
Article:
Calvert, MJ, Cruz Rivera, S, Retzer, A et al. (2022) Patient reported outcome assessment must be inclusive and equitable. Nature Medicine, 28 (6). pp. 1120-1124. ISSN: 1078-8956

https://doi.org/10.1038/s41591-022-01781-8

Patient reported outcome assessment must be inclusive and equitable

Melanie J Calvert[1-8], Samantha Cruz Rivera[1-3], Ameeta Retzer[1,4], Sarah E Hughes[1,2,4], Lisa Campbell[10], Barbara Molony-Oates[11], Olalekan Lee Aiyegbusi[1,2,4,5] Angela M Stover[12], Roger Wilson[13-15], Christel McMullan[1,2,6,16], Nicola E Anderson[1,21], Grace M Turner [1,6], Elin Haf Davies[17], Rav Verdi[15], Galina Velikova[18], Paul Kamudoni[19], Syed Muslim[1,2,8], Adrian Gheorghe[20], Daniel O'Connor[10], Xiaoxuan Liu[1,2,21,22], Albert W. Wu[23], Alastair K Denniston[1-3,9,21,22,24]

Corresponding author:
Prof Melanie Calvert
m.calvert@bham.ac.uk

Affiliations

[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]DEMAND Hub, University of Birmingham, Birmingham, UK
[4]National Institute for Health Research (NIHR), Applied Research Collaboration (ARC) West Midlands, Birmingham, UK
[5]NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham and University of Birmingham, Birmingham, UK
[6]NIHR Surgical Reconstruction and Microbiology Research Centre, University Hospital Birmingham and University of Birmingham, UK
[7]Health Data Research UK, London, UK
[8]UK SPINE, University of Birmingham, Birmingham, UK
[9]Health Data Research UK, London, UK
[10]Medicines and Healthcare products Regulatory Agency (MHRA), London, UK
[11]Health Research Authority, London, UK
[12]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, US
[13]NCRI Consumer Forum National Cancer Research Institute, London, UK
[14]Health Research Authority Patient Involvement Network
[15]Patient partner, University of Birmingham, Birmingham, UK
[16]Trauma Science Research, University of Birmingham, Birmingham, UK
[17]Aparito Limited, Wrexham, Wales, UK
[18]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK
[19]EMD Serono Inc, Healthcare Business of Merck KGaA, Darmstadt, Germany
[20]Imperial College London, London, UK
[21]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.
[22]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
[23]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.
[24]National Institute of Health Research Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and University College London, Institute of Ophthalmology, London, UK

Patient-reported outcomes are increasingly collected in clinical trials and in routine clinical practice, but strategies must be taken to include under-served groups in order to avoid increasing health disparities.

Patient-reported outcomes (PROs) collected in trials can provide valuable evidence on the risks and benefits of treatment from a patient perspective, to inform regulatory approvals, clinical guidelines and health policy. PROs are increasingly collected routinely in clinical settings, at an aggregate level for audit and benchmarking, for real-world evidence generation, and as an input or predicted output for clinical decision tools and artificial intelligence (AI) in health. [1,2] At an individual patient level, PROs can be used to facilitate shared-decision making, screen or monitor symptoms, and provide timely care tailored to individual needs.[3] PROs are also increasingly used in value-based healthcare initiatives.[4]

Efforts to capture and report PRO data should be inclusive and equitable, addressing the diverse needs of all patients with the condition of interest, including groups historically and currently underserved by research.[5,6] Issues of diversity, equity and inclusion (Box 1) have recently been highlighted in PRO ethical guidelines, which have identified a number of concerns to be addressed in PROs research.[5]

Lack of representation

Underserved groups are often poorly represented in research and may receive suboptimal clinical care, due to a range of cultural, socio-economic, and logistical reasons, in addition to narrowly defined inclusion criteria for research. Lack of representation is compounded by historical mistrust of research and medical institutions that persists in many groups.

