

## Patient reported outcome assessment must be inclusive and equitable

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

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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. <sup>1,2</sup> 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.<sup>3</sup> PROs are also increasingly used in value-based healthcare initiatives.<sup>4</sup>

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.<sup>5,6</sup> 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.<sup>5</sup>

### 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

<b>Digital inclusion</b>
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. <sup>7</sup>
<b>Diversity, Equity, and Inclusion</b>
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. <sup>8,9</sup>
<b>Health data poverty</b>
Health data is often not representative of the diversity within a population, and so some groups do not benefit from healthcare innovations <sup>10</sup>
<b>Interactive Voice Response (IVR)</b>
This allows participants to complete an automated questionnaire via a telephone keypad or by speech recognition.
<b>Patient-Reported Outcomes</b>
A measurement of the patient's health provided directly by the patient, rather than interpreted by a clinician. <sup>11</sup>
<b>Under-served groups</b>
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.<sup>12</sup>

**User-centered design**

Design processes that are iteratively conducted with end users.<sup>8</sup>

**Value-based healthcare**

“The equitable, sustainable and transparent use of the available resources to achieve better outcomes and experiences for every person.”<sup>13</sup>

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) <sup>10</sup> 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.<sup>6</sup> People  
98 with learning disabilities and low literacy have experienced exclusion from the routine  
99 monitoring of their health and wellbeing afforded by PROs.<sup>14</sup>

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.<sup>15</sup>

105 A recent study investigating the incorporation of PROs in clinical trials demonstrated that  
106 certain patient groups are not represented.<sup>16</sup> 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.<sup>17</sup>

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.<sup>8,18</sup> 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.<sup>18</sup>

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.<sup>19</sup> 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.<sup>19</sup> 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.<sup>19</sup>

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.<sup>20</sup> 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.<sup>5</sup> 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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 169

<b>Table 1. Actions to promote representation and participation of under-served groups in PROs</b>	
<b>Considerations</b>	<b>Actions</b>
<b>Diversity</b>	
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. <sup>21</sup>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Assess whether PRO measures perform consistently across groups (e.g., based on measurement equivalence or differential item functioning)</li> </ul>
<b>Clinical Characteristics</b>	
Consider the type and severity of disease, the range of symptoms and functional impacts, comorbidities, and physical and cognitive disabilities. <sup>21</sup>	<ul style="list-style-type: none"> <li>• When heterogeneity in disease symptoms, signs, and impacts exist, assess concepts that are most important to a broad range of patients.</li> <li>• Minimise functional impacts that may limit ability to complete PROs (e.g., issues of dexterity).</li> <li>• Use accessible formats that address the needs of the target population.</li> <li>• 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.</li> </ul>
<b>Cultural needs and languages</b>	
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"> <li>• 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.</li> <li>• Use validated translations and culturally validated</li> </ul>

describe their symptoms differently and may have different values or preferences. <sup>21</sup>	<p>PROs developed in accordance with international guidance.<sup>22</sup></p> <ul style="list-style-type: none"> <li>• Provide translators or interpreters for interviewer-led completion.</li> </ul>
<b>Literacy and health literacy</b>	
Include individuals with all levels of reading, writing, and problem solving abilities, where possible. <sup>21</sup>	<ul style="list-style-type: none"> <li>• Format PROs to adhere to accessibility principles including Easyread versions, large font sizes, and ample white space</li> <li>• Allow flexibility for patients to choose where to complete PROs and to request assistance from people they know or professionals.</li> <li>• Clearly convey the purpose and benefit of PROs to both patients and professionals by reducing intimidation and frustration caused by form filling in general.</li> <li>• 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).</li> </ul>
<b>Digital inclusion</b>	
Consider ways to promote digital inclusion	<ul style="list-style-type: none"> <li>• 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)</li> <li>• Offer hardcopy for those without smartphones or internet access.</li> <li>• Provide training and support to patients and staff</li> </ul>
<b>Regulatory Engagement</b>	
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"> <li>• Discuss inclusivity in the context of the disease being investigated.</li> <li>• Discuss potential barriers to inclusivity and discuss possible regulatory enablers, such as adoption of regulatory guidance detailing approaches to increased enrolment of underserved population<sup>23</sup> and legislation requirements to deliver and support this.</li> <li>• Use regulatory agency patient engagement tools and resources (e.g., MHRA Innovative Licensing Pathway Patient tools and FDA patient focused drug discovery guidance).</li> </ul>

170

171

172

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.<sup>21</sup>

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.<sup>14</sup> An equity checklist, such as Benkhalti and colleagues'  
190 checklist to guide equity considerations in health technology assessment, can be an  
191 effective tool.<sup>24</sup>

## 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.<sup>24</sup> PRO measures must be accessible if individuals are to accurately  
196 communicate information about their health.<sup>25</sup> 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.<sup>6</sup>

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.<sup>6</sup> 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.<sup>25</sup> 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

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268

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