

BMJ Open Evaluation of patient-reported outcome protocol content and reporting in UK cancer clinical trials: the EPiC study qualitative protocol

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ABSTRACT

Introduction Patient-reported outcomes (PROs) are increasingly included within cancer clinical trials. If appropriately collected, analysed and transparently reported, these data might provide invaluable evidence to inform patient care. However, there is mounting indication that the design and reporting of PRO data in cancer trials may be suboptimal. This programme of research will establish via three interlinked studies whether these findings are applicable to UK cancer trials, and if so, how to best enhance the way PROs are assessed, managed and reported in clinical trials. This study will explore with key stakeholders factors that influence optimal PRO protocol content, implementation and reporting and make recommendations for training and guidance.

Methods and analysis Semistructured interviews will be conducted with members of key stakeholder groups. The purposive sample of up to 48 participants will include: (1) trial chief investigators, trial management group members, statisticians and research nurses of cancer trials including primary or secondary PRO recruited via the National Cancer Research Institute (NCRI) Clinical Studies Group and Consumer Liaison Group and the UK Clinical Research Collaboration Registered UK Clinical Trial Unit Network; (2) NCRI Consumer Liaison Group members; (3) international experts in PRO oncology trial design; and (4) journal editors and funding bodies. Data will be analysed using directed thematic analysis employing a coding frame and modified as analysis progresses. Formal triangulation of coding and member checking will be employed to enhance credibility.

Ethics and dissemination This study was approved by the University of Birmingham Ethics Committee (Ref: ERN_17-0085). Findings will be disseminated via conference presentations, peer-reviewed journals, patient groups and social media (@CPROR_UoB; <http://www.birmingham.ac.uk/cpror>).

PROSPERO registration number CRD42016036533.

INTRODUCTION

Patient-reported outcomes (PROs) are increasingly included within cancer clinical

Strengths and limitations of this study

- This novel study will capture perspectives on the barriers and enablers of optimal PRO practice from a comprehensive range of stakeholders with experience of patient-reported outcome (PRO) data collection and reporting.
- The semistructured interview format ensures a replicable process while allowing sufficient freedom to explore new and emerging concepts.
- The recruitment strategy involves seeking participants through networks occupied by Evaluation of Patient-Reported Outcome (PRO) Protocol Content and Reporting in UK Cancer Clinical Trials Senior Management Group members. However, any limitation to sample representativeness and diversity will be mediated through the use of other recruitment avenues including the authorship lists of the protocols/publications included in phase I.
- Study is at risk of self-selection and social desirability bias. Participants are likely to take part if they have a pre-existing interest in PROs specifically and when recounting their experiences and insights are likely to wish to portray themselves in a positive manner due to the nature of this study.

trials to provide the patient perspective on the physical, functional and psychological consequences of treatment and the degree and impact of disease symptoms.¹ The number of randomised controlled clinical trials including PROs is now substantial across all cancer disease sites, and these often include PROs as secondary endpoints.² PROs are typically collected using multidimensional questionnaires in electronic or paper format and are completed by patients while they are participating in clinical trials. The results provide information about the symptoms or quality of life effects of a particular therapy



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and may inform future treatment choices and help physicians and patients decide the most suitable treatment and care for the individual. Rigorous study design and standardised data collection methods are required to collect the highest quality PRO data and adhering to good practice minimises errors, measurement variability, missing data and systematic bias, upholding trial validity.³

The use of PROs in cancer clinical trials has been exhorted by major international health policy and regulatory authorities as well as patients with cancer.⁴⁻⁶ PRO trial results inform clinical decision making; health technology assessment; health economic evaluations; labelling claims; healthcare policy; and commissioning⁷⁻¹⁰ when rigorously captured. PRO data can enhance clinician–patient communication relating to treatment options and contribute to complex healthcare decision making^{11 12} by providing information on relative benefits and side effects of new drugs or treatment options.¹³⁻¹⁷ Using this information, patient–clinician consultations may result in more informed choices, positive results and favourable experiences of care.^{18 19} As such, guidance included in trial protocols must ensure appropriate PRO data collection and management,^{20 21} and results must be fully reported in resulting publications so that PRO information is readily publicly accessible to patients and integrated into clinical practice and policy.²¹

Recent international evidence,²²⁻²⁵ however, suggests PRO information is often omitted from protocols, leading to impaired data collection. Such research also suggests that PRO results are poorly reported in trial publications, or may not be reported at all.²² Our previous review of 75 National Institute for Health Research Health Technology Assessment trials²³ found that relevant PRO information is commonly omitted from trial protocols, even where a PRO is the primary outcome. As a result, PRO data may not be used effectively to inform patient–clinician decision making at the point of diagnosis and beyond. This represents a waste of limited healthcare and research resources, devalues the contribution of trial participants providing PRO data and has serious ethical implications.

