The agenda of the global patient reported outcomes for multiple sclerosis (PROMS) initiative: Progresses and open questions

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The agenda of the global Patient Reported Outcomes for Multiple Sclerosis (PROMS) Initiative: progresses and open questions

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Abbreviations

AISM	Associazione Italiana Sclerosi Multipla (Italian Multiple Sclerosis Society)
ECF	European Charcot Foundation
ECT	Engagement Coordination Team
ECTRIMS	Congress of the European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
e-Health	Electronic health technologies
EMA	European Medicines Agency
ePROM / ePROMs	electronic Patient Reported Outcome Measure / electronic Patient Reported Outcome Measures

EU	European Union
FDA	Food and Drug Administration
HTA	Health Technologies Assessments
m-Health	medical device
MoXFo	MOving eXercise research in multiple sclerosis FOrward
MS	Multiple Sclerosis
MSDA	Multiple Sclerosis Data Alliance
MSFC	Multiple Sclerosis Functional Composite
MSIF	Multiple Sclerosis International Federation
PCORI	Patient Centered Outcomes Research Institute
PRO / PROs	Patient Reported Outcome / Patient Reported Outcomes
PROM / PROMs	Patient Reported Outcome Measure / Patient Reported Outcome Measures
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMS	Patient Reported Outcome for Multiple Sclerosis
RRI	Responsible Research Innovation

HIGHLIGHTS

- PROMS is a global multi-stakeholder initiative that makes MS patients' change scientifically relevant experiential knowledge
- We envision a PROMs ecosystem in which all stakeholders are co-responsible of the impact of patient engagement, from research to care
- We aim to integrate a PROMs core data set from practice to care, to be included in registries
- We aim to rethink research, trials, and practice via e-PROMs to enable a holistic, comprehensive and personalized care
- We aim to develop a PROMs ecosystem that could be adapted and uptaken to other neurological diseases

Abstract

On 12 September 2019, the global Patient Reported Outcome for Multiple Sclerosis (PROMS) Initiative was launched at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). The multi-stakeholder PROMS Initiative is jointly led by the European Charcot Foundation (ECF) and the Multiple Sclerosis International Federation (MSIF), with the Italian MS Society (AISM) acting as the lead agency for and on behalf of the global MSIF movement. The initiative has the ambitious mission to (i) maximize the impact of science with and of patient input on the life of people affected by MS, and (ii) to represent a unified view on Patient-Reported Outcomes for MS to people affected by MS, healthcare providers, regulatory agencies and Health Technologies Assessments agencies. Equipped with an innovative participatory governance of an international and interdisciplinary network of different stakeholders, PROMS has the potential to guide future breakthroughs in MS patient-focused research and care. In this paper we present the progresses of the global PROMS Initiative and discuss the open questions that we aim to address.

Keywords

Multiple Sclerosis progression, Patient Engagement, Patient Reported Outcomes, Personalized care, Responsible Research Innovation, digital health.

Introduction

Patient Reported Outcomes (PROs) and Patient Reported Outcomes Measurements (PROMs) have not reached their full potential of delivering benefits to patients

In a time of challenges that call for mission-oriented health research[i] such as those in healthcare, we need new multi-stakeholder and multidisciplinary organizational models of cooperation that guarantee a long-

term return on investment, not only economic but also able to prioritize a kind of innovation normatively underpinned by the social Sustainable Development Goals of 2030 United Nation Agenda[ii,iii]. One of the explicit driver of this change, in line with the Responsible Research Innovation (RRI) recommendations of the European Union[iv], is to enable the science with and of patient input[v] within health research organizations. Science with and of patient input began as an extension of patient advocacy but has evolved 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 power of the science with and of patient input relies on the development and implementation of an innovative framework to engage patients and on the collection and use of patient-generated health data[vi]. Among patient-generated health data, Patient Reported Outcomes (PROs) represent a major opportunity to measure the impact of health research, treatment and care on outcomes that matter most to patients and are of value for healthcare stakeholders.

There is no unique definition of PROs: "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" in accordance to the Food and Drug Administration (FDA)[vii] or "any outcome evaluated directly by the patient him/herself and based on patient's perception of a disease and its treatment(s)" in accordance to the European Medicines Agency (EMA)[viii]. The FDA definition of PROs designates both active and passive information as PROs, while the EMA definition seems to restrict PROs to active reports only. E-Health (e.g., patient portals to capture patient-generated health data) and m-Health (e.g., wearable devices and sensors) technologies continue to expand the opportunities to measure PRO also in a passive manner.

