

Patient Reported Outcomes used in Multiple Sclerosis Trials: Critical Assessment and Insights from People Living with MS

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Introduction

- The impact of many important symptoms of multiple sclerosis (MS), including fatigue, cognitive impairments, depression, and pain cannot be assessed directly by an external observer¹
- The effective measurement of the subjective impact of MS symptoms, and how this impact evolves with disease progression, can only be achieved through patient-reported outcome (PRO) measures that are both relevant and meaningful for People living with MS (PlwMS)
- Clinical trials increasingly include PRO instruments as study endpoints, which aim to provide insight into treatment effects that are important to PlwMS²
- Regulatory guidance aimed at improving the design and selection of PROs for clinical trials stresses the importance of having a conceptual framework and patient input from the start and throughout the development of the tool;³⁻⁸ however, many PRO instruments used in MS clinical trials either pre-date this guidance or are not specific to MS

Objective

- The Patient-Reported Outcomes that Matter to People Living with Multiple Sclerosis (PROMPT-MS) initiative aims to:
 - Improve understanding of how PROs are structured and defined
 - Examine whether existing PROs measure what they are supposed to
 - Understand what outcomes and measures are most relevant to PlwMS

Methods

Initiative overview

- The PROMPT-MS initiative is supported by a Steering Committee of PlwMS and healthcare and research professionals
 - This steering committee provides expert guidance on collecting patient insights, on literature search design and methodology, and critically reviews the findings

Profiling the PRO development process and structure

- PROs used in clinical trials to measure the burden of MS symptoms and the effect of therapies on disease characteristics were identified from a literature review, published in 2017,¹ and with expert guidance from the Steering Committee
 - The development of these PROs and the degree of involvement of PlwMS were assessed

Gathering insights from people living with MS

- PlwMS (N=22) were interviewed to gain insights into their experiences and opinions of currently used PROs; these insights were used to validate and further contextualise the findings of the PRO profiling exercise
- The objectives of these interviews were to provide insights on how well current PROs address the reality and priorities of PlwMS, highlight areas where definitions of PROs could be refined or updated to reflect the point of view of PlwMS, and discuss the use of PROs to measure fatigue, QoL, and the physical and psychological impact of MS

Results: PRO development process and structure

- Six PRO tools were selected for evaluation and discussion with PlwMS (**Table 1**)
 - The modified Fatigue Impact Scale (mFIS)^{1,2} and the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS)³ aim to assess fatigue
 - The 8-item Leeds MS QoL instrument (LMSQoL)⁴ and the multidimensional, health-related MS QoL tool (MSQoL-54)⁵ are disease-specific tools that aim to measure QoL
 - The 29-item MS Impact Scale (MSIS-29)⁶ is a disease-specific tool that aims to measure the physical and psychological impact of MS
 - The EuroQOL five-dimension (EQ-5D) questionnaire was included as a standardized, non-disease-specific instrument for measuring QoL^{7,8}

Table 1: Structure and Development of PROs

mFIS	FSIQ-RMS	LMSQoL	MSQoL-54	MSIS-29	EQ-5D
<ul style="list-style-type: none"> • Derived from a combination of existing fatigue questionnaires and interviews with 30 PlwMS¹ • Not based on a conceptual framework⁹ 	<ul style="list-style-type: none"> • Developed in 2019³ and focuses on MS-related fatigue • Designed with the involvement of PlwMS³ • Based on a conceptual framework 	<ul style="list-style-type: none"> • Development involved PlwMS from the outset via two focus-group sessions of 30 PlwMS⁴ • Not based on a conceptual framework 	<ul style="list-style-type: none"> • No involvement of PlwMS in the development; concept was compiled through literature reviews and covered aspects understood to be relevant to PlwMS (e.g. fatigue and cognitive function)⁵ • Not based on a conceptual framework 	<ul style="list-style-type: none"> • Development involved multidisciplinary expert opinions, literature review and input from semi-structured interviews with PlwMS representing the full range of MS disease types (n=30)⁶ • Not based on a conceptual framework 	<ul style="list-style-type: none"> • Developed by agreement among scientists and clinicians; details of patient involvement have not been published⁷ • Not based on a conceptual framework

Results: Qualitative insights

- The insights gathered from the semi-structured interviews are summarized for fatigue PROs in **Figure 1A**, disease-specific QoL and physical/psychological tools in **Figure 1B** and for the non-disease specific EQ-5D tool in **Figure 1C**