While there has been some qualitative research investigating PRO administration in trials,^{24 26} there has been little qualitative work investigating the factors affecting PRO trial design, protocol development and reporting.

The Evaluation of Patient-Reported Outcome (PRO) Protocol Content and Reporting in UK Cancer Clinical Trials (EPiC) study is a mixed method study investigating PRO protocol content and reporting in UK cancer clinical trials aiming to identify factors that enable and inhibit good practice. The research will take place over three stages; the methods pertaining to phase I are presented in detail elsewhere.²⁷

This paper provides a summary of the phase II qualitative component, in which semistructured interviews will be conducted to explore the potential barriers and enablers relating to optimal PRO protocol content, implementation and reporting with cancer trialists, research nurses (RNs), consumer representatives, international

experts, journal editors and funders. Through the inclusion of individuals from each of these groups, the collection and reporting of PRO data can be considered by the individuals involved at every phase of the research process—including study conception and design and patients' experiences of providing PRO data as trial participants—until the point at which results are communicated. Phase III of the study will incorporate findings and examples of best practice from both phases I and II into our publicly accessible, web-based training resource (www.birmingham.ac.uk/prolearn).

AIMS

Semistructured telephone and face-to-face interviews will be conducted (AR) to explore the perspectives and experience of key stakeholders in relation to:

1. the potential barriers and enablers to optimal PRO protocol content, implementation and reporting
2. the PRO-specific training needs of each stakeholder group
3. the optimal methods of implementing such training and ensuring uptake of both the forthcoming SPIRIT-PRO²⁸ and published CONSORT-PRO²⁹ guidelines.

PARTICIPANTS AND SETTING

The primary inclusion criteria are that participants must have experience of designing or reviewing clinical trials including PROs within a professional capacity or completion of PROs through participation in a trial. Interviewees will be sampled from four groups: (1) trial chief investigators, trial management group members, statisticians and RNs with experience of involvement in a cancer trial including primary or secondary PRO; (2) National Cancer Research Institute (NCRI) Consumer Liaison Group members with experience of involvement in the design of trials with PRO endpoints; (3) international experts in PRO oncology trial design, including members of multi-country cancer and quality of life research organisations, national regulatory bodies, advisory bodies and global corporations; and (4) journal editors and key representatives from funding bodies. Based on the experience of the research team, it is anticipated that recruitment of approximately 8–12 individuals from each group will be required to reach data saturation. Thus, up to 48 participants may be required. Individuals will be purposively selected based on having occupied a role within trials in management, data collection, as a patient partner or a participant. The categorisation of participants into the above four groups will allow the research team to attain maximum variation with regards to experience and role. Recruitment will continue for each distinct group until data saturation is achieved.

Group 1 will be identified from: (1) the authorship lists of the trial protocols/publications included in phase I or (2) NCRI Clinical Studies Groups and Consumer Liaison Group and the UK Clinical



Research Collaboration Registered UK Clinical Trial Unit (UKCRC-UKCTU) Network, facilitated by an EPiC study management member who is also the UKCRC-UKCTU network director. Trials from phase I will be purposively selected to ensure representation across the following criteria: clinical area, SPIRIT-PRO and CONSORT-PRO checklist score^{23 28–30} and funding source. Group 2 participants will be identified via the NCRI Consumer Liaison Group, facilitated by an EPiC study management member who is also the NCRI Psychosocial Oncology and Survivorship Clinical Studies Group chair. Group 3 will be identified using the personal contacts of the study management group, in particular via an EPiC study senior management group member who is also director of the Centre for Patient-Reported Outcomes Research at the University of Birmingham. Group 4 will be identified using publicly available information via the appropriate journal/funder website.

DATA COLLECTION

Potential participants will be approached via email (either directly where contact details are in the public domain or via the centre from which they were identified where appropriate) and provided with a brief outline of the project aims, the consent form and information sheet and details of how to register interest. Individuals interested in taking part will be contacted by the research fellow (AR) and will be given an opportunity to ask further questions before deciding whether to take part in the study. An interview date will be set for those wishing to participate. Participants will be first offered a telephone interview. In cases where the individual wishes to participate in an interview but would prefer to do so in person rather than via telephone, this will be arranged if feasible.

Participants will be sent a consent form to complete. The researcher will request that the consent form is returned prior to the interview. In cases where a consent form has not been received by the researcher in advance of the interview, verbal consent will be audio-recorded and taken via a standardised script immediately prior to the interview. If a participant would prefer their verbal consent is not audio-recorded, verbal consent will still be taken prior to interview but on the understanding that a consent form will be sent by the researcher to the participant immediately after the interview to be signed and returned.

The interviews will last for approximately 1 hour. Participants will be interviewed using a predefined topic guide (online supplementary appendix 1) with sufficient scope to explore novel themes where appropriate and will be audio-recorded. Interview recordings will be professionally transcribed verbatim. All participants will remain anonymous, and all data will be treated as confidential.

