Author’s response to reviews

Title: PATIENT LED PROMs MUST TAKE CENTRE STAGE IN CANCER RESEARCH

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Author’s response to reviews:
Comments from second review and author’s responses.

Reviewer 6

General comments: There are some very important ideas in this paper and it brings together some threads very well. However, they currently remain buried within lots of other information. I feel this important paper needs focussing in this regard. Also, while the tone of the piece reads like an opinion piece, some things discussed here are not a matter of opinion, but of scientific debate. I'm not qualified to label them all, but there is a distinction (I have tried to highlight examples of this in my detailed comments). It is perhaps a matter of personal style, but for example, when I read someone writing in the first person - I expect it to be coming from a place of personal experience - which is highly valid in parts of this paper. At other points, (for example 'Before I go further I need to clarify two terms') it reads like a transcript of a presentation. I would rephrase it (and the many other examples where it is not coming from a place of personal experience or belief) as such 'At this point in the discussion, it is helpful to clarify two terms'. I think the whole piece would benefit from being edited to make sure the thread of 'patient experience' is woven throughout what sometimes reads as a confusing tapestry of recent advances in cancer. For example, the 'survival/survivorship' section has central arguments which are truncated, whereas if they were integrated more into the areas discussing recent advances, it would be more clear why these advances are being included. I am more than happy to offer more detailed feedback and support to get this paper published.
Thank you for these thoughts. I find them problematic for a number of reasons. First, one intention here has been to demonstrate passion and removing the personal dilutes that – although the example of clarifying the two terms is valid. Secondly these ideas create conflict with earlier reviewers, for example the Survival/survivorship section was introduced to ensure that these arguments were more clearly signposted. Thirdly the matter of opinion and the fact of debate are inseparable. One of the most important roles of patient involvement is to challenge scientific positions, not mold our opinions to conform to them. I would maintain that I have done this and that my positions, whether supported by science or not, are valid opinions. The other reviewers have expressed no problem with this.

From here onwards are specific comments about particular part of the paper. Please note my line references were corrupted in the PDF so I've included original quotations followed by comments, so the original quotations can be found using a text search.

Abstract: "The ethics of current drug adoption practices and the use of new drugs is being questioned socially and politically raising the challenge of finding the relative value of new treatments in terms of cost and benefit" This feels like an opportunity to also mention patient and public involvement in health technology assessment (e.g. NICE in the UK). This is mentioned later in the paper but the point is fragmented.

Good point. Added.

Plain Summary: "Science is making a difference to a few patients with metastatic disease but it has been achieved at a high cost" Consider adding 'Science and evidence based-medicine' to link to the next sentence. "asking medical research to find the true value of new treatments" this seems to be saying that society - including medical researchers, need to redefine value in new ways.

Society is raising that question. Have modified the passage.

Background "rather than commenting on technical quality." consider adding that it is about integrating a subjective view of quality, rather than a purely objective 'technical' assessment.

Good point. Added.
"After 14 years as an involved patient in cancer research" - I think this needs defining, for example - 'a member of the NCRI Board'

I think that is a distraction. My research CV runs to more than one A4 page, what is relevant to one reader is not to another. If people are interested in that they will look me up. Others will assume that the journal editors have done that homework for them.

"Being brutal, this analysis suggests that data are garnished to claim fancy conclusions, a 2 few weeks added life is hyped as a significant benefit while data on the outcomes patients 3 worry about are missing" Consider rewording along the lines of 'The outcome measures used here do not include any quality of life measures, or other outcomes prioritised by patients'. I would also consider not using the word 'brutal' as this is a professional dissection of the research practice, not a personal attack - thus more appropriate language is 'a detached and honest appraisal' - I am also concerned 'brutal' would not make sense for some people with English as a second language. Valid points, especially re ‘brutal’. I have made some alterations but the main body of the sentence still reflects the passion issue.

"majority of studies included would have been industry sponsored studies” Can we actually include data on this so we can say 'a majority WERE' as this is more powerful and can then cite other papers about systematic bias (I've linked to one later)

Nice tweak, thank you.

"Genetics is the scientific wonder of the age" - consider rewording to 'genomics' or even 'genomic medicine' as genomics is wider than humans! "Finding the whole mutation structure of a single cancer will open up routes to treating those mutations, it does not guarantee that any mutation can be treated. But we have already seen that cancer is clever" I'm not comfortable with the wording here at all - happy to give more detail but in summary: 1. Say genomic variations or variations of known significance - mutations is not a helpful word - although it is widely understood, it is a value judgement on a variation - saying to some people 'good or 'bad', thus coming from a 'eugenic' (meaning 'good-genes') philosophy. This is a very truncated response and something I can share more on if helpful. 2. Rather than 'treating' a mutation - the author suggests it is about understanding, thus 'molecular mapping of cancers' might be a better use of
language. I refer the author to this highly relevant book chapter I wrote with colleagues which goes into much more detail:
https://www.researchgate.net/publication/314636167_Involving_the_Public_in_Rare_Cancer_Care_and_Research_Shaping_the_Future_for_Rare_and_Uncommon_Cancers

DOI: 10.1002/9781119196235.ch3 3.

