Author’s response to reviews

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

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This document is a compilation of the 5 Reviewer reports annotated with my responses:

Reviewer #1:
PATIENT LED PROMs MUST TAKE CENTRE STAGE IN CANCER RESEARCH

* Important topic - widely recognised that QOL measures are outdated and unsatisfactory and not patient centred. Quality of life encompasses a range of factors that cancer patients report consistently as being under-represented and considered by clinicians and in cancer research. Thank you.

* Timely - National Cancer Strategy - Achieving World Class Cancer Outcomes - putting patient experience on a par with clinical outcomes and safety
Now referenced.

* Concept of designing patient pathways around PROMS and patient experience is important and deserves further work to develop and apply
Thank you.

* Recognises that a range of stakeholders and various strands of activity, both in the UK and across Europe.
* Highlights the need for a co-ordinating and integrating vision and strategy for measuring and reporting life quality via PROMS

* Writer shows his breadth of experience as a patient as well as someone with considerable knowledge and experience of patient involvement.
Thank you.

* Understandable focus on metastatic disease and treatment decisions for late-stage disease which may or may not consider properly life quality. However, 70% of cancer patients now survive for 5 years and living with and beyond cancer is an under-researched area where life quality and PROMS have an important part to play.
Very valid point. Have added short section on survival and mentions in other places of this and of other treatment modalities.

* Opportunity to give more consideration to the development of patient experience pathways and how this might be taken forward via Cancer Alliances and the National Cancer Strategy
I see this as an international issue where UK could offer leadership. Alliances are inevitably locally focussed and while I would hope they would be involved, especially in managing ‘pathway descriptions’, I think leadership lies elsewhere.

* Opportunity to leverage the world-leading insight available at the Yorkshire and Humberside based Haematological Malignancies Research Network which has information about patient experience and journeys for every blood cancer patient treated across 19 NHS Trusts over a period of over 10 years.
Thank you. Any collaboration which brings clinical and academic groups together with a clear vision must reach out for local examples like this.

Reviewer #2:
Minor point: 'PROMs' should appear with a small 's' throughout.
I am trying to teach MS Word to do what I want.
I would broadly agree with the statement on pg.7: "...while data on the outcomes patients worry about are missing." Emerging evidence in oncology trials points to worryingly high rates of under-reporting with regards to patient-reported outcomes (PROs).

Macmillan is currently researching this (with CPROR) and I have been told that this is true, though we must await publication for a reference. I have therefore to rely on Tannock’s evidence.

The following statement on pg. 7 is a little unclear: "Academic studies which involve patients in their development processes may be exempt from these criticisms, though we cannot be sure because Tannock reviewed all published studies during the time when involvement started." I would suggest revising and clarifying. I am not aware of evidence to suggest patient involvement in oncology trial design leads to higher PRO reporting rates, but I think that this is an interesting research question that would merit investigation - perhaps the author could call for this?

Very valid points accepted. This paragraph re-written.

Also pg. 7: "It can be argued that most of these drugs will work best early in the disease when a single pathway mutation is causing the cancer but clinical and regulatory structures discourage that from happening." Can the author explain why this is the case?

The TRACERX study is now published and my statement is an extrapolation of the results of this lung cancer study into other tumour areas. I have modified the statement by changing “will” to “may”. The extension of the use of imatinib in GIST to adjuvant therapy as standard for medium/high risk patients is another example but I was not willing to reference a rare cancer study alone. Arbiraterone is also travelling this journey with prostate cancer as recent publications demonstrate.

Minor point pg. 7 - should read 'déjà vu'

Eeek.

I can understand the author's slightly provocative stance in parts, as presumably this article is to serve as catalyst to start a meaningful debate around the improvement of PROMs utilisation in
cancer research. However, my own view is the statement appearing on pg. 10 "Quality of life appraisal in research is currently a shambles." is too strong. I would not agree that QoL methods are poor across the board. This is too much of a sweeping statement and ignores those trialists currently conducting robust QoL work (of which there are certainly examples - as we are seeing in our current review of pre-2014 UK Portfolio Cancer trials that include a PRO primary or secondary endpoint [the Macmillan-funded 'EPiC' project]). However, I do agree that there is too much variation in quality and overall standards need to be consistently higher.