Digital inclusion Many people face barriers to using digital services, including a lack of digital skills or lack of access to infrastructure. Digital inclusion seeks to design services so that they meet all users' needs.[7]
Diversity, Equity, and Inclusion Respecting and valuing all forms of difference in individuals, acknowledging and allowing for case-specific resource allocation for different individuals to reach the same outcomes, while positively striving to meet the needs of different people and taking deliberate action to create environments where everyone feels respected and able to reach their potential.[8,9]
Health data poverty Health data is often not representative of the diversity within a population, and so some groups do not benefit from healthcare innovations [10]
Interactive Voice Response (IVR) This allows participants to complete an automated questionnaire via a telephone keypad or by speech recognition.
Patient-Reported Outcomes A measurement of the patient's health provided directly by the patient, rather than interpreted by a clinician.[11]
Under-served groups The definition of under-served is context-specific and depends on the target population, question being asked, and intervention being tested. Under-served groups may reflect demographic, socio-economic and health status factors. Examples include, but are not limited to: age, race, ethnicity, sexual orientation, gender identity, socio-economically or educationally disadvantaged, individuals with disabilities, rare

disease, those with language or literacy barriers, pregnant women, those living in remote areas, or areas where local service provision is weak or failing.[12]
User-centered design Design processes that are iteratively conducted with end users.[8]
Value-based healthcare "The equitable, sustainable and transparent use of the available resources to achieve better outcomes and experiences for every person."[13]

Box 1. Key terms

PROs can provide valuable evidence on the efficacy and safety of drugs and biologics, which can vary depending on intrinsic and extrinsic factors, including sex, race, ethnicity, and age. Clinical trials should provide information that informs the use of therapeutic agents within the target population. However, despite regulatory guidance and public expectations, the composition of study populations in most clinical trials does not always reflect such characteristics, which limits analysis of treatment outcome by subgroup. This failure to achieve meaningful diversity limits information about drug response and measures of safety and efficacy, which may result in health data poverty (Box 1) [10] In this context clinical trial results, and PRO data specifically, become biased, being limited to those populations involved in research, with sectors of the population excluded, or even harmed, as a result. Lack of representative PRO data collection limits understanding of the impact of disease or treatment on patients' symptoms and quality of life, and thus the evidence base on which to provide clinical care, make regulatory decisions, and inform health policy. This comment will consider current challenges related to PRO data collection in under-served groups and identify approaches for greater inclusion.

Barriers to completion

With an increasing focus on PRO data collection to support patient-centered care it is essential that the needs of under-served groups are addressed (Box 1). A key barrier to PRO data collection in under-served groups is a lack of valid and reliable measures that have been developed in, or are salient to, the target population. Many PRO measures are developed with limited patient input and may not address concepts that matter to under-served groups. Even when individuals from under-served groups are invited to complete PRO measures, they may experience significant barriers to PRO data completion. Individuals with disabilities, such as sight impairment, arthritis, or cognitive function, and those in poor health, may find completing the measures burdensome or challenging.[6] People with learning disabilities and low literacy have experienced exclusion from the routine monitoring of their health and wellbeing afforded by PROs.[14]

Importantly, the move to electronic PRO collection, whilst helpful for some, has created new barriers for others. Barriers to digital inclusion are widespread in under-served populations, with poor accessibility arising from a range of issues (Box 1). Estimates suggest that 37% of the world's estimated 7.8 billion population are digitally excluded, with older people, people on low incomes, and other marginalized groups most likely to be affected.[15]

A recent study investigating the incorporation of PROs in clinical trials demonstrated that certain patient groups are not represented.[16] Investigators examined PRO capture across 10 National Clinical Trials Network (NCTN) Oncology clinical trials and found that 24.7% of study participants declined to complete the PROs, and that 62.2% of the participants who agreed to the PRO component declined electronic PRO capture. Racial or ethnic minorities,

those with less education, and older patients were less likely to consent to electronic PRO collection.

AI health technologies trained and tested on PRO datasets that do not include members of these under-served populations are increasingly being utilized in healthcare. There is a risk that individuals from these groups may systemically receive suboptimal care as a result.[17]

Racial and ethnic disparities

Specific challenges have been identified in the inclusion of minority ethnic groups in research and with the use of translated and culturally validated PROs.[8,18] A review of ethnicity reporting and PRO use of cancer trials registered in the National Institute for Health Research (NIHR) portfolio found that only 14/84 (17%) of trials collecting PROs reported ethnicity data. Eight (57%) studies were multi-centered, multi-national trials and the remaining were UK based (43%), suggesting a diverse target population, however, none reported using translated PRO measures even when available.[18]

