REVIEW

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Measuring outcomes that matter most to people with multiple sclerosis: the role of patient-reported outcomes

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Purpose of review
Patient-reported outcome (PRO) represents a unique opportunity to measure the impact of health research, and care on outcomes that matter most to people with multiple sclerosis (PwMS).

Recent findings
How to incorporate PROs in MS clinical trials and, practice remains a matter of debate. The variety of measures available for use in MS has some benefits, but the lack of a set of standard measures has significant disadvantages. To help meeting the challenge, different PROs standard sets have been developed (PROMIS) for use across a broad range of chronic health conditions, and SymptoMScreen, specifically for MS. However, many of them were not co-created with PwMS and lacking understanding about what matters to patients. The newly proposed MS care unit model together with emerging initiatives such as iConquerMS and PROMOPROMS, are shaping new meaningful PROs. However, the uptake of PROMs in all settings can be effective only by a commonly held strategic agenda shared by all relevant stakeholders.

Summary
The newly born PRO Initiative for MS (PROMS) aims to develop a strategic agenda shared by all relevant stakeholders to help meeting the challenge of developing PRO measures that correspond to the needs of all stakeholders.

Keywords
multi-stakeholder initiatives, multiple sclerosis, patient engagement, patient-reported outcome, personalized medicine

INTRODUCTION

In a time of challenges that call for mission-oriented research [1] such as those in the healthcare, the future of sustainability requires new multistakeholder and multidisciplinary organizational models of cooperation that guarantee a long-term return on investment, not only economic. An important driver of this change is enabling science with and of patient input. What began as an extension of patient advocacy has now evolving into an emerging discipline aimed at understanding and incorporating patient needs and perspectives into the processes of developing, regulating, and delivering new therapies as well as improving care: the science with and of patient input [2].

This is also the thinking behind Public Engagement within the Responsible Research Innovation (RRI) European Union's Horizon 2020 program. Within this frame, Patient Advocacy Organizations are playing an important role, as boundary organizations, to define and implement the 'how to' of patient engagement [3]. Within this strategic frame, the RRI EU-funded MULTI-ACT project [4], coordinate by the Italian MS Society, is attracting the interest of the health-research community [5▪▪]. The innovative model proposed by the MULTI-ACT project argues that excellence, validity, and

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KEY POINTS

- The power of the science with and of patient input relies on new RRI multistakeholder models used to engage patients and evaluating impact of health research, treatment, and care on patient-reported outcomes (PROs) that matter most to patients.
- There are several limitations to the use of PRO as primary outcome in clinical trials because of the lack of a set of standard measures.
- Partnership with people with multiple sclerosis is instrumental to increase clinical meaningfulness of PROs and their uptake in the decision-making drug and treatment approval process.
- The multiple sclerosis care unit model and new emerging PROMs, developed in partnership with people with multiple sclerosis, will facilitate the integration of new clinical meaningful PROs for multiple sclerosis in clinical practice
- The newly born PROMS aims to develop a common strategic agenda and roadmap shared by all relevant stakeholders to meet the challenge.

relevance are connected by engaging patients in the research continuum as key stakeholder (science with patient input) and by evaluating impact of research on the outcomes that matter to patients (science of patient input). The power of the science with and of patient input relies on the innovative framework used to engage patients and on the sources of patient data. In particular, the patient-reported outcomes (PROs) and their measurement instruments (patient-reported outcome measures [PROMs]) data are supporting every aspect of the healthcare continuum from research to clinical trials and practice through to public health. PROs refer to direct patient reports of their experience with a disease and its treatment [6,7]. PROs are playing an increasing role in multiple sclerosis clinical trials and practice and are essential for understanding the effects that multiple sclerosis and multiple sclerosis treatments have on patients' lives. This review discusses the role of PRO in measuring the impact of health research, treatment and care on outcomes that matter most to people with multiple sclerosis and propose directions for the future.

