Author's response to reviews

Title: QUALZICE: A QUALitative exploration of the experiences of the participants from the ZICE clinical trial (metastatic breast cancer) receiving intravenous or oral bisphosphonates

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Author's response to reviews: see over
Dear Editors,

Re: MS: 1929828551963221 - QUALZICE: A QUALitative exploration of the experiences of the participants from the ZICE clinical trial (metastatic breast cancer) receiving intravenous or oral bisphosphonates

Thank you very much for your response to the above paper and for providing us with the opportunity to respond to the comments and amend the paper. We are grateful to the reviewer’s for their comments.

We have addressed each reviewer’s comments (in bold) in turn, with our response underneath. Changes to the paper have been highlighted in red. As requested, we have included the trial registration numbers at the foot of the abstract.

Please do not hesitate to contact me if you require any additional information.

Yours faithfully,

Dr Annmarie Nelson
Reviewer One

Unfortunately in my opinion this manuscript fails to engage with the issues around trials (particularly of more complex interventions) and does not provide anything particularly new.

We would argue strongly that this paper does provide new knowledge, even aside from that which is presented in the data. The paper cited is a case in point, which looks generally at reported experiences of trial participation but is not associated with an ongoing and discrete clinical trial, or designed to consider discrete trial outcomes. As reported in this journal recently\(^1\) (Rapport et al 2013), qualitative studies embedded within RCTs are methodologically complex, and within clinical trials of medicinal products (CTIMPS), extremely rare.

Our team, based at a Marie Curie funded academic research centre within a Cancer Research UK (CRUK) funded cancer trials unit, is the first in the UK to carry out a sustained programme of work with ongoing embedded qualitative studies, now explicitly identified as secondary outcome measures in trial protocols, in a portfolio of phase 2 or 3 clinical trials. We are also working with other units such as the Medical Research Council (MRC), and methodology hubs such as Qualitative Enquiry Supporting Trials (QUEST) funded by NISCHR, Welsh Government and the Collaboration and Innovation for Difficult or Complex Randomised Controlled Trials (ConDuCT) Bristol methodology hub. This is the first of the mature studies to be presented to a trials audience.

I felt that the results section was highly descriptive and that it failed to provide anything particularly relevant to anyone beyond those running a trial of these exact treatments or certainly very similar ones. For example I felt that excess detail was provided about the nature of participants side effects (more relevant to a paper looking at the result of the trial). Yet important factors such as the inability to blind participants to randomisation result in trials of this nature were not mentioned.

The audience cited by reviewer one is precisely where we are aiming – CTIMP trials. This paper is a pragmatic presentation of patient experience of a phase 3 clinical trial. We intend to show that such studies are possible and worthwhile. In that respect, and relevant to some of the other reviewers points, is the presentation of such studies to a trials audience. The first iteration of this paper was written as a social science discussion paper, which looked in detail at issues around equipoise, motivations to join the trial, altruism, and other ethical issues. The CI and TMG members were not receptive to such a style and requested that we rewrite as presented – in a style more accessible and familiar to them. This paper is intended for a trials audience and the journal selected and style of presentation reflect this aim with the intention of complementing the forthcoming main ZICE publication with a richer set of information on side effects and quality of life impacts. This paper if read alongside the results from the main trial can usefully inform clinical considerations on the use and acceptability of these treatments for this patient group.

\(^1\) [http://www.trialsjournal.com/content/14/1/54](http://www.trialsjournal.com/content/14/1/54)
I would argue that the discussion section did not engage with the wider literature on this topic. For example, how did these findings compare with the conclusion of Cox 2000 (Enhancing cancer clinical trial management: recommendations from a qualitative study of trial participants’ experiences).

We are familiar with this work from 2000, which interviews participants on various trials in relation to participating in trials. There is a body of literature looking at general perspectives of trial processes, especially that by Jenny Donovan et al. We. Where our study differs is that it is intended to contribute to the outcomes of a specific trial. This paper offers an analysis of in depth experience of a single trial from a large sample of participants. There are no other papers, to our knowledge, that have embedded qualitative research within a CTIMP trial specifically to contribute to trial outcomes.

The recommendations are not particularly novel and some of them do not have particularly wide application (for example the dental card – a good idea but not relevant to a wide audience).

As above, this paper presents a qualitative study as an output of a single clinical trial in the same way as a quantitative paper would present. It is not intended to be a discussion paper of wider issues around trial issues, although such a paper is in draft based on data sets from several trials.

Reviewer Two

Thank you for the very positive and very helpful comments, we have amended the text on several items.