Have made changes. My aim is not an in depth review, it is an (opinionated) overview from someone who is not a scientist. Much of this is playing with words, taking them from colloquial to scientific, so I have been judicious.

Avoid 'clever' - implies intelligent design, which I really don't think this paper should tread into. I would suggest 'highly adaptive' but a qualified cancer researcher should be consulted to comment on this. It's fine for an informal conversation but not in this context. It is interesting how the term clever is often used informally in this context but I accept the point.

Acronym - need explaining or this is jargon "2003 the mystery of why a GIST"
Thank you – missed that one.

"It may also mean new side effects from the new treatment or additional side effects if the original treatment is still being taken because some tumours are still responding" - for balance mention pharmacogenomics may also lead to more targeted drug treatments or flag potential negative side effects which people are genetically predisposed to.
Good point. Addition made.

"A multitude of tools - I have identified 18, there are certainly more, ranging from generic 6 to disease specific" - simply state briefly how many you found and how, and acknowledge the limitations of your method - you have essentially done this, but the reader will expect this to have been fact checked or it is not useful to illustrate this important point. In other words, if someone wanted to replicate your search, what would they do?
Fair point. Tweaks made. It is worth noting that as a patient I do not have unlimited access to full text papers so my searches are confined to what can be done using publicly available search tools and data.
"Data which are cherry-picked to support a pre-determined clinical or commercial view - a concern expressed verbally to me by regulatory officer" this concern has been systematically addressed - you must cite this - this is not to be whispered - this is to be shouted!: https://www.ncbi.nlm.nih.gov/pubmed/26694022 In addition - the whole HTA process relies on this kind of evidence which has inherent bias! You should also mention All Trials here is this is central to this discussion if systematic reviews of human trials are being conducted without all the data.

There are now better papers – referenced. All Trials initiative now explicitly supported.

"I am not aware of an incidence of this in cancer research" - this is perhaps a style point but when I read this I ask myself is the writer stating it doesn't exist or that they don't know about it. If the former, then state it as so, if the latter, then this needs to be removed or rectified. ".

Interesting questions raised here. I have in fact (in the 10 months since the paper was first submitted) now found one cancer trial with subjective/quality primary endpoint so statement is modified at any rate.

The idea that you can have Patient Reported Outcome Measures without patient provided inputs to inform the methods and processes used, is irrational and probably unethical" this is a crucial point and should be included in the abstract.

Thank you. Nice suggestion. Have added to plain language summary as well.

"Macmillan is involved" use Macmillan Cancer Support (when used for the first time, acceptable to truncate afterwards) as avoids confusion with the publisher brand. "Birmingham University" The University of Birmingham "Other prominent UK groups working on quality of life related projects are in Leeds, which has been using information technology to gather data atin the frontline of healthcare in a number of very practical trials, and Oxford where the Quality and Outcomes of Person-centred Care Policy Research Unit (QORU) has a programme is informing policy-makers and commissioners." Split this into two sentences.

Thank you. Changes made.
Reviewer 7

The author appears to have addressed the concerns of the previous reviewers. I think this is a timely perspective on something which exercised me when I worked on technology appraisals for treatments in oncology where the aim was the extension of survival or progression free survival - the lack of focus on HRQoL when this seemed to me to be of paramount importance. It's clearly a personal perspective and that gives it much of its force.

Thank you.

I would say that it identifies key areas of importance - the need for publication of all trial data - I would reference the ALL TRIALS initiative here - apologies if this has been done and I missed the reference, the key importance of adverse event data, the need for consideration of HRQoL in a patient-relevant way - and the need for standardised reporting (as well as simple publication).

All Trials now explicitly supported and referenced. Thank you for valuable point about stating importance of adverse event data – added.

I don't think I have much to add except that I wanted a clearer summary articulation of what the initiative the author is calling for might look like.

I have problems with this. My style (as those that know me know) is consensual. I have great fears that by putting forward a model the debate will then focus on that model because it is simple to look at, when we need the focus to be on addressing the issues and taking the opportunities.

I was also struck by the fact that many of the treatment types discussed are given at a point at which they qualify for End of Life status under the NICE criteria - where a higher threshold of cost-effectiveness is used. I wondered if the patient perspective on that had been explored fully and whether the author feels there is scope to do so.

This is a really important point which should get picked up in the debate I want when it actually starts. It is not just a patient viewpoint but a public one too, this is a significant social issue. I have added it, largely to bring the issue up (at the risk of creating further confusion) rather than to discuss it. There is some CRUK funded research into public acceptability of high cost drugs, and by implication NICE thresholds, at Oxford University.
This paper seems to me to have been fully reviewed already and my comments are mostly relevant to things that I think are interesting - rather than suggestions of changes which need to be made. It's clearly a patient perspective piece and I'm commenting largely as an academic in this area - I think it will provoke valuable discussions when published. Thank you.