Evolution of patient-reported outcomes use in clinical trials

There are enough PRO to warrant entire collections of measures [8]. Most PRO measures are categorized as either generic or targeted. However so far, PROs have been mainly used in postmarketing, observational studies. PROMs are increasingly used as secondary or tertiary outcomes in multiple sclerosis clinical trials on disease-modifying therapies and symptomatic treatments, whereas in rehabilitation trials are used as primary or coprimary outcomes. There are currently 14 disease-modifying agents that have been approved by the appropriate regulatory agencies. Although some clinical trials show promising results [9], based on a recent literature search of PROs used in randomized phase III trials of multiple sclerosis disease modifying drugs (DMDs), it is not possible to reach any conclusion about the overall benefit of DMDs or the relative benefit of one over another on the well-being of individuals living with multiple sclerosis [10]. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both consider that the voices of patients in medicine regulation are essential, as they bring the unique perspective of someone living with a disease [11]. This perspective complements the medical and scientific information that is used when evaluating medicines for regulatory approval. For example, patients can highlight unmet needs for their condition that they consider to be particularly important, which might differ from the standard end points evaluated in clinical trials and patient perceptions frequently differ from those of clinicians [12–15]. However, the uptake of PROs as primary outcome in the decision-making processes of regulatory agencies for drug approvals is still challenging and controversial. The outcome of the Multiple Sclerosis Outcome Assessments Consortium qualification processes of a Clinical Outcome Assessment instrument, developed to assess treatment benefit in clinical trials of therapies for multiple sclerosis, reinforces the EMA's guidance on the design of multiple sclerosis clinical trials for which the Expanded Disability Status Scale is still the gold standard [16].

There are several limitations to the use of PROMs [17] in clinical trials. Based on the variability of PRO data from these trials and the variety of measures implemented it is not possible to reach any conclusion about the overall benefit of DMDs or the relative benefit of one over another on the well-being of individuals living with multiple sclerosis. The lack of a set of standard measures has significant disadvantages and some available measures are of uncertain validity and were created without using modern test development methodology [18]. These aspects represent some of the challenges that prevent the use of PROs as primary outcomes in clinical trials. To help meeting the challenge, different standard sets of PRO measures have been developed. Among these, the National Institutes of Health (NIH) supported the creation of two standard sets of PRO measures, one appropriate for use across neurological conditions

(Neuro-QoL) [19] and one for use across a broad range of chronic health conditions (PROMIS) [20]. The above standard sets of PRO measures are consistent with FDA guidance regarding PROs and the EMA Reflection Paper on the use of health-related quality of life measures the NIH [21]. The 'SymptoMScreen' PRO measurement tool is another valuable addition to existing PRO measures that are available in multiple sclerosis and could be highly useful in studies of large populations seeking to minimize respondent burden [22].

Evolution of patient-reported outcomes use in clinical practice

Accompanying acceptance of the need to integrate patient perspectives into clinical trials is an increase in the demand for research-based methods and tools to measure the effectiveness of incorporating patient input into the clinical practice and, ultimately, its impact on patients' health and quality of life [23▪▪]. Given the plethora of functional domains affected in patients with multiple sclerosis, a multidisciplinary care team, such as the recently proposed multiple sclerosis care unit model [24▪▪], is needed to improve patient engagement and the uptake of PRO in clinical practice. There was broad agreement that the patient voice should be heard more in discussions around multiple sclerosis care [25]. Many of the existing PROs were not developed in partnership with patients and with insufficient understanding about what matters to patients. This makes also challenging to prove the clinically meaningfulness of PROs, one of the main requirement for the uptake of PRO in the decision-making drug-approval process. Within this frame, iConquerMS is a multiple sclerosis people-powered research network established in 2014 with funding by the Patient-Centered Outcomes Research Institute (USA) [26]. It is dedicated to engaging all multiple sclerosis stakeholders to enable research on topics that matter most to people affected by multiple sclerosis. The initiative is based on the patient-reported outcomes measurement information system Global Health Survey, and the Neuro-QoL Adult Short Forms. To date, iConquerMS over 5000 PwMS have joined the initiative. Another initiative, based in Europe, that could help meeting the challenge is the A new functional PROfile to MOnitor the PROgression of disability in Multiple Sclerosis [27▪▪] project promoted and funded by the Italian MS Society. The PROs, related to domains that most care to multiple sclerosis patients (case study) defined by the PROMOPROMS initiative (manual ability, bladder functions, motor, cognitive, psychosocial fatigue, anxiety, and depression, quality of life), are currently used to measure disease progression and the efficacy of treatments (drugs and/or rehabilitation) in clinical practice and could be potentially measured via digital health technologies.