Recruitment: could you clarify how participants were recruited and by whom. It would also be helpful if you could clarify how you came to the decision to cease data collection (i.e. how did you know that a representative sample had been recruited to each group)?

The original statement about recruitment has been altered slightly to make recruitment more explicit:

“Eligible participants from the ZICE trial were approached by the research nurses at the recruiting site, when they were given study information to consider whether they would like to enter QUALZICE. At their next visit, if they agreed, their contact details were passed to the researcher in order to arrange an appointment. Written consent was taken at the time of the interview by the researcher.”

Data collection: it would help the reader if you could provide a bit more detail on the questions that participants were asked. As above, it would be helpful if you could explain your reasons for ceasing data collection. You say interviews lasted between 30 minutes and an hour – could you provide the mean time? You seem to have a lot of data from relatively short interviews.

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Thank you; we have included an account of decisions to cease data collection. We have also added a table detailing the interview questions.

The sample size is large for a qualitative study. IPA recommendations are for a sample of 6-10, and you have 6-10 per group - a total of 42. A sample size of 42 is too large to provide an in depth account of individual experiences, and I think this is reflected in your results. I think the data presented lacks the depth and interpretation necessary for an IPA analysis, and appears to be more of a thematic analysis. However, I think that a thematic analysis is suitable for your research aims.

While we acknowledge the reviewer’s comment regarding sample size, we were dealing with six distinct groups of participants and each group was treated as a separate data set until overarching themes emerged. Please note that this paper presents a partial analysis of data, as specified in the introduction. The data set is indeed extensive and will be presented in several papers.

We agree that there is limited depth to the analysis presented here. Our fuller analysis was not preferred by the CI and team for the purposes of this journal, which is a pragmatic presentation of results to engage a trial audience. There is inevitably a tension between a full analytic presentation and that which is required to engage with a clinical audience. We will, of course, seek to publish a fuller paper aimed at a social science journal in due course.

For an IPA study (in which researcher interpretation of data is a key element), I would expect to see greater reflexivity and consideration of the potential biases brought to the analysis by the researchers. It would be useful if you could say a bit more about your attempts to ensure trustworthiness / reliability of the analysis. Are the discussion and conclusions well balanced and adequately supported by the data?

A section has been added considering validity, rigour and reliability, which also addresses reflexivity.

The discussions and conclusions are important and reflect the findings reported. However, you cover a lot of issues in the results section, and only some of these issues are discussed. I would also expect to see some consideration of the existing literature, and how your research fits.

Thank you, we have added further references to reflect our engagement with the literature in this field.

I think the strengths and limitations of your study could be highlighted. I would expect to see a section in the discussion entitled ‘strengths and limitations.’

A strengths and limitations section has been added to the discussion.

Writing style is clear. There is a typo on page 30 in the fifth line of the second paragraph.

Thank you for identifying this typo, which has been amended.
Reviewer Three

Many thanks for the positive comments and the recognition that this is an important paper in the field.

The theme 'interviewers actions' is an interesting theme-- but one would wonder if such actions had an influence on the other themes that emerged from your data and if in fact needed to be considered in this paper, at least in brief?

Thank you for highlighting this omission. The reviewer kindly highlights the need to present justification of the researcher role and effect on the analysis.

We have added a section addressing reflexivity to the text.

I feel that the figure gives a satisfactory overview of the theme 'Patients experiences' but in the presentation of written results, (perhaps due to a lack of numbering?) it is hard to distinguish between sub themes. Are all subthemes equal? If so the figure would seem to suggest otherwise. Perhaps the figure could be made clearer in terms of changing of font or font size to show the relationships between the sub-themes and then considering numbering or font changes within the written results might better link the figure to the results.

The paper now more clearly distinguishes between themes and subthemes, through the use of a numbering system. We have also redrawn the diagram to make the themes presented clearer.

The section on recruitment: ‘Sampling of participants was purposive .... This sentence should be reconsidered- it suggests a possible bias in your recruitment whereas the selection criteria provided in the paper shows that a recruitment bias is unlikely.

We would respectfully disagree with the point about purposive sampling. This is an established sampling technique for such a study whereby a homogenous sample with similar characteristics is deliberately sought, ‘based on a specific purpose rather than randomly’ (Tashakkori and Teddlie, 2003a, p. 713).

The change to an interview schedule is not unusual in such a study, it might have been useful to provide it in the paper, perhaps giving the final version but highlighting changes.

The interview schedules are outlined in the newly added table two in the document.