Figure 1A. PlwMS Feedback on Fatigue PROs

Figure 1B. PlwMS Feedback on MS-Specific QoL and Physical/Psychological PROs

	Strengths	Weakness	Suggested improvements
mFIS	<ul style="list-style-type: none"> Good psychosocial assessment Scale is clear and relevant Accurate description on the fatigue scale Cognition and fatigue questions are relevant 	<ul style="list-style-type: none"> Only measures over a four week recall period Lacks recognition of impact on emotion and every day life impact Scoring can be confusing and can miss out on important areas 	<ul style="list-style-type: none"> Rewording of questions to lay language Inclusion of more psychosocial questions Simplify scoring
FSIQ	<ul style="list-style-type: none"> Broad range of questions covering subjects relevant to PlwMS Focuses on practical situations Measures coping with MS symptoms Includes cognitive, physical and psychosocial elements The tool is simple whilst reaching a good level of detail Easy digital access Explores the impact of each symptom presented 	<ul style="list-style-type: none"> Only covers a recall period of 24 hours and impact for 7 days Length of the PRO may be burdensome Psychosocial questions are not comprehensive enough 	<ul style="list-style-type: none"> Increase recall period

	Strengths	Weakness	Suggested improvements
MSQoL-54	<ul style="list-style-type: none"> Questions provide a holistic view of the PlwMS's experience of MS Questions address most of the emotional aspects The wide spectrum of symptoms demonstrates an understanding of the PlwMS's reality Answers not restricted to set scale The instrument considers fluctuations of the MS symptoms 	<ul style="list-style-type: none"> The scale scores are not well described and have gaps (particularly for recall time of symptoms) Focuses too much on what PlwMS cannot do rather on what they can do Lack of exploration around pain Wording of questions is hard to relate to Length of the PRO may be burdensome 	<ul style="list-style-type: none"> Update the questions to the current knowledge of pain in MS Update the language to a more modern and reliable style Questions should be phrased more positively
LMSQoL	<ul style="list-style-type: none"> Good choice of questions Makes the connection between mental health issues and MS 	<ul style="list-style-type: none"> The relationship between the physical and emotional symptoms is not addressed The relationship between fatigue and cognitive or sexual function is not addressed 	<ul style="list-style-type: none"> Remove the question relating to appearance ('I have felt good about my appearance') Use a different scoring scale Many questions in this PRO would benefit from a follow up discussion with a health care professional
MSIS-29	<ul style="list-style-type: none"> Questions worded in a relatable style Covers a diverse range of relevant topics Explores not just the physical but also the psychological impact Good level of detail 	<ul style="list-style-type: none"> Not enough focus on psychological impacts compared with physical impacts The Items relating to physically demanding tasks are described too vaguely Does not address pain sufficiently Does not measure impact of MS on daily life 	<ul style="list-style-type: none"> Clearly describe the impact of MS on the items being measured