Online collection of PROs may lead to profound racial disparities, as highlighted by Mass General Brigham's PRO data collection spanning 10 hospitals, 200 clinics, and more than 75 specialties in the US.[19] Prior to the COVID-19 pandemic only 17% of PROs were collected using an online patient portal, with the remainder collected via tablet in clinic.[19] PRO completion rates were equitable, irrespective of self-identified race or ethnicity recorded within the electronic health record. In March 2020, all tablets used for PRO collection were removed from clinics to limit the spread of COVID-19. This rapid transition prompted a shift in the capture of PROs, from primarily in-clinic to the online portal; this shift introduced profound disparity in data collection. Patients who self-identified as Black provided PROs at half the rate of white patients, and patients who identified as Hispanic almost stopped completing PROs altogether.[19]

Low and middle income countries

Further consideration should be given to PRO data collection in low- and middle-income countries (LMICs). Participants from LMICs tend to be under-represented in the development of PRO measures and there are also indications of a correlation between economic development and research participation, whereby PRO research is more likely to be conducted in upper-middle income economies, such as Brazil, Russia, India, China and South Africa, than in low-income economies.[20] The challenges of conducting PRO research in LMIC settings include: lower literacy levels, which require the use of interview administered questionnaires, which can in turn introduce bias; variable adherence to standardized protocols for conducting RCTs; and cultural diversity. Such challenges require particular attention from research funders and investigators when designing, budgeting and conducting research. Outcomes should be culturally relevant and practical aspects of data collection must be carefully considered for each context.

A growing number of LMICs are proactively looking at collecting and using local evidence to strengthen their healthcare decision-making processes, as a core strategy for progressing towards universal health coverage. A stronger focus on collecting PRO data in LMICs presents a valuable opportunity to entrench patients' perspectives in the health policy discourse.

Widening participation

Barriers to participation in PRO completion, such as access to technology, disability, language and cultural requirements, should be addressed both in the interests of fairness and to ensure results are as accurate and generalizable as possible. Resources required to widen participation should be considered, for example, costs of alternative modes of PRO administration, addressing accessibility requirements, and development of culturally relevant translations.

Existing good practice guidance such as minimizing participant burden, streamlining PRO administration, and using PRO alerts can be effectively used to promote inclusion and accessibility.[5] Communication of the rationale for PRO assessment (who will access the data and how it will be used) to potential participants may address the concerns of those wary of participating in research or providing information in a routine care setting. The representation and participation of under-served groups in PROs can be increased by the actions in Table 1.

Table 1. Actions to promote representation and participation of under-served groups in PROs

Considerations	Actions
Diversity	
Consider how individuals from all relevant demographics within the target population (including age, sex, pregnant women, sexual orientation, race, ethnicity, level of education and socioeconomic status) can be included. [21]	• Involve individuals that are representative of the target population in the identification of key concepts to measure, the development and selection of PROs, the co-design of PRO systems, and data collection. • Assess whether PRO measures perform consistently across groups (e.g., based on measurement equivalence or differential item functioning)
Clinical Characteristics	
Consider the type and severity of disease, the range of symptoms and functional impacts, comorbidities, and physical and cognitive disabilities. [21]	• When heterogeneity in disease symptoms, signs, and impacts exist, assess concepts that are most important to a broad range of patients. • Minimise functional impacts that may limit ability to complete PROs (e.g., issues of dexterity). • Use accessible formats that address the needs of the target population. • Allow proxy completion (someone to report the participant's outcomes on their behalf as though they are the patient) for individuals who are unable to complete e.g., due to cognitive impairment. Please note regulatory requirements regarding the use of proxies.
Cultural needs and languages	
Include individuals from relevant cultures and languages within the target population to ensure results are generalizable. People from distinct cultures may	• Be aware of cultural values and preferences including: whether key concepts of interest are appropriately captured via the PRO; and data collection is sensitive to the needs of those within the target population. • Use validated translations and culturally validated

