The need for ethical guidance for the use of Patient-Reported Outcomes (PROs) in research and clinical practice

Cruz Rivera, Samantha; Mercieca-Bebber, Rebecca; Aiyegbusi, Olalekan Lee; Jane A, Scott; Hunn, Amanda ; Fernandez, Conrad ; Ives, Jonathan; Ells, Carolyn ; Price, Gary; Draper, Heather; Calvert, Melanie

DOI:
10.1038/s41591-021-01275-z

Document Version
Peer reviewed version

Citation for published version (Harvard):
Cruz Rivera, S, Mercieca-Bebber, R, Aiyegbusi, OL, Jane A, S, Hunn, A, Fernandez, C, Ives, J, Ells, C, Price, G, Draper, H & Calvert, M 2021, 'The need for ethical guidance for the use of Patient-Reported Outcomes (PROs) in research and clinical practice', *Nature Medicine*, vol. 27, no. 4, pp. 572-573. https://doi.org/10.1038/s41591-021-01275-z

The need for ethical guidance for the use of Patient-Reported Outcomes (PROs) in research and clinical practice

Samantha Cruz Rivera[1,2], Rebecca Mercieca-Bebber[3], Olalekan Lee Aiyegbusi[1,2,4] , Jane Scott[5], Amanda Hunn[6], Conrad Fernandez[7], Jonathan Ives[8], Carolyn Ells[9], Gary Price[1], Heather Draper[10], Melanie J Calvert[1,2,411-12]

[1]Centre for Patient Reported Outcomes Research, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[2]Birmingham Health Partners Centre for Regulatory Science and Innovation, University of Birmingham, Birmingham, UK
[3]Faculty of Medicine, Sydney Medical School, Central Clinical School, University of Sydney, Sydney, Australia

[4]National Institute for Health Research (NIHR) Applied Research Centre West Midlands, Birmingham, UK

[5]PRO Center of Excellence, Global Commercial Strategy Organization, Janssen Global Services, Warrington, UK

[6]A J Hunn Associates, UK

[7]Division of Haematology-Oncology, IWK Health Care Centre, Halifax, Nova Scotia, Canada

[8]Bristol Medical School, Bristol Population Health Science Institute, University of Bristol, Bristol, UK

[9]School of Population and Global Health, McGill University, Montreal, Quebec, Canada

[10]Social Science and Systems in Health, University of Warwick, Warwick, UK

[11]NIHR Birmingham Biomedical Research Centre, NIHR Surgical Reconstruction and Microbiology Research Centre, University of Birmingham, Birmingham, UK

[12]Health Data Research UK, London, UK

Corresponding author

Prof Melanie Calvert

m.calvert@bham.ac.uk

Professor of Outcomes Methodology, NIHR Senior Investigator
Director Centre for Patient Reported Outcomes Research

To the Editor - Patient-reported outcomes (PROs) are increasingly used in clinical research to provide evidence of the benefits and risk of therapy from a patient perspective. PRO data from clinical trials can inform regulatory approvals and drug labelling, clinical guideline development and health policy.[1] Approximately one third of clinical trials include PROs collected using patient questionnaires.[2] Beyond trials, PRO data is also increasing capture in observational research and routine clinical care to provide information on the burden of disease, real-world evidence of treatment safety and effectiveness,[3] for audit and benchmarking,[1] and to monitor patient status and provide timely care tailored to individual needs. For instance, a recent study demonstrated that systematic web-based collection of symptoms led to improved health-related quality of life (HRQL), survival, quality-adjusted survival, and reduced emergency room (ER) visits and hospitalisation, among patients receiving chemotherapy for advanced solid tumours.[4] Patients value PRO trial results as they can enhance clinician-patient communication regarding treatment options, helping patients to feel more empowered in shared decision-making around their care.[5]

Despite the benefits of incorporating PROs in research and routine practice several ethical challenges can hinder the uptake and benefit to patients of PRO data. The PRO content of trial protocols and reporting of PRO results are often suboptimal; missing data rates are high, and delay of PRO data publications are predominant. A recent study evaluating 228 NIHR (National Institute of Health Research) Cancer portfolio studies demonstrated that 50,000 patients were involved in studies that failed to publish the PRO data collected, which is considered to be unethical.[6]

