Author’s response to reviews

Title: Patient advocate involvement in the design and conduct of breast cancer clinical trials requiring the collection of multiple biopsies

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Author’s response to reviews:

Reviewer #1: I found this to be an interesting paper, clearly written, well structured and detailed.

The background, history and rationale for the increasing need to obtain multiple biopsies from breast cancer patients is well described and justified in this generally well written paper - as might be expected from this experienced authorship. However, as the title so clearly emphasises, this commentary is about the active involvement of patients in the work described. I therefore felt it was a pity that a better history of relevant involvement, especially with respect to the effect that such involvement has both on the attitude of Ethics Committees and prospective
participants, was not so thoroughly indicated. Active involvement of patients and citizens - especially in breast cancer trials - is not new: this particularly difficult requirement of explaining the rationale for a difficult `ask` of prospective participants might have benefited from also providing more of a history so that any reader might appreciate the solid foundation there is for this type of collaboration leading to a better chance of successful recruitment and more acceptable trial propositions. [1] [2] At the same time, it is important that successful recruitment itself is not seen as the aim, since this could constitute manipulation for an objective other than the ultimate benefit of breast cancer patients. This criticism was highlighted and considered within the working group for an early research project in 1995/96: 'Using a Consumers' Advisory Group to increase accrual into trials' project (NCP/D18) see website report and (late) publication. [3]

The design and implementation of a randomised controlled trial for thrombolysis for acute ischaemic stroke around the year 2000 benefitted considerably on the input of patients, in various ways, as reported by Liedeke Koops and Richard Lindley in the BMJ in 2002. [4] Of especial interest was the acceptance by the Ethics Committee in passing this trial having appreciated the wide input of patients and carers into its design, especially in connection with the difficult decision-making for prospective participants in challenging circumstances.

Patient and citizen involvement in trial design and execution is continually evolving as medical developments occur. I believe it to be important to show that each new building block is placed on was has gone before so that readers can appreciate this history and evolution - that it is not a new phenomena but is growing, changing and responsive to demands and needs. [5]

References regarding importance of PPI added. The impact of PPI on the issues surrounding multiple biopsies across our trials and how this has progressed is now clearer.

Minor comments:

Line 20: "may not want to offer". Suggest perhaps `be diffident about offering`; `be wary of offering`; `fight shy of`; or `be reluctant to`.

Agree – amended.

Line 31: Grammar - `they are`, not `it is` (plural - `trials`).
Line deleted

Line 54: See comment above about motive. Maybe a small paragraph somewhere in the main paper about the ethics?

Discussion on ethical issues added

Line 58: Suggest insert `active` - i.e. encourage further active patient and participant.

Line deleted

Page 3. Line 8. `promote the acceptability`. I think it is important to mention somewhere in this abstract that acceptance is contingent on the fact that the rationale of the need for extra biopsies will be explained.

Line deleted

Page 4 line 34. `is delivered to individual patients in the future` is ambiguous. Would benefit from re-wording.

Line deleted

Page 5 line 30. `to assist communication with the Research Ethics Committee.` Reference to the thrombolysis/stroke trial [4] could be of benefit here.

Other reference added.

Lines 35-37. `should be provided with detailed information` - important to re-iterate the importance too of emphasising the importance of explaining the rationale/reason for these increased biopsies - as in lines 24-27 of page 6.

Line deleted but the statement regarding explaining the rationale has been added elsewhere

Page 7 - issues around slow recruitment.

It might be useful to refer to the ProtecT trial. [6] Qualitative research was embedded into the ProtecT trial which proved valuable in addressing the issues about clinicians’ reluctance to broach the topic confidently to potential participants. It found that they were inclined to leave the
least popular option until last (active monitoring in this case) because they thought it would be unacceptable. The language they used was also found to be unsatisfactory; for example, men though that `watchful waiting` conveyed the idea that they would just watch while things deteriorate, and the term `active monitoring` was recommended. Use of `10 year survival` was problematic too. Altering the order of presentation of options and training in use of suitable language saw a rise in accrual rates.

We don’t believe that reference to ProtecT would be relevant to this paper.

Page 9 lines 6 & 7.

Could training of clinicians be suggested perhaps?

Added

Line 20: comma required after `biopsies`.

Added

End of line 25: `whose consent to clinical trials` - `whose consent to participating in clinical trials`.

Added

Perhaps mention the benefit of mutual education that this type of working provides - improving communication both ways?