Fair comment. “Shambles” has gone. Have been given a sneak insight to EPIC conclusions but of course cannot reference it.

I also agree with the central tenet of the piece: "We need to move quality-of-life research on, to become a new centre of influence in cancer care. The first priority is that we must have a single, consistent quality of life approach. The data must be produced and analysed in a way which facilitates comparison be described from a patient viewpoint."

Thank you.

I have to disagree with the statement on pg.10-11 re the development of the National QoL metric. Having been party to some of the discussions surrounding this initiative, it is not my belief that the development is being run by a 'marketing company'. Rather, the initial work on this is being led by a respected oncology research group at the University of Leeds, coordinated by an experienced oncology clinician and researcher, backed by a patient advisory group. Marketing company comment dates from first drafts in October 2016. Removed. Many leading QoL research groups were consulted during the project but initial research was by IPSOS-MORI (a marketing research company) supported by Prof Velikova from Leeds. The view that NHS England presents (confidential memo – Feb 2017) differs from the Reviewer’s. I was a patient on the steering group for the initial phase of the work. The project has moved on towards pilot stage later this year. Regardless of all this my re-write presents the public view expressed by NHS England at the Cancer Outcomes Conference, June 2017.

It is good to see reference to the SISAQOL initiative, however, there is much more work underway, across many organisations, that has not been sufficiently highlighted. I would think it
essential to mention the work of both CPROR and ISOQOL with regards the development of the 2013 CONSORT PRO reporting guidelines and the forthcoming SPIRIT PRO Extension - both of which will be extremely important in driving up standards of PRO research internationally. In fact, there is early evidence that the CONSORT PRO extension is already having such an impact. In addition, the COSMIN group have developed guidelines to improve the development/evaluation of PROMs and the COMET group have conducted important work surrounding the development of 'Core Outcome Sets' in cancer research in order to improve the comparability of PRO trial results in this field. Moreover, CPROR (launched Nov 2016) is currently implementing its strategy to: (i) build capacity for applied and methodological PROs research, (ii) support clinicians, trials units, ethics committees, funders, regulators and policy makers to ensure high quality, ethical, efficient PRO data collection, (iii) provide education, training and support for optimal use and integration of PROs in clinical trials and routine care, (iv) ensure that PRO data collected in routine care and trials meets the needs of patients and the public, clinicians and policy makers.

Thank you. This was very valuable input and helped me with further contacts I had not found. Substantial re-write as a result.

The conclusion is strong and makes a compelling case for the use of QoL 'pathways'.

Thank you

Reviewer #3: The author's rationale is clearly expressed and the argument well made, identifying both the need for, and method of, patient led work on outcomes moving centre stage in cancer research .

Thank you

In my understanding the author identifies two key issues which he argues need resolution in order to improve outcomes for cancer patients

One- a proliferation of quality of life (qol) measures, with no coherent overview or coordination visible.

Secondly, a lack of PPI in defining and designing outcome measures.
Earlier, stronger signalling of these as distinct & interrelated issues would lend clarity for readers.
Thank you. I have signalled this more strongly in the Abstract.

I did have some concerns about how the overall argument is developed: I was initially uncertain about the relevance of paras on genetics and on sarcomas, P.8.
If this is to say research here may well not lead to any substantial gains in patient benefit, that point needs to be made more explicitly. I do wonder if it is necessary to the case being made, and might have the effect of muddying the overall argument?
I take the point about relevance of sarcoma to the argument and have deleted it. I think genetics is important as it is the current ‘hot topic’ and the downsides are not so often mentioned amid the hype. The publication of the TRACER-X study helps me re-define this and link more strongly to ‘precision/personalised’ medicine.

