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 MS, including but not limited to fatigue, cognitive impairments, depression, and pain, cannot be assessed directly by an external observer[1]
- The effective measurement of the subjective impact of MS symptoms, and how this impact evolves with disease progression, can only be achieved through PRO measures that are both relevant and meaningful for PlwMS
- Clinical trials increasingly include PRO instruments as study endpoints, which aim to provide insight into treatment effects that are important to PlwMS[2]
- 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 the 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 health care professionals**
    - This steering committee provides expert guidance on collecting patient insights and literature search design and methodology, and critically reviews the findings
- **Profiling the PRO development process and structure**
  - A representative sample of **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,[9] 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 contextualize 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**

MS, multiple sclerosis; PlwMS, people living with MS; PRO, patient-reported outcome; QoL, quality of life.

1. Manjaly ZM et al. *J Neurol Neurosurg Psychiatry*. 2019;90;642-651; **2.** Nowinski CJ et al. *Neurotherapeutics*. 2017;14;934-944; **3.** FDA Guidance for Industry 2009. Accessed May 25, 2021. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf; **4.** FDA Roadmap to patient-focused outcome measurements in clinical trials 2014. Accessed May 25, 2021. https://www.fda.gov/media/87004/download; **5.** Walton MK et al. *Value Health*. 2015;18;741-752; **6.** Terwee CB et al. *Qual Life Res*. 2018;27;1159-1170; **7.** Rothman ML et al. *Value Health*. 2007;10(Suppl 2):S66-S75; **8.** Guidance for industry, *Health Qual Life Outcomes*. 2006; 4: 79; **9.** Khurana V et al. *Eur J Neurol*. 2017;24;1099-1107.

Results

PRO Development Process/Structure and Qualitative Insights

Six PRO tools were selected for evaluation and discussion with PlwMS: PRO development process findings

mFIS[1,2]	FSIQ-RMS[4]	LMSQoL[5]
• Aims to assess fatigue • Derived from a combination of existing fatigue questionnaires and interviews with 30 PlwMS[1] • Not based on a conceptual framework[3]	• Developed in 2019[4] and focuses on MS-related fatigue • Designed with the involvement of PlwMS[4] • Based on a conceptual framework	• Disease-specific tool that aims to measure QoL • Development involved PlwMS from the outset via two focus-group sessions of 30 PlwMS[5] • Not based on a conceptual framework
MSQoL-54[6]	**MSIS-29[7]**	**EQ-5D[8,9]**
• Disease-specific adaptation of the non-specific SF-36 tool • No involvement of PlwMS in the development; concept was compiled through literature reviews and covered aspects understood to be relevant to PlwMS (eg, fatigue and cognitive function)[6] • Not based on a conceptual framework	• Disease-specific tool that aims to measure the physical and psychological impact of MS • 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)[7] • Not based on a conceptual framework	• A standardized, non-disease-specific instrument for describing and valuing health-related QoL[8,9] • Developed by agreement among scientists and clinicians; details of patient involvement have not been published[8] • Not supported by a published conceptual framework

PlwMS feedback on fatigue PROs

Strengths	Weakness	Suggested improvements
mFIS • Good psychosocial assessment • Scale is clear and relevant • Accurate description on the fatigue scale • Cognition and fatigue questions are relevant	**mFIS** • Only measures over a 4-week recall period • Lacks recognition of an emotional impact of MS • Lacks recognition of impact of MS on everyday life • Scoring can be confusing	**mFIS** • Inclusion of more psychosocial questions • Rewording of questions to lay language • Simplify scoring
FSIQ-RMS • 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	**FSIQ-RMS** • 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	**FSIQ-RMS** • Increase recall period

EQ-5D, EuroQoL five-dimension (EQ-5D) questionnaire; FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis; LMSQoL, The 8-item Leeds MS QoL instrument; mFIS, modified Fatigue Impact Scale; MS, multiple sclerosis; MSIS-29, The 29-item MS Impact Scale; MSQoL-54, The multidimensional, health-related MS QoL tool; PlwMS, people living with MS; PRO, patient-reported outcome; QoL, quality of life; SF-36, Short-Form-36.

1. Fisk JD et al. *Clin Infect Dis*. 1994;18;Suppl 1;S79-S83; **2.** Larson RD. *Int J MS Care*. 2013;15;15-20; **3.** The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee 1997. Accessed on May 25, 2021. https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/MSQLI_-A-User-s-Manual.pdf; **4.** Hudgens S et al. *Value Health*. 2019;22;453-466; **5.** Ford HL et al. *Clin Rehabil*. 2001;15;247-258; **6.** Vickrey BG et al. *Qual Life Res*. 1995;4;187-206; **7.** Hobart J et al. *Brain*. 2001;124;962-973; **8.** Fogarty E et al. *Mult Scler*. 2013;19;1190-1196; **9.** Rabin R, de Charro F. *Ann Med*. 2001;33;337-343.