PRO data collection is associated with a number of ethical considerations which must be addressed. An ethical consideration is defined as one that requires a choice based on moral considerations drawing on established principles, theories and values, which might have implications on the individuals or society's welfare. The differing use of PROs in research and routine care settings, and review/use of data by clinical teams, may lead to uncertainties for patients about why data is being collected and data privacy - how their data is being viewed and used. Research indicates that in some instances PRO measures may not reflect the perspectives of vulnerable groups or older people challenging bioethical principles and threatening the scientific validity of results.[7] Patient burden associated with completing multiple questionnaires is also a concern. Of particular note is the lack of guidance surrounding how staff should manage situations where PRO data reveal “concerning” levels of psychological distress or physical symptoms that

may require an immediate response.[8] Evidence suggests research staff are handling such data inconsistently, which may lead to inequitable patient care, co-intervention bias and confusion.

Furthermore, PROs could be used for long-term follow-up to assess the impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on patients' quality of life and alert the clinician of potential life threating symptoms.[9] The increased use of telehealth will also influence the increased use of PRO data to monitor patients' symptoms. Therefore, there is a need to ensure that this is done in an ethical way that protects patient safety and data.

To address these challenges, the PRO Ethics Steering Group comprised of PRO methodologists, patient partners and ethicists and is developing international, consensus-based guidelines for use by researchers and patient partners in preparing ethics submissions and for use by Research Ethics Committees and Institutional Review Boards in the assessment of PRO research. The guidelines will focus specifically on ethical considerations of PRO research and data collection in clinical practice, using the EQUATOR (Enhancing Quality and Transparency of Health Research) Network methodological guideline development.[10] The development process will include a literature review, modified Delphi exercise and international consensus meeting involving members of Research Ethics Committees, experts in research ethics, patient partners, trialists and PRO researchers. Given the dearth of guidance currently available, we plan to hold the Delphi exercise and consensus meeting with a view to publishing the guideline in 2021.

Author contribution:

SCR and MJC conceived the idea. SCR developed the first draft. All authors made substantial revisions, and approved the final manuscript.

Ethics Statement

MJC receives funding from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR ARC West Midlands at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UK Research and Innovation), Macmillan Cancer Support and UCB Pharma. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. M.J.C. has received personal fees from Astellas, Takeda, Merck, Daiichi Sankyo, Glaukos, GlaxoSmithKline (GSK) and the Patient-Centered Outcomes Research Institute

(PCORI) outside the submitted work. OLA declares personal fees from Gilead Sciences Ltd and GSK outside the submitted work. JS is an employee of Janssen-Cilag UK and holds stock in Johnson and Johnson. RMB is supported by the Australian Government by a National Health and Medical Research Early career fellowship.

References

1. Calvert, M., Kyte, D., Price, G., Valderas, J.M. & Hjollund, N.H. Maximising the impact of patient reported outcome assessment for patients and society. *BMJ* **364**, k5267 (2019).
2. Vodicka, E.*, et al.* Inclusion of patient-reported outcome measures in registered clinical trials: evidence from ClinicalTrials. gov (2007–2013). *Contemporary clinical trials* **43**, 1-9 (2015).
3. Calvert, M.J., O'Connor, D.J. & Basch, E.M. Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes. *Nat Rev Drug Discov* **18**, 731-732 (2019).
4. Basch, E.*, et al.* Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer TreatmentOverall Survival for Patient-Reported Symptom Monitoring in Routine Cancer TreatmentLetters. *JAMA* **318**, 197-198 (2017).
5. Brundage, M.*, et al.* Cancer patients' preferences for communicating clinical trial quality of life information: a qualitative study. *Qual Life Res* **12**, 395-404 (2003).
6. Kyte, D.*, et al.* Systematic evaluation of Patient-Reported outcome protocol content and reporting in Cancer trials. *JNCI: Journal of the National Cancer Institute* **111**, 1170-1178 (2019).
7. Hagell, P., Reimer, J. & Nyberg, P. Whose quality of life? Ethical implications in patient-reported health outcome measurement. *Value in Health* **12**, 613-617 (2009).
8. Kyte, D., Draper, H. & Calvert, M. Patient-Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical Trials. *JAMA* **310**, 1229-1230 (2013).
9. Aiyegbusi, O.L. & Calvert, M.J. Patient-reported outcomes: central to the management of COVID-19. *Lancet* **396**, 531-531 (2020).
10. Moher, D., Schulz, K.F., Simera, I. & Altman, D.G. Guidance for Developers of Health Research Reporting Guidelines. *PLOS Medicine* **7**, e1000217 (2010).