Ethical points, p10, 12-13, are well made.
As is the later link to England’s Cancer Strategy: and timely as the Strategy moves further into implementation.
Thank you.

Imminent James Lind Alliance work to identify unanswered research questions in Cancer Survivorship will be strong on patient collaboration and adds to timeliness of this submission.
Good point, thank you. The NCRI/JLA link is now mentioned.

Now for something more fundamental: the author makes a compelling case for a life quality description that cancer patients and clinicians can grasp and share, and identifies possible positive outcomes for commissioners too.
"Data on on the outcomes patients worry about are missing", citing a review of RCTs in 3 of the larger cancer patient groups. His own evidence however appears to draw on a narrower range of studies, viz. drug industry sponsored trials. The author’s focus is then on systemic therapies'only, and in area acknowledged to be low on PPI, and omits patients undergoing
surgery and or radiotherapy. Patient outcomes for these groups are of equal importance-including them would make the argument both more rounded and convincing.

I have strengthened this segment and broadened mention to other treatment modalities. However the definitive study of QoL reporting being undertaken by Macmillan and CPROR is yet to publish. I can only hint at what I have been told.

On P4, lines 9&10, we are told that research has been making a difference to a few of those with metastatic disease. This is unsubstantiated: no difference elsewhere?

This apparent selectivity risks undermining the author's purpose. The addition of some qualifiers could help.

This is in the Abstract and the theme is now more fully expanded in the main paper.

Elsewhere, the addition of some concrete examples could help understanding: I am familiar with this field, most readers won't be.

To be specific: "I have been told about..." P13, lines 11&12, helpful to cite one or two of these.

A brief example of substantial PPI impact in proms work would help readers grasp possibilities at the level of the individual study. Recent innovative collaboration between NCRI's Consumer Forum and a large pharmaceutical co, in developing an app for patient use in trials demonstrates that such work is possible, and thence may merit mentioning.

This section has been expanded and much more detail is offered and referenced.

The assertion of a "shambles" in qol measures is not backed up. Citing, e.g. the number of measures of fatigue in cancer: 20+ would surely bring the point home.

"Shambles" has gone. Very relevant point. Each of the bullet points has been expanded.

Re language, I found some inconsistencies in assumptions about what the reader will understand-especially important for a submission to this journal. P8, lines 26-P9, line 2.

This short para makes what I believe is an important point – that scientists are not unanimous that current research paths are all valid. We need to listen to different viewpoints until they are definitively proved wrong.
And in the specific case of the new work proposed, , we are told this "could be supported " by patient-led work, P14, line 18, surely the logic of the case here is that they must be? Good point. Have strengthened the language.

As to the overarching case put forward for new pathways, the author does outline a method for measures better describing pathways, bringing together data from a range of clinical and research resources. The risk that too many of these resources suffer from the very lack of patient values, patient centredness or patient defined outcomes the author argues have led to the very state of play - that risk is not addressed. This reviewer would welcome acknowledgement of this risk and a suggested approach to mitigating it.

Very important point which raises the question of how far an initial paper, which is essentially calling for a debate about a vision, should go into addressing an answer or a range of answers. I think this treads into the ‘next steps’ area, though the point about risk is taken.

In conclusion, if the author’s aim is to start a debate, then in this reviewer's assessment, he makes the case for such a debate. A debate that could resonate well beyond cancer and engage patients and clinicians in other conditions. This point is made, but in a rather low key way. Thank you. I have beefed that up a bit.

Some points where the case made would benefit from additional evidence or clarification have been identified but these are not to undermine the importance to patient benefit and to the game changing potential of PPI that this submission offers. Thank you. The references have been extended significantly.

