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

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

VERSION 1 - REVIEW

REVIEWER	Philip van der Wees Radboud university medical center The Netherlands
REVIEW RETURNED	30-Jun-2016

GENERAL COMMENTS	This study protocol reports the procedure and methodology of a systematic evaluation of PRO protocol content and reporting in UK cancer trials. This is a relevant topic with increasing importance of using PRO data in healthcare decision making. The protocol is sound, provides detailed information, uses relevant reporting standards, and is registered in PROSPERO. The posed objectives and hypotheses are relevant. Major comments: - The authors have planned conducting regression analysis to explore factors associated with the inclusion of PRO-specific protocol items. I suspect that the included trials have been conducted by a limited number of research groups – with more than one trial per research group. Would this imply multi-level regression analysis? - The authors aim to extract the name/type of PROs used in the trials. I would be interested in descriptive statistics of the health domains (e.g. symptoms, physical functioning, mental functioning, social functioning) measured with the included PRO measures. Minor comments: - On page 7 under checklists a reference to potentially relevant ISOQOL reporting standards checklists is lacking.

REVIEWER	Jo Chalmers University of Nottingham, UK
REVIEW RETURNED	06-Jul-2016

GENERAL COMMENTS	This is an important and well-designed study to determine how well

	patient reported outcomes are described and reported in cancer trials. The sample is stated as being UK cancer trials on the portfolio. Does this include multi-national trials recruiting in the UK, or is the study based on UK sponsored trials? It would be helpful to include this detail. The Strengths and limitations section does not address the anticipated limitations of this study. Will the study include any PRO, or is the focus on health-related quality of life instruments? Will composite scores of patient reported and physician reported aspects be included in the sample? The Inclusion / exclusion section should describe in more detail what this is based on – according to the flowchart this initial screen is determined by information easily retrieved from trial registries and sponsor websites. State which version of the protocol will be used –e.g. final version at the point the trial ends, or the initial approved protocol. Typo in the abstract – “and to” is missing between publications and highlight

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Philip van der Wees
Institution and Country: Radboud university medical center, The Netherlands
Competing Interests: None declared
This study protocol reports the procedure and methodology of a systematic evaluation of PRO protocol content and reporting in UK cancer trials. This is a relevant topic with increasing importance of using PRO data in healthcare decision making. The protocol is sound, provides detailed information, uses relevant reporting standards, and is registered in PROSPERO. The posed objectives and hypotheses are relevant.
Major comments:
- The authors have planned conducting regression analysis to explore factors associated with the inclusion of PRO-specific protocol items. I suspect that the included trials have been conducted by a limited number of research groups – with more than one trial per research group. Would this imply multi-level regression analysis?
In designing the analyses, we explored the option of multi-level regression. However during extraction of the study data from the NIHR portfolio database and clinical trial registries it became clear that research group information is poorly collected, ruling this out as a viable analysis option. No change has been made to the manuscript.
- The authors aim to extract the name/type of PROs used in the trials. I would be interested in descriptive statistics of the health domains (e.g. symptoms, physical functioning, mental functioning, social functioning) measured with the included PRO measures.
As part of the descriptive analysis described in the manuscript we will provide an overview of the measures used including the domains once collected. No change has been made to the manuscript.
Minor comments:
- On page 7 under checklists a reference to potentially relevant ISOQOL reporting standards checklists is lacking.
Thank you for highlighting this omission. We have now added the appropriate reference on page 7

now updated to page 10 of manuscript as other changes have shifted the page numbers.