This is now clearer in the discussion about the multiple biopsy forum

REFERENCES;

[2] Oral evidence to the Health Select Committee, House of Commons. March 28th 1995. (Published in Third Report on Breast Cancer Services. HMSO. July 1995 "The House of Commons Health Select Committee in their Report on Breast Cancer Services (HMSO July 1995) endorses the activity of the CAG-CT by stating: "We believe that patient involvement at all stages of a trial, including initial design, is essential, and that initiatives such as the Consumers` Advisory Group for Clinical Trials are to be welcomed". (p.lvi.para 205). They state that patients should be seen as "full and active participants".

[3] Jo Marsden, Jane Bradburn Patient and clinician collaboration in the design of a national randomised breast cancer trial. Health Expectations 2004; 7 (1) 6-17. This describes the CAG-CT research project "Using a consumers` advisory group to increase accrual into trials", funded by the NHS R&D (Cancer) Programme (NCP/D18) in 1995/6, based on a feasibility study which led to the multicentre U.K. Randomised Trial of Hormone Replacement Therapy (HRT) in Women with a History of Early Stage Breast Cancer. ISRCTN 29941643 (See INVOLVE website database.)


http://211.103.242.133:8080/ziyuan/CDDPdf/evd/200801/British%20Medical%20Journal/%E9%9A%8F%E6%9C%BA%E5%AF%B9%E7%85%A7%E8%AF%95%E9%AA%8C/bmj200232508415.pdf

"Consumer involvement can be a very important part of the development of new randomised controlled trials"

"The ideas of Hazel Thornton, Michael Baum, and Iain Chalmers prompted this research."

health economic analyses of a cluster randomised trial of professional skill development. Report to the `Health in Partnership` programme, UK Department of Health.]


Reviewer #2: This paper has the potential to be of considerable value to researchers who conduct clinical studies where the clinicians who treat potential participants may be concerned about the burden the studies may place on the participants. However, as it is currently written that message is not as clear as it could be nor is the particular approach that the authors took to address the issues. This is partly because the aspects of the involvement of the patient advocates that could be applied to other studies have not been described and highlighted in a way that would make that easy to do. It is also partly because the language in the paper is not very Plain English at all: there are some very long and unwieldy sentences. Also many abbreviated terms (jargon in other words) have been used which may not be familiar to all readers of this journal, especially those who are patients or members of the public. And the text jumps about from paragraph to paragraph in places making the thread of the story hard to follow.

The whole paper has been restructured and reworded taking these comments into consideration. Complicated terminology and abbreviations have been removed or explained.

The paper is so focused on the specifics of the studies that the authors have conducted that it does not bring out the key messages for other readers. In other words it is essentially talking to people who design and conduct clinical trials in breast cancer rather than to everyone who designs and conducts clinical studies and in particular to those who studies may be hard to recruit to because of the nature of what is proposed to be done to the participants. The readership of this
journal will want to see what the authors did that was new or innovative in working with patient advocates and the difference it made with a view to being able to use a similar approach themselves or promote it to others. As written the paper does not support this, but it could.

The whole paper has been restructured and reworded taking these comments into consideration. We hope our work with patient advocates and how this is benefited our research is now clearer.

I am keen to see the good work done by the authors in involving patient advocates reported in the journal and the approaches that other research teams could use shared. With this in mind I have made detailed comments and suggestions below, which I hope the authors will find helpful and accept as being constructive.

I found it hard to follow a clear thread or story even in the abstract and Plain English summary. It was not clear to me what the authors are presenting as new knowledge in the field. The second to last sentence of the abstract is what the involvement of patients and the public is all about and so is not new. The last sentence covers the essence of the new contribution of this paper but just as an assertion that the involvement is a good thing rather than drawing out something tangible that might attract the interest of other research teams.

The first paragraph of the abstract presents a clear background. The second paragraph gets into the detail of what has been done. However, the second sentence is confusing. I think it would be better to leave out the phrase ".. patient engagement, including Trial Management Group membership," in order to make a clear statement of the outcome of the involvement (acceptability to patients and successful delivery of the trials). And then go on to say what aspects of the involvement worked well in this case and could be used by others (which includes having patient advocates as members of the Trial Management Group and getting patient advocates to talk directly to clinicians and research staff who recruit participants in a number of different ways). Also, membership of a Trial Management Group is not "patient engagement", it is involvement.

This paragraph has been re-worded.

The third paragraph of the abstract carries on with examples of what the patient advocates did but then goes into detail that is not necessary. The example of the specific forum in February
2015 doesn't add anything and the date is meaningless in the context of the abstract. Further in the final sentence of that paragraph the significance of "using the design of trials in set-up as a focus point for discussion" is not clear. Why was that done and how did it help?

The paragraph has been re-worded. Specific reference to the forum has been removed.

