

Patient reported outcome assessment must be inclusive and equitable

Calvert, Melanie; Cruz Rivera, Samantha; Retzer, Ameeta; Hughes, Sarah; Campbell, Lisa ; Molony-Oates, Barbara ; Aiyegbusi, Olalekan Lee; Stover, Angela M ; Wilson, Roger ; McMullan, Christel; Anderson, Nicola; Turner, Grace; Davies, Elin Haf ; Verdi, Rav ; Velikova, Galina; Kamudoni, Paul ; Syed, Muslim; Gheorghe, Adrian; O'Connor, Daniel; Liu, Xiaoxuan

DOI:

[10.1038/s41591-022-01781-8](https://doi.org/10.1038/s41591-022-01781-8)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Calvert, M, Cruz Rivera, S, Retzer, A, Hughes, S, Campbell, L, Molony-Oates, B, Aiyegbusi, OL, Stover, AM, Wilson, R, McMullan, C, Anderson, N, Turner, G, Davies, EH, Verdi, R, Velikova, G, Kamudoni, P, Syed, M, Gheorghe, A, O'Connor, D, Liu, X, Wu, AW & Denniston, A 2022, 'Patient reported outcome assessment must be inclusive and equitable', *Nature Medicine*, vol. 28, no. 6, pp. 1120-1124. <https://doi.org/10.1038/s41591-022-01781-8>

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1 **Patient reported outcome assessment must be inclusive and equitable**

2

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48

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

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

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

65 **Lack of representation**

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

70

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

71 **Box 1. Key terms**

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

87

88 **Barriers to completion**

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

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

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

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

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

115

116 **Racial and ethnic disparities**

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

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

135

136 **Low and middle income countries**

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

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

154 **Widening participation**

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

161 Existing good practice guidance such as minimizing participant burden, streamlining PRO
 162 administration, and using PRO alerts can be effectively used to promote inclusion and
 163 accessibility.⁵ Communication of the rationale for PRO assessment (who will access the data
 164 and how it will be used) to potential participants may address the concerns of those wary of
 165 participating in research or providing information in a routine care setting. The representation
 166 and participation of under-served groups in PROs can be increased by the actions in Table
 167 1.

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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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<p>PROs developed in accordance with international guidance.²²</p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.	<ul style="list-style-type: none"> • 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 population²³ 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).

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173 **Involvement promotes recruitment**

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

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

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

192 **User-centered design**

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

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

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

213

214 **Improve clinical care for all**

215

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

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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.

228

229 **Author contributions**

230 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
231 provided patient input and all authors made substantial revisions and approved the final
232 manuscript.

233

234 **Competing interests**

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

268

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