Results

Qualitative Insights (Cont'd)

PlwMS feedback on MS-specific QoL and physical/psychological PROs

Strengths

MSQoL-54

- 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 are not restricted to set scale
- The instrument considers fluctuations in MS symptoms

LMSQoL

- Good choice of questions
- Contains detailed questions that can be informative and thought provoking for PlwMS
- Makes the connection between mental health issues and MS
- Good tool to track changes in MS symptoms

MSIS-29

- 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

Weakness

MSQoL-54

- 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 hard to relate to
- Length of the PRO may be burdensome
- Addressing matters of sexual function needs less direct/more considered wording

LMSQoL

- The relationship between the physical and emotional symptoms of MS is not addressed
- The relationship between fatigue and cognitive or sexual function is not addressed

MSIS-29

- 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

Suggested improvements

MSQoL-54

- Update the language to a more modern and relatable style
- Questions to be phrased more positively
- Update the questions to reflect more recent science and how patients live with MS in today's world

LMSQoL

- 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

- Clearly describe the impact of MS on the items being measured

PlwMS feedback on the non-disease specific EQ-5D tool

Strengths

- Covers relevant topics about general health ("covers the basics")
- The tool is quick, short, and simple

Weakness

- Tool is not MS-specific
- Not very detailed and overly simplified
- 5-digit number system is hard to relate to
- Items are sometimes perceived as too generic
- Does not address cognitive function

Suggested improvements

- The mobility questions do not reflect the realities of PlwMS
- Add an introduction relating to the purpose/aims of the tool

EQ-5D, EuroQOL five-dimension (EQ-5D) questionnaire; LMSQoL, The 8-item Leeds MS QoL instrument; MS, multiple sclerosis; MSIS-29, The 29-item MS Impact Scale; MSQoL-54, The multidimensional, health-related MS QoL tool; PlwMS, people living with MS; PRO, patient-reported outcome; QoL, quality of life.

Summary of Key Insights From PlwMS on PROs

Individuality

- There is **no one-size-fits-all** PRO
- Individuality is multi-stranded; the **personality and background** of the PlwMS play an important role in coping with MS and the resulting perceptions of how the disease changes their life and physiology

Personalisation

- PROs should be **tailored to the stage/type of MS**
- The **geographical and cultural background** of PlwMS should be taken into consideration

Recall Period

- There are mixed views on the right length of recall (from '24 hours ago', 'a week ago', or 'a month to a year ago'). **Factors such as fatigue, cognition and mood at the time of recall may play a role**. Additionally, MS symptoms fluctuate and the phrasing of the recall-based questions should reflect this

Choice

- PlwMS can be empowered to participate in PROs by offering a **choice of administration style** (eg, audio recording, digital, paper-based, face to face interview style) and in turn, this may lead to greater levels of insight
- **Different PlwMS like different ways of answering questions**, with answers ranging from a preference for scaling to a preference for interview style reporting of symptoms.
- PlwMS would like the **choice of using PROs** to measure changes over time in conjunction with routine clinical practice, as well as in clinical trials
- The ability to **choose when to complete a PRO** (eg, before coming into the clinical setting) could avoid stress and improve the quality of answers

Communication

- **Relatability is key**: patients stated that the style of questions are not formulated with enough specificity
- **PlwMS can feel misunderstood**, especially when explaining the impact of living with fatigue; often fatigue is not adequately captured by PROs, nor do they take into account the short and long term fluctuations of fatigue
- **Greater psychoeducational support** is required to help patients learn how to communicate their fatigue, and campaigns are needed to develop a greater awareness of cognitive impairments triggered either by MS or co-existing fatigue or depression

Clarity

- PlwMS need to **understand the purpose and importance of PROs** and how they support the delivery of optimal care

Scaling

- PlwMS require **symptom scales that reflect the experience** of the symptom in a way that is meaningful to them

Language and Terminology

- Careful wording of questions is essential to generate **valid and meaningful responses**
- PlwMS appreciate **simplicity in communication,** but the wording needs to find the right balance between an overcomplicating and patronizing tone

Autonomous Tracking

- PlwMS feel **empowered by being able to record changes in their illness** and use different methods to log their symptoms (e.g. keeping a diary, making lists, using digital tools)

Emotional Impact

- **The emotional impact of MS intrinsically runs throughout all other feedback** and highlights how aspects such as anxiety, depression, pain and cognitive impairment are intricately linked.

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

MS, multiple sclerosis; PlwMS, people living with MS; PRO, patient-reported outcome; QoL, quality of life.

Conclusions

- 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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