In the final paragraph of the abstract, as indicated above, the key message for others to take forward does not really come across clearly (to me). I don't think it helps by starting off talking about membership of the Trial Management Groups because that is just one of many ways patient advocates can be involved. The key point in that sentence is involvement throughout the study (and beyond design and into delivery surely?). Some examples could be given with the paragraph concluding with the specific things that were done in the cases used in the paper for trials that may be hard to recruit to. I think the key thing that has been done, which will be of wider interest, is for the research team to arrange for patient advocates to talk to clinicians and other research staff in the different sites where patients were recruited in order to directly address concerns they may have about recruiting patients to studies that may be seen to present a considerable burden (in this case taking multiple biopsies).

The whole of the abstract has been re-worded to give a clearer message.

The Plain English summary sets out a clearer story than the abstract. However, it is then too general and doesn't say what the particular benefit was of the involvement of the patient advocates that enabled the research team to recruit successfully to their trials. The second to last sentence is very clear but the paper doesn't actually do what it says in terms of presenting what the ICR-CTSU has learned. And then the final sentence is just too general. The statement is true and is the whole reason for involving patient advocates in designing and running clinical studies but it is not new knowledge and prompts a "so what" response. I wanted to see there what the authors had done that was different and helpful to others.

The plain English summary has been re-worded to give a clearer message.

The points above about there not being a clear thread or story apply to the full text as well so I have not repeated those as such. I have set out below some specific comments and questions in
addition to those general comments on the structure. This includes pointing out phrases that are hard to understand from a lay reader's perspective.

Background:

The background is clear for the most part but I think that the order of what is presented in the second half (on page 5) should be reviewed because it doesn't flow as logically as it could. The first five paragraphs on page 4 and the top of page 5 cover the background to why multiple biopsies are needed. It might be better to then go on to talk about the ICR-CTSU and its approach to designing and running studies with patient advocates (paragraph 8 but say "involving patient advocates" not "patient advocate involvement"), followed by combining the messages in paragraphs 6 and 7 which are the focus of the paper: how patient advocates can help with the recruitment of patients to studies "perceived as challenging for the patient".

The background has been re-worded to improve the flow and give a clearer message.

Paragraph 4 (page 4), I don't understand the final sentence - I can't work out what the data from the biopsies can predict and what the important point of that is.

This has been re-worded to clarify that Ki67 can predict for long term disease outcomes.

Paragraph 5, top of page 5, what does "vital treatment implications" actually mean? (jargon). Further down on line 6 should ".and may be due." actually be ". or may be due to."?

"vital treatment implications" has been removed from this sentence as it doesn’t add anything and may cause confusion.

Paragraph 6, page 5, presumably the biopsies are technically challenging for the clinicians but what aspect and why say this? The second sentence is very long and unwieldy. Better to separate it into two sentences?

The reason biopsies may be technically challenging has been reworded. The second sentence has been amended.

Paragraph 7, page 5, line 4, what are the "valuable insights"? Give some examples perhaps. And they can assist with the application for approval from a Research Ethics Committee rather than
"communication with" and say how. Similarly say how they help with communication with hospital research staff and for what. Split the last sentence into two because the two points in the sentence are different. The first applies to patients and clinicians and the second to patients only.

Done.

Final paragraph, spell out what the acronym PALLET stands for as has been done for the other trials in the paper.

Done.

The PALLET trial:

It would be helpful for lay readers, and others maybe too, if the description of the trial could say what sort of drugs palbociclib and letrozole are (and similarly in other places in the paper where drug names have been used without saying what sort they are.

Done.

First paragraph, 2nd sentence replace "..poses the requirement for multiple biopsies to be collected...." with "..means that multiple biopsies need to be taken.."? Simpler English!

Amended.

Next sentence add "and then" before "..at 2 weeks..".

Added.

And next sentence after that please explain (for lay readers) what "cores" are or use a simpler term that is not jargon.

Done.

And the final sentence of this paragraph is rather convoluted and hard to follow. It would probably be better as two separate and simpler sentences? Perhaps start with something like "During the development of the protocol the research team discussed with the patient advocates how best to explain the need for multiple biopsies to both trial participants and clinicians." And then go on to spell out what some of the possible concerns of each were thought to be and how
they were addressed rather than just say they were discussed and addressed. The reader will want to know what and how either here or later and we don't get either.

Amended.