Study dates: March 2016–September 2018.

ANALYSIS

Interview transcripts will be analysed using directed thematic analysis (AR) whereby findings from previous qualitative and review work²⁴ and the analysis of included protocols and publications from phase I will be used in addition to developing an initial coding framework.³¹ Additional codes will be developed as the analysis progresses and the framework will be modified accordingly.³¹ Formal triangulation of coding will be employed to enhance the credibility of the analysis. This will be undertaken at regular intervals during analysis when a subsample of transcripts will be coded by an additional researcher (DK/MC), and differences will be discussed to ensure intercoder agreement.

The findings from this phase, in combination with the phase I findings, will be used in phase III to highlight examples of best practice in PRO protocol design and reporting and inform the development of an online PRO training resource.

DISSEMINATION

The results of this study will be disseminated via presentations at local, national and international conferences, peer-reviewed journals and through social media including the Centre for Patient Reported Outcomes Research's Twitter account and the University of Birmingham departmental website (<http://www.birmingham.ac.uk/cpror>), as well as the NCRI (including the consumer forum), Macmillan Cancer Support and via international cancer trial groups. Participants will be anonymised, and all data collected will be treated as confidential. Only anonymised, non-identifiable characteristics and quotes will be used in any arising publications/reports.

PROTOCOL AND REGISTRATION

This study protocol for the wider programme of work is registered on PROSPERO (CRD42016036533). Registration details are available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036533.

DISCUSSION

Existing evidence and pilot data collected to demonstrate the feasibility of our approach suggests there may be substantial variation in PRO protocol content and reporting in UK cancer clinical trials. The qualitative component of the EPiC study will explore and explain the contributing factors with stakeholders and establish how clinical trial practice may be improved and supported through training and other resources. This work could benefit several groups including researchers and those involved in research dissemination and service delivery. Appropriate collection, analysis, rationale and reporting of PROs may result in comprehensive data on which treatment decisions may be based, benefiting patients,

but would also promote more effective use of public and charitable funds.

This work represents the PRO component within a far wider effort to promote effective, robust and transparent practice within clinical trials. Initiatives focusing on improving practice relating to various aspects of clinical trials^{32–34} have been lauded and are changing practice through their use.^{35–37} The inconsistent use of PROs in cancer clinical trials is well documented; however, the findings from this programme of research have the potential to address these shortcomings through the development of tailored PRO training and guidance for key stakeholders.

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Contributors The study concept and design was conceived by DK, TK, FE, JA, JMB, LC, CC, AnG, AdG, DMG, AL, RMT, GV, MB, RM-B, MTK and MC. AR and KA will recruit, screen and consent participants and will undertake the interviews with input and supervision from DK and MC. AR prepared the first draft of the manuscript. DK, TK, FE, JA, JMB, LC, CC, AnG, AdG, DMG, AL, RMT, GV, MB, RM-B, MTK and MC all provided edits and critiqued the manuscript for intellectual content.

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Competing interests JA, LC, CC, AnG, AdG, DMG, DK and AL are all members of the National Cancer Research Institute Psychosocial Oncology and Survivorship CSG subgroup: 'Understanding and measuring the consequences of cancer and its treatment'. FE receives consultancy fees from Bristol-Myers Squibb, Seattle Genetics, TEVA and Incyte; and research funding from Lundbeck, TEVA and Amgen. GV receives grants from the National Institute for Health Research and Yorkshire Cancer Research, and personal fees from Roche, Genentech, Eisai and Novartis. MC has received personal fees from Astellas Pharma and Ferring and chairs the ISOQOL Best Practice for PROs in Trials Taskforce. JMB receives grants from the National Institute of Health Research, Yorkshire Cancer Research, Macmillan and Roche. JA is in receipt of grant funding from EU FP7 Framework. AdG is in receipt of grants from Candlelighters, National Institute for Health Research, Macmillan Cancer Support, Prostate Cancer UK and Yorkshire Cancer Research. MTK and RM-B have received project funding from Abbvie and Alcon. MTK co-chairs the ISOQOL Best Practice for PROs in Trials Taskforce. DK and RM-B are members of the ISOQOL Best Practice for PROs in Trials Taskforce.

Patient consent Not required.

Ethics approval The study was approved by the research ethics committee at the University of Birmingham (Ref: ERN_17–0085) on 20 February 2017.

