## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Evaluation of Patient-Reported Outcome Protocol Content and Reporting in UK Cancer Clinical Trials: The EPiC study qualitative protocol |
| **AUTHORS** | Retzer, Ameeta; Keeley, Thomas; Ahmed, Khaled; Armes, Jo; Brown, Julia; Calman, Lynn; Copland, Chris; Efficace, Fabio; Gavin, Anna; Glaser, Adam; Greenfield, Diana; Lanceley, Anne; Taylor, Rachel; Velikova, Galina; Brundage, Michael; Mercieca-Bebber, Rebecca; King, Madeleine; Calvert, Melanie; Kyte, Derek |

## VERSION 1 – REVIEW

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| **REVIEWER** | Anna Cox<br>University of Surrey, UK |
| **REVIEW RETURNED** | 17-May-2017 |

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| **GENERAL COMMENTS** | I enjoyed reading this protocol for the qualitative phase (phase II) of the EPiC study which seeks to provide data to explain why PRO information is omitted from protocols and/or trial publications and also inform the development of future training for those involved in clinical trial development.<br><br>This protocol describes the EPiC study as 'a mixed method study investigating patient reported outcome (PRO) protocol content and reporting in UK cancer clinical trials aiming to identify factors that enable and inhibit good practice' and subsequently outlines the qualitative phase (phase II) of the study. In my opinion, this qualitative phase could provide valuable data with the potential to explain why PRO information is omitted from protocols and/or trial publications and also inform the development of future training for those involved in clinical trial development. However, I have some questions and suggestions regarding the protocol which the authors may find useful to consider:<br>I found the protocol introduction to be too similar in content to the introduction of the protocol for phase I of the EPIC study and wonder if an opportunity has been missed to introduce this specific phase of the study.<br>The stated aim of the study could be revisited, at present it reads 'Semi-structured telephone and face-to-face interviews will be conducted (AR) to explore the perspectives and experience of key stakeholders. The aim of these interviews is to explore…'. Is the primary aim of this qualitative study to explore stakeholder perceptions of the barriers and enablers to including PRO information in protocols/publications outlining UK cancer clinical trials? |

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| | Is the secondary aim to consider stakeholder perceptions of how clinical trial practice and reporting could be improved and supported through training and other resources?<br><br>Four stakeholder groups are listed within the section 'participants and setting'. The breadth of participants is a strength of this protocol and I wonder if more detail could have been provided regarding the members of each group and the value they bring to the study. For example 'International experts in PRO oncology trial design' may benefit from more qualification. I would also have found it useful to see specific inclusion and exclusion criteria for participants within each of these groups.<br><br>Additional clarification regarding the sampling of participants could strengthen the protocol. The protocol states that 'individuals will be purposively selected based on experience of optimal and poor PRO data collection and reporting', how is this determined pre-selection as there does not appear to be a screening stage? It states that the research team will 'seek to attain maximum variation with regards to experience and role', this would benefit from more detail in terms of the factors which the authors are seeking variability in and how this will be achieved.<br><br>The consent procedure outlined in the data collection section is unclear. At first point of contact the potential participants will be emailed a consent form, then asked to give audio recorded verbal consent at the start of the interview, but if this is not recorded the interview will still take place but written consent will be sought following the interview. I would recommend that there is a record of each participant's consent prior to any data being collected. It is also unclear whether the participants choose whether the interview is conducted in person or over the telephone, or where the face-to-face interviews will be held.<br><br>With reference to the analysis section I am not familiar with 'directed' thematic analysis and would have liked to see a reference for this approach in order to learn more. The rigour of the study could be questioned in light of only one author analysing the data. I am not familiar with 'formal triangulation of coding' so cannot comment if this will enhance the credibility of the analysis.<br><br>Asking 'international experts' and other skilled professionals to discuss what caused poor reporting of PROs in their trials is potentially sensitive. I wonder if the authors could strengthen the protocol by outlining some of their considerations regarding anonymity and confidentiality in the ethics and dissemination section. |

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| **REVIEWER** | Tenbroeck Smith<br>American Cancer Society<br>250 Williams Street<br>Atlanta, GA 30303 USA |
| **REVIEW RETURNED** | 15-Aug-2017 |

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| **GENERAL COMMENTS** | The emphasis on using PROs in clinical trials is rising, regulatory agencies require PRO data to support certain labeling claims. However, PRO implementation and reporting in clinical trials is often suboptimal. This qualitative study of cancer clinical trials PRO facilitators, barriers and best practices is well timed to provide needed information that could improve clinical trial PRO implementation.<br><br>The paper is well conceived and well written.<br><br>Here are two minor points for the authors' consideration:<br>1) Between collection and reporting of PROs is storage, cleaning and analyses. While these issues may be elicited by the current Interview Topic Guide, I wonder if a few probes on these specific topics might be helpful, especially at the end of the interview if the topics haven't arisen.<br>2) The authors mention "formal triangulation of coding". Please specify what sort of triangulation. Intercoder reliability, cross-checking with other sources, both? |

## VERSION 1 – AUTHOR RESPONSE

Reviewer 1
1) The protocol introduction to be too similar in content to the introduction of the protocol for phase I of the EPIC study and wonder if an opportunity has been missed to introduce this specific phase of the study.