Second paragraph please say what insights the patient advocates provided and what was done (changed) as a result to help the trial recruit successfully. There is a bit about explaining the reasons (simpler English than "rationale") for taking multiple biopsies but it could say more about how that was done to cover the range of different patients and their needs for information. For example as well as putting the things listed in the participant information sheet was this also explained by the person recruiting participants at the time consent was sought? In the final sentence what was the result of the review of the participant information sheet by the patient advocates? Did the original include what the advocates felt was enough information and if not what was added. What did they consider to be "all relevant and useful information"? And how was that received by the Research Ethics Committee? Did it help in getting ethical approval? Did the Research Ethics Committee say anything about it?

Done.

The final paragraph contains useful information for others running trials but could say a bit more. Is there any published evidence of this or was it from the [lived] experience of the patient advocates (which is no less valuable). I think there is some published evidence on the point in the last sentence around perceptions of better care and more information being provided to patients who participate in clinical studies. Do people normally refer to "their BC disease"?

Whole paragraph amended.

PALLET Trial launch meeting:

The first sentence is the first mention in the paper of the protocol development group and is done in a way that implies it is something all studies have and will be understood by all readers, which I don't think is the case. Perhaps it would be better to describe all the elements of the research team in the previous section and which of them included patient advocates. Then go on the describe the launch meeting for the trial and what was done that was new / innovative as far as involving patient advocates is concerned.
The concerns about the possible reluctance of clinicians to discuss the trial are based on personal anecdotal experience of the patient advocates rather than published evidence, which is fine. Therefore there is nothing to refer to in order to find out more so it would be helpful to know more about them. For instance: how many instances have there been; what studies; what had clinicians said; had the patient advocates been able to do anything in those instances; if not then how were those experiences being used to address the issues in the PALLET trial; is the belief that "clinicians considered the additional required procedures too onerous" based on what was said by clinicians in other situations, etc.

Additional references have been added.

The third sentence of this section is very long and unwieldy. It covers too many points for one sentence so break it up. And the purpose of the presentation by the patient advocates (one of the "interventions" the paper is all about) is split between the beginning and the end of the very long sentence, which makes it harder to follow that in needs to be.

Amended.

I am not convinced that Table 1, which is referred to in this paragraph, is the best way to present the output and impact of the presentation made by the patient advocates. Or at least the table needs more work to make what is presented clearer. Shouldn't the two references for the table be in the reference list at the end rather than be listed under the table? The use of very short statements in bullet points hides a lot of detail that will not necessarily be understood by all readers. There is nothing included as "less likely to accept" for time and quality control. Even if it is the opposite of the "more likely to accept" it would be better for the table to be complete. I am not sure "quality control" makes sense and would be what a patient would express as a concern. The point listed seems to fit with "information". How realistic / feasible is it to state the requirement for "all" information and options, especially the former? Under "comfort and safety" and the "less likely to accept" for whom does "challenging biopsy site refer? The patient, clinician or both? For the second bullet point in the same box wouldn't it be simpler to say "risk of tumour spreading to neighbouring tissues"?

Table updated.
Meeting to address slow recruitment:

First sentence, what were the "logistical issues at sites"?

Don’t think this will add anything to this paper.

Second sentence, I am, not sure what is added by including the date of the teleconference because no other dates related to the trial have been included. Also, if that meeting happened a year after the one mentioned in the next section then wouldn't it make sense to swap round the two sections so they are in chronological order. Or delete the dates if they don't really add anything?

Dates deleted.

Second sentence - suggest breaking it after ",..at recruiting centres" and then have a separate sentence to introduce the discussion led by the patient advocates. The term "issue of clinician reluctance..." is rather odd English. :Perhaps rephrase something like "the patient advocates led a discussion about the reasons that clinicians were reluctant to approach patients and ways to address them"?

Amended.

Next sentence but one: "reason" rather than "rationale" and explain what ",..the appropriate setting" and "..good post-biopsy care" mean. Also insert ",..were." between "biopsies" and "performed".

Amended.

The next sentence is rather oddly worded. Maybe two simpler sentences would be easier to follow. And it is not clear to what the reference [11] refers. The issue being covered has been mentioned earlier without using this reference so it would be helpful to indicate precisely what the reference covers and what aspect of this the paper is adding.

Done.

Final sentence: "clinician preference", "pathway" and "treating clinician" are jargon terms. What does offering "all options" really mean? "All possible options" perhaps?
We don’t believe these are jargon terms. Some clarifications added.

First sentence of the second paragraph, delete "at the time of the teleconference" because that is obvious from what was said in the first part. Second sentence does not flow logically. Should the word "because" be added after ".increased overall" instead of "and"?

Whole paragraph updated.

Multiple biopsies patient advocate forum:

I found this section hard to follow. There didn't seem to be a clear thread or story to it. I was confused about the timing of it because the date given is a year before the teleconference for the PALLET trial referred to in the section above but the first sentence states that it followed on from the issues identified in that trial.