The ideal would be to find a happy medium between PROs that work at population level in clinical trials [28] and PROs that can be individualized for use in clinical practice. The ideal would be to find a happy medium between PROs that work at population level in clinical trials and PROs that can be individualized for use in clinical practice. Electronic health technologies (e-Health) could help meeting this challenge and could play an increased role in filling the gaps between PROs use in clinical trials versus clinical practice in multiple sclerosis [29]. Therefore, data about patients' experiences outside the clinic are not only 'nice to have' but also critical to understanding and improving those outcomes. A great deal of momentum surrounds the application of new technologies, such as mobile devices and other digital platforms, to both deliver care and generate real-world data on patients' experiences. Within this frame, e-Health is becoming increasingly relevant in multiple sclerosis clinical management [30]. e-Health describes an emerging field of technologies designed to be worn on the body or embedded into mobile and portable solutions (e.g., smartphones, watches, bracelets, and clothing) and able to provide individual's data such as those from sensors (passive monitoring) as well as self-reported data or questionnaires, such as electronic PRO (active monitoring) [31]. There is a clear drive to collect PROs electronically using electronic ePRO systems. In this context, the use of ePROs instead of paper formats in clinical trials could facilitate the robust analysis and reporting of PRO data. However, the user interfaces of ePRO systems need to be adequately assessed to ensure they are not only fit for purpose but also acceptable to patients who are the end users [32] and effective for the different context of use, that is, clinical trials [33] and clinical practice. The advancement of ePRO is likely to also enable successful development of therapeutics in progressive multiple sclerosis that depends not only on identification of relevant pathways and effective therapies but also on available outcome assessments capable of demonstrating treatment effects on disease progression [34,35].

Stakeholder engagement and cooperation

Despite differences in viewpoint, the different stakeholders agree that PRO and PROMs have not reached their full potential of delivering benefits to people with multiple sclerosis. In particular people with multiple sclerosis are frustrated that functional domains that matter most to them are not addressed by current PROs; clinicians acknowledge

the importance to include patient-reported outcome measures (PROMs) to understand treatment effects or compare treatment options; regulatory authorities recognize that current outcomes (Expanded Disability Status Scale, relapse rate, Magnetic Resonance Imaging features) do not fully capture the experience of people with multiple sclerosis; Healthcare Technology Assessment Agencies aim to integrate the 'patient voice' in coverage decisions; Pharma acknowledge the importance to include patient PROs in Medicine Life Cycle Management and consumer-driven healthcare is gaining ground. Efforts to enable the uptake of PROs and PROMs into clinical trials, regulatory agencies/Health Technology Sector decision-making processes and practice could be greatly enhanced and informed by a commonly held strategic PRO agenda and roadmap shared by all relevant stakeholders. The newly born multistakeholder Patient Reported Outcome Initiative for multiple sclerosis (PROMS) [5▪▪] aims at achieving a unified vision PRO that meets the expectations of multiple sclerosis patients and that can serve the Healthcare Providers, Regulatory Agencies and Health Technology Sector Agencies. The initiative is jointly led and coordinate by the European Charcot Foundation and Multiple Sclerosis International Federation, with the Italian Multiple Sclerosis Society acting as lead agency on behalf and for the multiple sclerosis movement. The strategic priorities of PROMS are centered around the validation and development of PROs that matter most to people with multiple sclerosis. However, an important driver of the multistakeholder initiative will be to show that PRO will also measure outcomes that correspond to all the stakeholder needs. In this context, the EU-funded MULTI-ACT project [4] provides a new Collective Research Impact Framework (CRIF) which will be translated into an online toolbox and a set of guidelines to improve the governance of multistakeholder research initiatives and stakeholder coaccountability in health research and innovation. The core component of such CRIF applies innovative guidelines for patient-engagement and a multistakeholder perspective to assess the impact of health research considering five dimensions of accountability (efficacy/mission, social, economic, excellence and patient-reported). Among the MULTI-ACT CRIF indicators, the PROMOPROMS [27▪▪] set of outcomes will be used to evaluate impact of health research and care on people with multiple sclerosis-reported dimension.

CONCLUSION

We have reviewed the main challenges concerning the use of PROs in multiple sclerosis and the initiatives that are developing the field. We have attempted to stimulate discussion and encourage critical reflection that an important driver to meet the challenges is enabling science with and of patient input via multistakeholder and multidisciplinary organizational models. We argued the potential of the EU-funded MULTI-ACT project to enable the development of these models.

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Conflicts of interest

There are no conflicts of interest.

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