Reviewer #4: I read with interest this article which reflects a personal view of a leading advocate of patient involvement in cancer research. The article raises an important question about the role of patient reported outcomes measures in cancer. It provides a thoughtful overview of the new developments in cancer treatments and how these have been evaluated and eventually delivered to cancer patients. The article invites all cancer clinicians and researchers to take a step back and review the progress over the past few decades, how we can learn from this and take things
forward with a big focus on the patients and their experiences. I found the article very interesting to read and really thought provoking.

Thank you.

My main comment is about clarifying a bit more the proposed concept of the pathway that involves quality of life and patient reported outcome measures. Perhaps a worked example that might help in that respect or a figure? The way I understood the concept is to merge together clinical data at diagnosis, trajectory of disease, available treatments at each time point of this trajectory and combine with patient experiences. In some sense this concept is similar to the 'Big Data' notion, where data collected routinely from various sources are pulled together to be analysed and used to inform research and treatment.

I have elaborated further on the pathway but the feasibility of such an idea has not been examined yet, although no-one has indicated they think it impossible. I don’t want to impose my ideas on how the concept is visualised, that must come organically as work unfolds. I suspect a range of different approaches may be tried and refined. It certainly is a ‘big data’ idea and bringing QoL data into their work is starting to be considered by some of the NCRAS thinkers. Their disciplines on data quality and consistency would certainly challenge current QoL work. A couple of early ideas about how pathways might be visualised, using HES, Waiting Times and Registry data alone, were shown at the recent Cancer Outcomes conference. At this time I see this as ‘downstream’ from the first and urgent need – integrated thinking about a shared vision.

In the section Research - it may be useful to make a point that many of the new targeted cancer treatments are oral treatments and therefore patients are not that closely monitored by the hospital to detect side-effects. Therefore using PROMs to monitor side effects and to advise patients on their management seems to be particularly a useful way forward.

Useful point but I want that Research section to focus on the big picture and diversions into detailed points would divert attention. I am aware of patients at DGHs sent home with several weeks supply of very expensive tablets and no proactive follow-up, no management of compliance etc.
Minor comment. Sector 'Treatment' maybe entitled better as 'Treatment delivery' or 'Decisions about treatments'.
I have gone for Delivering Treatment.

Under section 'The role of PROMs'.
SISAQOL project is focusing on international consensus and standards in analysing quality of life data but does not cover PROMs questionnaires or data collection. It will be worth clarifying this.
This is where the link with the complementary work of CPROR is important.

QORU - please spell out.
Where the author refers to NHS England cancer dashboard, please add a link to the website.
Done.

Reviewer #5: General comment

Many thanks for inviting me to review this compelling and considered personal reflection on the status of quality of life assessment and the importance of patient involvement. It is powerful and insightful paper.
Unfortunately, I am not able to comment on the cancer-specific detail – and would recommend review by an oncology clinical academic.
However, the focus on the importance of appropriately involving patients in the generation, use and interpretation of PROMs is a concern that I fully endorse.
Thank you.

Specific comments - PROMs section

I think that the points that the authors make are of note. However, I do believe that it’s important that the author recognises that, whilst that most certainly are limitations in many areas and with many available PROMs, in certain areas there is significant progress.
Point well made. Have extended those sections.
There is a dearth of references in support of the arguments put forward. And, whilst I appreciate that this is an important document written from the perspective as an involved and experienced patient, I wonder if a collaborative approach which involves a collaborator who could supplement the PROMs element (and probably a clinician who could supplement the Cancer-specific aspects?), would strengthen the paper further.

The paper is now heavily referenced. I have always felt that a paper like this gains both impact and value by coming unequivocally from a patient. That does not mean it should side-step the rigour implied by peer-review.

In particular, I would like to see a stronger counter-argument which evidences where PROMs were, where we are now, and the direction that (we hope) PROMs should be heading in.

There has been some significant re-writing. I hope you feel that this has been achieved.