Response: Addressed by removing some previous text and including text relating to aims of qualitative work (lines 143-148)

2) The stated aim of the study could be revisited, at present it reads 'Semi-structured telephone and face-to-face interviews will be conducted (AR) to explore the perspectives and experience of key stakeholders. The aim of these interviews is to explore…'. Is the primary aim of this qualitative study to explore stakeholder perceptions of the barriers and enablers to including PRO information in protocols/publications outlining UK cancer clinical trials? Is the secondary aim to consider stakeholder perceptions of how clinical trial practice and reporting could be improved and supported through training and other resources?

Response: Aim clarified in lines 169-170.

3) Four stakeholder groups are listed within the section 'participants and setting'. The breadth of participants is a strength of this protocol and I wonder if more detail could have been provided regarding the members of each group and the value they bring to the study.

Response: More detail provided in lines 157-162.

4) ‘International experts in PRO oncology trial design’ may benefit from more qualification.

Response: More detail added in lines 187-189.

5) I would also have found it useful to see specific inclusion and exclusion criteria for participants within each of these groups.

Response: Detail added in lines 179-181.

6) Additional clarification regarding the sampling of participants could strengthen the protocol. The protocol states that ‘individuals will be purposively selected based on experience of optimal and poor PRO data collection and reporting’, how is this determined pre-selection as there does not appear to be a screening stage? It states that the research team will ‘seek to attain maximum variation with regards to experience and role’, this would benefit from more detail in terms of the factors which the authors are seeking variability in and how this will be achieved.

Response: Sampling clarification is provided in lines 192-199 and 204-208.

7) The consent procedure outlined in the data collection section is unclear.

Response: Clarification provided in lines 228-230.

8) It is also unclear whether the participants choose whether the interview is conducted in person or over the telephone, or where the face-to-face interviews will be held.

Response: Clarification provided in lines 225-227

9) With reference to the analysis section I am not familiar with ‘directed’ thematic analysis and would have liked to see a reference for this approach in order to learn more.

Response: Clarification in lines 243-244

10) The rigour of the study could be questioned in light of only one author analysing the data. I am not familiar with ‘formal triangulation of coding’ so cannot comment if this will enhance the credibility of the analysis.

Response: Clarification provided in lines 248-251

11) Asking ‘international experts’ and other skilled professionals to discuss what caused poor reporting of PROs in their trials is potentially sensitive. I wonder if the authors could strengthen the protocol by outlining some of their considerations regarding anonymity and confidentiality in the ethics and dissemination section.

Response: Additional text included in lines 264- 66

Reviewer 2
1) Between collection and reporting of PROs is storage, cleaning and analyses. While these issues may be elicited by the current Interview Topic Guide, I wonder if a few probes on these specific topics might be helpful, especially at the end of the interview if the topics haven't arisen

Response: added to topic guide

2) The authors mention "formal triangulation of coding". Please specify what sort of triangulation. Intercoder reliability, cross-checking with other sources, both? –

Response: Clarification included in lines 248-251.

## VERSION 2 – REVIEW

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| **REVIEWER** | Tenbroeck Smith, Strategic Director PROs<br>American Cancer Society, USA |
| **REVIEW RETURNED** | 21-Nov-2017 |

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| **GENERAL COMMENTS** | The revised protocol is stronger. I especially like the updated Strengths and Limitations section.<br><br>The authors might consider adding a question about informants comfort with cleaning, scoring and statistically analyzing PRO data, and their access to experts to help with these things.<br><br>As I noted in my previous review…<br>The emphasis on using PROs in clinical trials is rising, regulatory agencies require PRO data to support certain labeling claims. However, PRO implementation and reporting in clinical trials is often suboptimal. This qualitative study of cancer clinical trials PRO facilitators, barriers and best practices is well timed to fill a needed gap. The paper is well conceived and well written. |

## VERSION 2 – AUTHOR RESPONSE

Many thanks for the review. The previous review stated that "Between collection and reporting of PROs is storage, cleaning and analyses. While these issues may be elicited by the current interview Topic Guide, I wonder if a few probes on these specific topics might be helpful, especially at the end of the interview if the topics haven't arisen." In response to this I added an additional question at the end of the Topic Guide, submitted as an online appendix, where I asked, "Do you have experience of undertaking/overseeing the storage, cleaning and analysis of PRO data?". In response the most recent review, I have added an additional probe of, "Do you feel you have access to expertise in these areas, either in your team or externally?".