describe their symptoms differently and may have different values or preferences.[21]	PROs developed in accordance with international guidance.[22] • Provide translators or interpreters for interviewer-led completion.
Literacy and health literacy	
Include individuals with all levels of reading, writing, and problem solving abilities, where possible.[21]	• Format PROs to adhere to accessibility principles including Easyread versions, large font sizes, and ample white space • Allow flexibility for patients to choose where to complete PROs and to request assistance from people they know or professionals. • Clearly convey the purpose and benefit of PROs to both patients and professionals by reducing intimidation and frustration caused by form filling in general. • Ensure content and training is easy to understand by participants with different literacy levels and educational experience by conducting relevant readability assessments (e.g., Flesch-Kincaid Grade level or SMOG index score).
Digital inclusion	
Consider ways to promote digital inclusion	• Provide alternative modes of delivery (e.g., Bring-Your-Own-Device, provision of device, web-completion, voice response systems that do not require internet access, phone calls from staff, ability to complete PROs in clinic) • Offer hardcopy for those without smartphones or internet access. • Provide training and support to patients and staff
Regulatory Engagement	
Meet with the regulator early during drug development, ask questions and seek advice regarding patient and public engagement, and arrange a regulatory or scientific advice meeting.	• Discuss inclusivity in the context of the disease being investigated. • Discuss potential barriers to inclusivity and discuss possible regulatory enablers, such as adoption of regulatory guidance detailing approaches to increased enrolment of underserved population[23] and legislation requirements to deliver and support this. • Use regulatory agency patient engagement tools and resources (e.g., MHRA Innovative Licensing Pathway Patient tools and FDA patient focused drug discovery guidance).

Involvement promotes recruitment

Patient and public input are central to ensuring PRO research is inclusive, equitable and meets the needs of diverse groups. Input can be facilitated by engaging diverse patient partners in co-design, and the involvement of study cohorts that are representative of the full breadth of the target population. Patients representative of the target population should be involved in the identification of concepts that matter to them and should contribute to the selection and/or development of PRO measures.[21]

Representativeness in involvement activities can be achieved by addressing barriers that reduce the diversity of contributors, including: engagement through community groups, charities and support groups; ensuring opportunities to get involved are appropriately timed and located; and reimbursement for reasonable expenses. In drug development, a commitment to incorporate diversity and inclusiveness as part of patient-focused drug development efforts is necessary. Early engagement with regulatory agencies is recommended as they can offer advice and support to promote inclusivity.

The aims and benefits of completing PRO measures should be conveyed to participants, with flexibility in the modes of delivery, in order to increase the engagement and participation of individuals from diverse groups.[14] An equity checklist, such as Benkhalti and colleagues' checklist to guide equity considerations in health technology assessment, can be an effective tool.[24]

User-centered design

Empowering participants from under-served groups to inform the design and delivery of PROs allows for the identification and mitigation of barriers to successful PRO implementation. [24] PRO measures must be accessible if individuals are to accurately communicate information about their health.[25] User-centred design (Box 1), including usability testing, can help identify the needs of the target group(s) and create functional tools for patients and providers.[6]

User-centered design principles can also accommodate people with visual impairment, limited mobility, learning disabilities, low health literacy or numeracy, including the ability to interpret graphical representations of data.[6] Digital inclusion should always be considered, including alternative modes of delivery such as Bring-Your-Own-Device, assistive technologies, or alternative modes of administration such as mail or telephone, including interviewer or interactive voice response (Box 1). Participants may need physical help with turning pages, holding a pen, assistance with a telephone or computer keyboard. PRO collection involving participants with different languages requires the availability of validated language and culturally adapted PRO questionnaires.

Practitioners must be sensitive to recognising when proxy-reported measures may be needed, for example with advancing cognitive decline, to ensure accurate representation of a person's health and functioning.[25] However, it is important to note that in a regulatory setting use of such measures is discouraged and so early engagement and advice from regulatory agencies is recommended.

Improve clinical care for all

PRO measures and data collection must be reflective of diverse and multicultural societies, to improve research and promote equitable clinical care for the benefit of all patients and the public as a whole. Representative diversity in clinical trials is vital to ensure all new medicines and technologies that reach the market are applicable to all the population subgroups they are intended to serve. Targeted initiatives are needed to ensure that no groups are excluded from participation in PRO data collection, both in research settings and routine clinical care.

Inclusion of under-served populations in PRO data collection will help promote equitable healthcare and reduce health data poverty. Co-design of systems with representative patient input will be central to their successful realisation. Resource implications must be considered, and novel approaches evaluated, to promote shared-learning and best practice.

Author contributions

M.J.C., S.C.R and A.R conceived of the idea; M.J.C. developed the first draft; R.V and R.W provided patient input and all authors made substantial revisions and approved the final manuscript.