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REFERENCES

- Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 1: why evaluate health-related quality of life? *J Clin Pharm Ther* 2003;28:513–21.
- Efficace F, Fayers P, Pusic A, *et al.* Quality of patient-reported outcome reporting across cancer randomized controlled trials according to the CONSORT patient-reported outcome extension: a pooled analysis of 557 trials. *Cancer* 2015;121:3335–42.
- Kyte DG, Draper H, Ives J, *et al.* Patient reported outcomes (PROs) in clinical trials: is 'in-trial' guidance lacking? A systematic review. *PLoS One* 2013;8:e60684.
- Ahmed S, Berzon RA, Revicki DA, *et al.* The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. *Med Care* 2012;50:1060–70.
- Department of Health. *Equity and excellence: liberating the NHS*. UK: Department of Health, 2011.
- Ouwens M, Hermens R, Hulscher M, *et al.* Development of indicators for patient-centred cancer care. *Support Care Cancer* 2010;18:121–30.
- FDA. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. 2009 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>
- Higginson IJ, Carr AJ. Measuring quality of life: using quality of life measures in the clinical setting. *BMJ* 2001;322:1297–300.
- NICE. *Guidance on the use of trastuzumab for the treatment of advanced breast cancer*, 2002.
- EMA. *Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies [draft]*: European Medicines Agency, 2014. Oncology Working Party; Doc Ref. EMA/CHMP/292464/.
- Brundage M, Leis A, Bezjak A, *et al.* Cancer patients' preferences for communicating clinical trial quality of life information: a qualitative study. *Qual Life Res* 2003;12:395–404.
- Davison BJ, Goldenberg SL, Gleave ME, *et al.* Provision of individualized information to men and their partners to facilitate treatment decision making in prostate cancer. *Oncol Nurs Forum* 2003;30:107–14.
- Au HJ, Ringash J, Brundage M, *et al.* Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. *Expert Rev Pharmacoecon Outcomes Res* 2010;10:119–28.
- Basch E. Toward patient-centered drug development in oncology. *N Engl J Med* 2013;369:397–400.
- Blazeby JM, Avery K, Sprangers M, *et al.* Health-related quality of life measurement in randomized clinical trials in surgical oncology. *J Clin Oncol* 2006;24:3178–86.
- Ford HE, Marshall A, Bridgewater JA, *et al.* Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78–86.
- Dutton SJ, Ferry DR, Blazeby JM, *et al.* Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014;15:894–904.
- Macmillan. *Improving cancer patient experience: a top tips guide*. London, UK: Macmillan Cancer Support, 2012. http://www.macmillan.org.uk/Documents/AboutUs/Commissioners/Patientexperiencesurvey_TopTipsguide.pdf (accessed Aug 2015).
- NHS. *Cancer patient experience survey 2014: national report*. 2014 <https://www.quality-health.co.uk/surveys/national-cancer-patient-experience-survey> (accessed Aug 2015).



20. Calvert M, Thwaites R, Kyte D, *et al.* Putting patient-reported outcomes on the 'Big Data Road Map'. *J R Soc Med* 2015;108:299–303.
21. Chan AW, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586–42.
22. Brundage M, Bass B, Davidson J, *et al.* Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. *Qual Life Res* 2011;20:653–64.
23. Kyte D, Duffy H, Fletcher B, *et al.* Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014;9:e1110229.
24. Kyte D, Ives J, Draper H, *et al.* Inconsistencies in quality of life data collection in clinical trials: a potential source of bias? Interviews with research nurses and trialists. *PLoS One* 2013;8:e76625.
25. Mercieca-Bebber R, Friedlander M, Kok PS, *et al.* The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols. *Qual Life Res* 2016;25:2457–65.
26. Mercieca-Bebber R, Kyte D, Calvert M, *et al.* Administering patient-reported outcome questionnaires in Australian cancer trials: the roles, experiences, training received and needs of site coordinators. *Trials* 2017;18(Suppl 1):O30.
27. Ahmed K, Kyte D, Keeley T, *et al.* Systematic evaluation of patient-reported outcome (PRO) protocol content and reporting in UK cancer clinical trials: the EPiC study protocol. *BMJ Open* 2016;6:e012863.
28. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
29. Calvert M, Blazeby J, Altman DG, *et al.* Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309:814–22.
30. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010;7:e1000251.
31. Fereday J, Muir-Cochrane E. Demonstrating rigor using thematic analysis: a hybrid approach of inductive and deductive coding and theme development. *Int J Qual Methods* 2006;5:80–92.
32. Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
33. Williamson PR, Altman DG, Blazeby JM, *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
34. Goldacre B. Are clinical trial data shared sufficiently today? No. *BMJ* 2013;347:f1880.
35. Tenaerts P, Madre L, Archdeacon P, *et al.* The Clinical Trials Transformation Initiative: innovation through collaboration. *Nat Rev Drug Discov* 2014;13:797–8.
36. Simera I, Moher D, Hirst A, *et al.* Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med* 2010;8:24.
37. Moher D, Glasziou P, Chalmers I, *et al.* Increasing value and reducing waste in biomedical research: who's listening? *Lancet* 2016;387:1573–86.

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