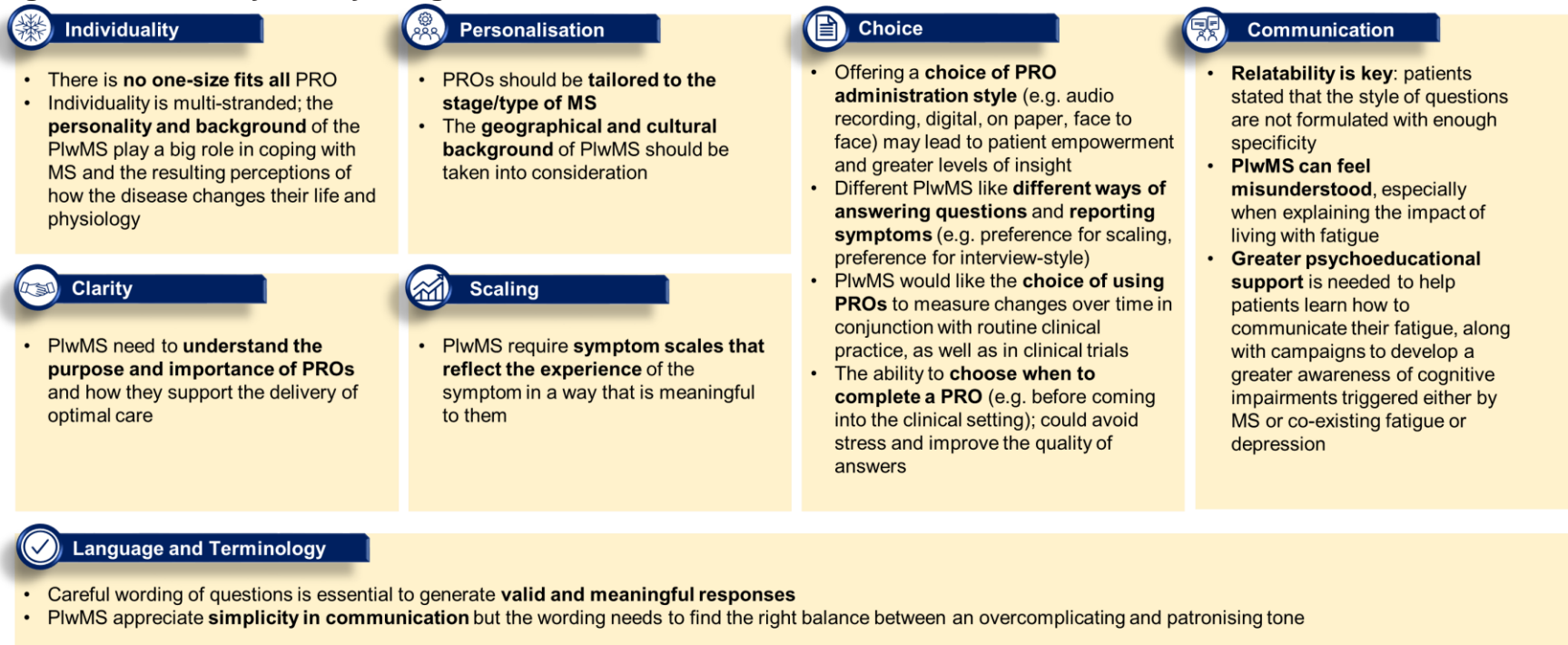
Figure 1C. PlwMS Feedback on Non-Disease Specific EQ-5D

	Strengths	Weakness	Suggested improvements
EQ-5D	<ul style="list-style-type: none"> Covers relevant topics about general health ("covers the basics") The tool is quick, short and simple 	<ul style="list-style-type: none"> Not very detailed and overly simplified Five-digit number system hard to relate to Items are sometimes perceived as too generic PRO is not MS specific Does not address cognitive function 	<ul style="list-style-type: none"> The mobility questions do not reflect the realities of PlwMS Add an introduction relating to the purpose/aims of the tool

Results: Qualitative insights

- The insights gathered from PlwMS suggest that the sensitivity of PROs may be improved by asking questions that make 'personal' sense to the individual PlwMS and consider the correct context; for example, the level of disability, type of MS, duration of disease and the culture and region/country in which the PlwMS resides (**Figure 2**)

Figure 2. Summary of Key Insights From PlwMS on PROs



Conclusions

- Our examination of the six PROs underpins the importance of the involvement of PlwMS in PRO development
- There is no 'one-size fits all' PRO; however, adaptations in accordance with regulatory guidance and patient insights could potentially increase the sensitivity of PROs by being more tailored to the needs of PlwMS and to what is important to them
- The development of more effective PRO measurement strategies for MS clinical trials, through addressing the limitations of current PROs in collaboration with PlwMS, has the potential to generate more patient-centric instruments with greater sensitivity to treatment effects
- A better understanding of what outcomes are important for PlwMS will help to develop PROs with greater relevance for PlwMS

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Disclosures

Trishna Bharadia in the last three years has received compensation for serving as a consultant, writer and/or speaker for or has received honoraria from: ⁶Health, Abbvie, Actelion (Janssen), Admedicum, Blue Latitude Health (Fishawack), Curatio, DHL Life Sciences, Envision Pharma, Faculty of Pharmaceutical Medicine, Future Medicine, Gilead Sciences, Greenphire, ISMPP, Kayentis, Medipace, Merck KGaA, NHR, Norgine, Novartis, NovoNordisk, Parexel, Roche, Synchrogenix (Certara), talkHealth, Teva, University College London, University of Surrey, WEGO Health, Wellcome Trust, Vitaccess. Disclosures do not show a conflict with the work being presented.

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