Reviewer: 2
Reviewer Name: Jo Chalmers
Institution and Country: University of Nottingham, UK
Competing Interests: None declared
This is an important and well-designed study to determine how well patient reported outcomes are described and reported in cancer trials.
The sample is stated as being UK cancer trials on the portfolio. Does this include multi-national trials recruiting in the UK, or is the study based on UK sponsored trials? It would be helpful to include this detail.
Thank you. The sample does include multinational trials recruiting in the UK, we have made this clearer in the manuscript (page 6) through the inclusion of the following text
"The NIHR portfolio includes UK-led trials and multinational cancer trials recruiting in the UK, supported by a range of funders, adjudged as high-quality clinical research studies"
The Strengths and limitations section does not address the anticipated limitations of this study.
As discussed above we have now added this information on page 3 (see above).
Will the study include any PRO, or is the focus on health-related quality of life instruments? Will composite scores of patient reported and physician reported aspects be included in the sample?
Our inclusion criteria does not make any distinction between PRO-types and hence we are looking for any PRO primary or secondary outcome so all PROs would be included.
The Inclusion / exclusion section should describe in more detail what this is based on – according to the flowchart this initial screen is determined by information easily retrieved from trial registries and sponsor websites.
State which version of the protocol will be used –e.g. final version at the point the trial ends, or the initial approved protocol.
As the flowchart shows our initial screen is determined by trial registry information. The final protocol version approved by ethics will be used in the analysis, this has been made clearer in the manuscript (page 6) through the inclusion of the following text:
"The most up-to-date trial protocol (final version approved by ethics) and all related subsequent reports/publications will be retrieved for review"
Typo in the abstract – "and to" is missing between publications and highlight
Thank you for highlighting this error, it has now been corrected.

VERSION 2 – REVIEW

REVIEWER	Philip van der Wees Radboud university medical center, The Netherlands
REVIEW RETURNED	18-Aug-2016

GENERAL COMMENTS	The authors have addressed my comments adequately.

REVIEWER	Jo Chalmers Centre of Evidence Based Dermatology, University of Nottingham, UK
REVIEW RETURNED	01-Aug-2016

GENERAL COMMENTS	The additions and changes made have improved the paper. I have two queries remaining: 1. In the additions to the limitations section, it now states that "The review will be limited to UK-led studies adopted to the National

	Institute for Health Research (NIHR) portfolio...". The is different from the addition you have made to the inclusion / exclusion section "The NIHR portfolio includes UK-led trials and multinational cancer trials recruiting in the UK...". This needs to be clarified and consistent in the paper. 2. The inclusion / exclusion section still needs the addition of detail for completeness - I didn't see any justification in the response for not doing so. There should be a reference to the flowchart, and the text should include that non-randomised trials, trials not yet completed, others?) are excluded.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Philip van der Wees
Institution and Country: Radboud university medical center, The Netherlands
Competing Interests: None declared
The additions and changes made have improved the paper. I have two queries remaining:
In the additions to the limitations section, it now states that "The review will be limited to UK-led studies adopted to the National Institute for Health Research (NIHR) portfolio...". The is different from the addition you have made to the inclusion / exclusion section "The NIHR portfolio includes UK-led trials and multinational cancer trials recruiting in the UK...". This needs to be clarified and consistent in the paper.
We agree, we have now omitted “and multinational cancer trials recruiting in the UK” in page 6 of the manuscript and is now consistent with the rest of the manuscript.
2. The inclusion / exclusion section still needs the addition of detail for completeness - I didn't see any justification in the response for not doing so. There should be a reference to the flowchart, and the text should include that non-randomised trials, trials not yet completed, others?) are excluded.
We have now added the following in the inclusion/exclusion section in page 6 of the manuscript:
“Non-randomised trials and trials not completed by the cut-off date (01/03/2014) will be excluded. Following a pilot, it was determined that trial registry information was frequently incomplete, therefore we plan to search for protocols using a range of resources.”

Also in page 7 for further clarity we have added “For each protocol sourced, we will retrieve all related subsequent reports/publications either via a direct email to the named trial contact or using recognized bibliographic databases (e.g. Medline, Embase, CINAHL).”

A reference to the flow chart “Figure 1” has been input in inclusion/exclusion section in page 6, and text in the flow diagram now includes “trials not completed by 01/03/2014.” Table 1 has now been re-named as Figure 1 in page 6 and in flow diagram page 8 of manuscript.