Reference should also be made to the 2009 FDA guidance for PROM development which recognised the limitations of many PROMs used to support drug evaluations. This specifically highlighted the limited engagement with patients to inform PROM content (hence, the limited face and content validity – and hence, most likely limited relevance to patients!) – and recommendations for greater transparency and a clearer audit trail from the voice of the patient to the derived item content of PROMs was recommended. Whilst the FDA did not ‘engage’ with patient engagement as research partners, this was an important step forward in ensuring greater transparency in the way in which the patients voice was incorporated into future PROMs -and specifically, where these are used to support drug evaluation.

Thank you. In the same week I received this comment I did some work with EMA and in discussion the point was made that they too have provided PROMs advice. The work of both agencies is now acknowledged and referenced.

Similarly, whilst I concur with the importance of engaging with patients as partners in PROM development, there are some groups that have made important moves towards greater patient involvement – the author should refer to the work of OMERACT in the Rheumatology field and more specifically de Wit, Hewlett, Kirwan and Dures.
There is also valuable work in Alzheimers, arthritis, haematology, diabetes – and I am sure others. Pointing to such work within the generic context of QoL is as far as I feel I can reasonably go without highlighting detail disproportionately and unbalancing the paper. My focus must be on cancer.

I’m a little confused by the distinction that the author makes between PROMs and QoL assessment – eg, ‘PROMs and quality of life could work together…’ (p11, lines 16-17). The term patient-reported outcome came out of the FDA report – to provide some consistency in the way in which authors were referring to patient-completed measures or questionnaires. It’s an over-riding concept that highlights the importance of assessment reflecting the patients’ perspective about how they feel, what they can and cannot and how they live their lives because of their health and associated healthcare (please see Patrick et al, 2007 Value Health for original definition). The ‘M’ is added (mostly in the UK) to indicate the operationalization of this concept into a measurement instrument. Moreover, numerous authors have described the dynamic, multi-dimensional aspects of quality of life – and linked this to the challenges of measurement. It would be helpful for the author to refer to such papers. For example, Ferrans et al (2005 – Conceptual Model of Health-related Quality of Life); Bakas et al (2012 – Review of HRQoL models); Pietersma et al (2014 – Domains of QoL); and Huber et al (2011 – How should we define Health? BMJ).

Thank you, useful background, some of which I had taken for granted and have now read fully. I have clarified my use of the two terms in the paper. QoL is an instrument which gathers data on multiple factors affecting the patient and provides some kind of overarching report. Typically several questions will allow one domain to be scored, then multiple domains can be collectively scored. PROMs are single factor instruments where typically a patient’s report is minimally processed and allowed to focus on one critical experience.

Minor points:

Page 7: line 8 and 9: I suggest that the author should revise the relation between Industry and patient involvement. Whilst, historically, one might argue that the PI focus was limited, this has/is changing and many companies have now appointed PPI leads.
Very valid point. Have made changes. I know of at least three different models of patient involvement in pharma, none of which is evaluated, so further research is needed.

Page 12:
The suggested split between the EORTC and CPROR is too simplistic. As I am sure that author is aware, the EORTC was responsible for the development of one of the most widely used cancer-specific PROMs. The suggested division should be revised.
Valid point. This whole section has been largely re-written and the interactions between groups emphasised.

Lines 32-40: Please edit to improve accuracy: The Royal College of Nursing Research Institute (RCNRI) at Warwick Medical School has two core work-streams that are relevant to this article: patient reported outcomes and patient and public involvement. It is important to note that it is not the RCNRI, per se, that is lobbying ISOQOL. Rather, leads for the PRO and PPI work-streams, who are members of ISOQOL. Moreover, I think that it's important to recognise that, informed by work of its members (ref to Haywood et al, 2015; 2016), ISOQOL has recently highlighted patient engagement as part of its future vision and mission statement (http://www.isoqol.org/about-isoqol).
Thank you. Very valid. Changes made and work done referenced..


Refs:
Refs 11 and 12 don’t appear in the text.
They are at Page 10 line 14 and Page 13 line 22 in the text of the first version.
Retained in re-edit.

Standard formatting of ref list is required.

Thank you. Done.