Competing interests

MJC receives funding from the National Institute for Health Research (NIHR), UK Research and Innovation (UKRI), NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR ARC West Midlands, UK SPINE, European Regional Development Fund – Demand Hub and Health Data Research UK at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Innovate UK (part of UKRI), Macmillan Cancer Support, UCB Pharma, Janssen, GSK and Gilead. MC has received personal fees from Astellas, Aparito Ltd, CIS Oncology, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work. In addition, a family member owns shares in GSK. **OLA** receives funding from the NIHR Birmingham BRC, West Midlands, Birmingham, NIHR ARC West Midlands, UKRI, Health Foundation, Janssen, Gilead and GSK. He declares personal fees from Gilead Sciences Ltd, Merck and GSK outside the submitted work. **SEH** receives funding from the NIHR Applied Research Collaboration (ARC) West Midlands and UKRI and declares personal fees from Cochlear Ltd and Aparito Ltd outside the submitted work. **AMS** has received unrelated consulting fees or speaking honoraria in the last 24 months from: Navigating Cancer, Association of Community Cancer Centers, Pfizer, Genentech, Purchaser Business Group on Health, and Henry Ford Cancer Center and receives unrelated research funding from PCORI, NIH, AHRQ, Bladder Cancer Advocacy Network, Hematology/Oncology Pharmacy Association (HOPA), Cancer and Aging Research Group (CARG), Sivan Innovation, and UroGen Pharma Ltd. **CM** receives funding from NIHR Surgical Reconstruction and Microbiology Research Centre (SRMRC), UKRI, and declares personal fees from Aparito Ltd outside the submitted work. **GT** receives funding from a NIHR Postdoctoral Fellowship Award. **NEA** receives funding from a NIHR Clinical Doctoral Research Fellowship Award and declares personal fees from GSK outside the submitted work. **GV** was past president of ISOQOL, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group, and has received consultancy fees from Roche, Eisai, Novartis, Seattle Genetics and Sanofi related to her clinical work in breast cancer and grants from the Yorkshire Cancer Research, Pfizer, IQVIA, Breast Cancer Now, and the EORTC Quality of Life Group. **PK** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. All other authors declare no conflicts of interest. The views expressed in this article are those of the author(s) and not necessarily those of the National Institute for Health Research, Medicines and Healthcare products Regulatory Agency, Health Research Authority or the Department of Health and Social Care.

References

1. Virji, A.Z., *et al. NEJM Catalyst Innovations in Care Delivery* **2**(2021).
2. Wu, A.W., *et al. Journal of clinical epidemiology* **66**, S12-S20 (2013).
3. Calvert, M., *et al. BMJ* **364**, k5267 (2019).
4. Stamm, T., *et al. NEJM Catalyst Innovations in Care Delivery* **2**(2021).
5. Cruz Rivera, S., *et al. Nature Medicine* **27**, 572-573 (2021).
6. Lavallee, D.C., *et al. Health Affairs* **35**, 575-582 (2016).
7. *NHS Digital. What we mean by digital inclusion* (2021) https://digital.nhs.uk/about-nhs-digital/our-work/digital-inclusion/what-digital-inclusion-is
8. Braveman, P., *et al. Journal of Epidemiology and Community Health* **57**, 254-258 (2003).
9. INVOLVE, *Strategies for diversity and inclusion in public involvement: Supplement to the briefing notes for researchers* (2012).
10. Ibrahim, H., *et al. The Lancet Digital Health* **3**, e260-e265 (2021).
11. FDA, *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (2009).
12. NIHR, *Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project* (2020)
13. Hurst, L., *et al.*, *Defining Value-based Healthcare in the NHS* (2019).
14. Jahagirdar, D., *et al. BMC Health Services Research* **12**, 431 (2012).
15. Kunonga, T.P., *et al. J Med Internet Res* **23**, e25887 (2021).
16. Pugh, S.L., *et al. Int J Radiat Oncol Biol Phys* **108**, 950-959 (2020).
17. Seyyed-Kalantari, L., *et al. Nature Medicine* **27**, 2176-2182 (2021).
18. Slade, A.L., *et al. Trials* **22**, 306 (2021).
19. Sisodia, R.C., *et al. Journal of the American Medical Informatics Association* **28**, 2265-2268 (2021).
20. Masyuko, S., *et al. PLoS One* **16**, e0245269 (2021).
21. FDA, *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (2018).
22. Wild, D., *et al. Value in Health* **8**, 94-104 (2005).
23. FDA, *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry* (2020).
24. Benkhalti, M., *et al. Int J Technol Assess Health Care* **37**, e17 (2021).
25. Hughes, S., *et al. Journal of the Royal Society of Medicine* **114**, 381-388 (2021).