see the reply to the comment # 3 - Referee # 2).

On a minor note, I think the authors need to identify early in the manuscript that the study is a randomised controlled trial (as opposed to a clinical research observational study). There are issues which are different to recruiting into observational studies as opposed to RCTs.

Reply: This is now reflected in the title, abstract and throughout the manuscript.