The second sentence of the first paragraph is a bit confusing. It starts by saying the aim was to educate patient advocates but the next sentence says patient advocates were invited in addition to clinicians and research nurses. And the second sentence says the forum was also to facilitate discussion between the patient advocates and clinical investigators.

Whole paragraph amended

I am not sure what the point is of the second paragraph about circulating tumour DNA. There is no other mention of this in the rest of the paper and it doesn't seem to be relevant to the key points in the paper. I can see why it would have been covered in the forum but can't see a clear link to the rest of the paper. And the first sentence is very long and unwieldy.

Clarification added that clinicians are reluctant to take tissue samples from metastatic sites so this may offer a viable alternative that will alleviate clinician concerns and technical difficulties associated with tissue biopsies.

In the third paragraph what was the "useful feedback" from the patient advocates? Some detail of what was covered and whether it was used would be relevant to the paper and strengthen it. It introduces Table 2, which is further discussed in the fourth paragraph. I found Table 2 very
confusing. The statements under the "trial concept" column heading don't seem to fit that description, nor relate to each other or the text in the other columns or what is written in the fourth paragraph.

Table 2 removed and paragraph re-written.

The fifth paragraph mentions that outputs from the forum were used in applications for ethical review but doesn't say what the outcome of those were. It would strengthen the paper to include information about what different the involvement of the patient advocates made to the outcome of applications for ethical review. In particular did it help them get approval more easily or quickly and with less or no conditions that might have been expected or had happened for previous applications without the involvement?

Clarification added.

Conclusions:

This seemed to be a collection of un-linked paragraphs rather than a set of conclusions. What would be helpful here to enable to paper to have as much impact as possible, ie be useful to others, is a description of the approach or model of involvement of the patient advocates and the difference that made to the studies presented, which could then be applied to other studies where recruiting participants may be difficult.

The first paragraph repeats what is in the background so isn't necessary. The last sentence contains some odd wording, especially the last part.

The second paragraph describes some of the detailed findings that would be more useful in the earlier sections. It gives some examples, which is good. The point in the second to last sentence is not well set out. If you don't approach patients then they can't consent so it is obvious that will have a greater effect on recruitment than patients who are approached declining to consent? Isn't the point here that few patients actually declined to consent because of the need for multiple biopsies but that many were not given the opportunity to make a decision because they were not asked? As such those two things are not comparable so you can't really say one has a greater effect on recruitment than the other.
The last sentence of the second paragraph is a good general point that is not specific to the particular studies and which there should be more of in the conclusions.

The first sentence of the third paragraph is rather oddly worded and is not as clear as it could be. Also it is referring to the particular focus of the breasts cancer studies rather than drawing this out as a general point that could be used in other studies. In the second sentence, who requires further education and communication from whom?

The fourth paragraph is more what I was expecting to see in the conclusions and starts to draw out the key messages for the readership of the journal. However, it does not go far enough and some of what has been said is not complete and or not clearly worded. "Well organised patient advocate involvement....." yes but what and how specifically? "Feedback from clinical trials to the patient advocate groups is very important", again yes but what specifically and to what end? Similarly, the next sentence. And then the final very long sentence is hard to unravel because the ordering of it is not clear.

The final paragraph is clear and to the point and what the whole of the conclusions section should be like. It uses the specifics of the studies discussed to draw out points that can be applied more widely. We just need the detail, perhaps in the form of a proposed "model" for or approach to the involvement of patient advocates.

Whole conclusion section re-written with these comments in mind.

Reviewer #3: This is an interesting case study account of the contribution of patients/public to the design and conduct of cancer trials, which could be of interest to readers of this journal.

The authors have not, however, provided an overview of the literature on PPI in clinical trials in their introduction; nor have they considered how their work contributes to existing knowledge about PPI in clinical trials in their discussion/conclusion. I suggest that the authors consult the following works, in order to better contextualise their case study in the paper's introduction and discussion sections:
Relevant references now added.

3. http://bmjopen.bmj.com/content/4/7/e005234.short

My other comments are as follows:

1. In the plain English summary, I found the 3rd sentence to be difficult to follow.

The plain English summary has been re-written.

2. in the abstract, 2nd paragraph, 2nd line, I wonder if 'cancer' should be inserted between 'breast' and 'trials'.

Cancer added.

3. references - are references 10 and 12 the same?

References updated.

4. page 9, 2nd paragraph, last line, I wonder if 'to the patients they discuss it with' should be reworded to read 'to the patients with whom it is discussed'.
This sentence has been deleted.