Reviewer 8

The topic of this paper is important and it's required more practical evidence from the perspective of patients about how design and implement PROMs in the field of cancer research. At the present moment we have a lot of theoretical background about that it's important to include in research these types of measures that become directly from patients, but the practice in the real world is limited. Thank you.

PLAIN SUMMARY (Second paragraph) When the author speaks about ethics of current drug adoption practices, I prefer detail this information with a comment that not reinforces a 100% of evidence that patients with metastatic disease are taking their last chemotherapy few days before they die. In the field in what I have experience, related to paediatric cancer, children are not receiving treatment close to the time that they pass away. When doctors know that no treatment is working they are transferred to the palliative care unit and at this moment is most important the quality of life of patients and families than the research that can be behind the innovative drug that they could have been taking before. I suggest to rephrase the second paragraph of this section with the aim to be less forceful. Thank you.

Important point. I have modified the statement. I don’t think it helps to add distinctions between adult and paediatric care on what is one point among many when I am trying to generalise.

(Last paragraph) A deeper definition about PROMs would make more easy to understand the focus of the paper, at least from the perspective of patients. We know that patients read scientific papers every time more, and a short definition about what means PROMs would ensure a better understand of the content of the paper from the very beginning. Thank you.

I have added a simple phrase to help the lay reader establish what QoL is about.
ABSTRACT (Section) I agree the content of the last paragraph, when the author suggests that patients can contribute to design the pathways related to QoL and PROMs measures. This point of view is realistic and ensures items that can measure areas of interest for patients. Thank you. Thank you.

RESEARCH (Section) (First paragraph) The stark findings of a paper in what Dr. Ian Tannock is one of the authors were published on 1975. These findings are radical and the author needs to be sure that are valid on 2017 at least in the European scope. When we check the bibliographic reference of the conference on 2014 we can understand that perhaps are valid, but I recommend to rephrase this paragraph with the aim to ensure that we are speaking about evidence that were on 1975 and in the present moment are working in the same way. Thank you. I have added reference to more recent papers which have similar conclusions.

I appreciate the comments in the paper about the new ways of treat cancer: immunology, genetics and personalised medicine. This approach open new topics for discussion related to the PROMs and they are related to the evolution of innovative drugs for oncology diseases. Thank you. In general, when you speak about personalised medicine the main conclusion after read the text is that it isn't working properly. Perhaps will be nice improve the content of this section with a general comment that can emphasises the need of more research. These types of treatments are very innovative and more evidence is needed to discover diseases or status of the diseases where it can work. For this reason I suggest to be less strict in the text. Thank you. I think we have to be very cautious about the ‘personalised medicine’ hype. It is easy to get carried away with the enthusiasm. For most cancers this remains a dream. For some cancers, including my own, even the first stage does not exist, there are no targeted therapies at all.

DELIVERY TREATMENT (Section) First paragraph When you refer to DGH would be nice if you contextualize it in UK, this is important for the reader and helps to understand about the reality are you speaking. Good point. Alteration made.
SURVIVAL (Section) It's positive to include in the paper the reference about the experience of James Lind Alliance about the priorities for research. Thank you.

Thank you. Added.

THE ROLE OF PROMs (Section) I agree with the fact that QoL methods are really scarce in the real world of innovative treatments under study. There is an important gap between theory and practice. The author lists different comments about tools and criteria; I think that it's possible to improve the description of this listed items. For example, when you explain that you have identified 18 tools I propose to add a general description about the field (area of disease) in what they can be applied. It's positive the reference to the EMA and FDA guidance about Quality of Life endpoints. Thank you.

I only wanted the issue of 18 tools to illustrate the fact that I had looked to see what was around so I could justify the multitude of tools statement. The matter of what tool is used where and when is for a different paper.

BUILDING NEW PURPOSE FOR PROMs (Section) Also it's a positive reference and very well described the expertise that has CPROR in the field of PROMs, and the other experiences that you detail in this section.

Thank you.

CONCLUSION (Section) I agree with the content of the first and second paragraph of this section. At the centre of any development of PROMs always we need to put the patients and at the same time we need to define items that patients can understand. We need to know that the level of health literacy can be different between the patients that perhaps are going to be involved in the process to design this metrics and the huge pool of patients that can provide feedback about PROMs. The implementation of pathways to provide frameworks for developing research ideas would be an interesting way to standardize this important contribution of patient involvement. Would be nice a more wide description about what the author consider a pathway (we can understand between lines) in order to offer more detailed information to the readers and perhaps would be interesting to include an example at this point.
Thank you. As I responded to Reviewer 7 I have problems with putting forward a detailed vision, or a model, because the debate will then focus on the process and the model when we need the focus to be on a consensual vision which moves us to resolve the issues and take the opportunities.

Many thanks for inviting me to review this paper that is the outcome of the experience of the author as a patient advocate in the field of oncology. It can be a powerful paper to promote improvements in this field. I trust on it. I hope that my comments would be useful. Good work. Congratulations.

Warm regards
Thank you, your support and input is appreciated.