Despite differences in point of view, relevant stakeholders agree that Patient Reported Outcomes Measurements (PROMs), and the PROs that they yield, have not reached their full potential for delivering benefits to people with multiple sclerosis (MS) and the healthcare continuum:

- **What outcomes matter most to patients?** Patients are frustrated that outcomes that matter most to them are not always adequately addressed[ix].
- **Which existing PROMs should clinicians use to have impact on clinical practice?** There is a desire by clinicians to include PROMs to assess treatment effects or compare different care options[x].
- **How could the use of PROMs be improved to inform health policy and models of assistance to drive meaningful changes for patients' quality of life?** Consumer/patient-driven healthcare is gaining ground[xi,xii].
- **How could the use of PROMs be improved in medicine life cycle management and decision-making approval processes?** Industry, regulatory agencies and Healthcare Technology Assessment (HTA) agencies recognize that, for example, current conventional outcomes in MS, like the Expanded Disability Status Scale (EDSS), relapse rate, or Magnetic Resonance Imaging features, do not fully capture the experience of people with MS[xiii,xiv].

In this article we present the global Patient Reported Outcome for MS (PROMS) Initiative and its progresses, and discuss the open questions that we aim to address.

A new global multi-stakeholder initiative on Patient Reported Outcome for MS (PROMS)

In recognition of the need for a common strategic agenda and roadmap shared by all relevant stakeholders to facilitate the uptake of PROs into the health research and care continuum for MS, a preparatory workshop was held in Lerici, Italy, in summer 2018, and approximately one year later the global Patient Reported Outcome for Multiple Sclerosis (PROMS) Initiative was launched on 12 September 2019 at the

35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS, Stockholm, Sweden)[xv]. The PROMS is a unique multi-stakeholder initiative cooperatively managed by an independent non-profit academic/clinical organization, the European Charcot Foundation (ECF[xvi]) and patient organizations, i.e. the Italian Multiple Sclerosis Society (AISM), acting as the lead agency for and on behalf of the global Multiple Sclerosis International Federation (MSIF[xvii]) movement.

The mission of the PROMS Initiative is to (i) maximize the impact of science with and of patient input on the health, healthcare and quality of life of people affected by MS, and (ii) represent a unified view on PROs for MS to people affected by MS, healthcare providers, regulatory agencies and HTAs.

Innovative participatory governance

To fulfil its mission, the PROMS Initiative recognizes the crucial importance of a framework to guide effective participatory governance and an impact assessment system to align the results to the PROMS mission and agenda[xviii]. The governance of PROMS is one of the first examples of participatory governance[xix] in MS research (Figure 1) and includes four interdisciplinary working groups, comprising 60 international experts from different stakeholder categories (patients, patient organizations, industry, research/clinician, healthcare organizations and health economics). PROMS currently involves people from five out of six World Health Organization regions, and aims to involve people from all six regions to ensure that whole MS community is included.

The core of the PROMS participatory governance is an innovative framework used to engage patients. Within this framework, patient advocacy organizations play an important role, as boundary organizations between science and society, to define and implement the 'how to' of patient engagement. Hence, the Engagement Coordination Team (ECT), including people affected by MS, was established to support the PROMS Initiative, integrating the unique experience of living with MS to the initiative. For the PROMS Initiative, the term "patient" (person with the disease) refers to any individual with lived experience of the disease. While "People affected by the disease" refers to a broader stakeholder group that is also engaged as part of the PROMS Initiative, and includes family members, caregivers and similar individuals/groups in addition to patients. The concept of the ECT was developed within the EU-funded RRI MULTI- ACT project [xx] and is also utilized by other relevant multi-stakeholder research initiatives[xxi]. Applying the MULTI-ACT/ECT governance approach is considered instrumental to engage the relevant people affected by MS community, that can reflect diversity and complexity of their experiential knowledge. The ECT is leading the design and implementation of a plan for the engagement of people affected by MS in the PROMS agenda, as the initiative develops over time, in the implementation, monitoring and evaluation phases. The ECT is co-chaired by an MS organization representative and a person with or affected by MS. ECT members are also embedded within the working groups to jointly identify how and where to engage the MS community in a meaningful way, as well as help the Scientific Steering Committee and working groups to identify which priorities of the PROMS agenda will benefit from patient engagement activities.

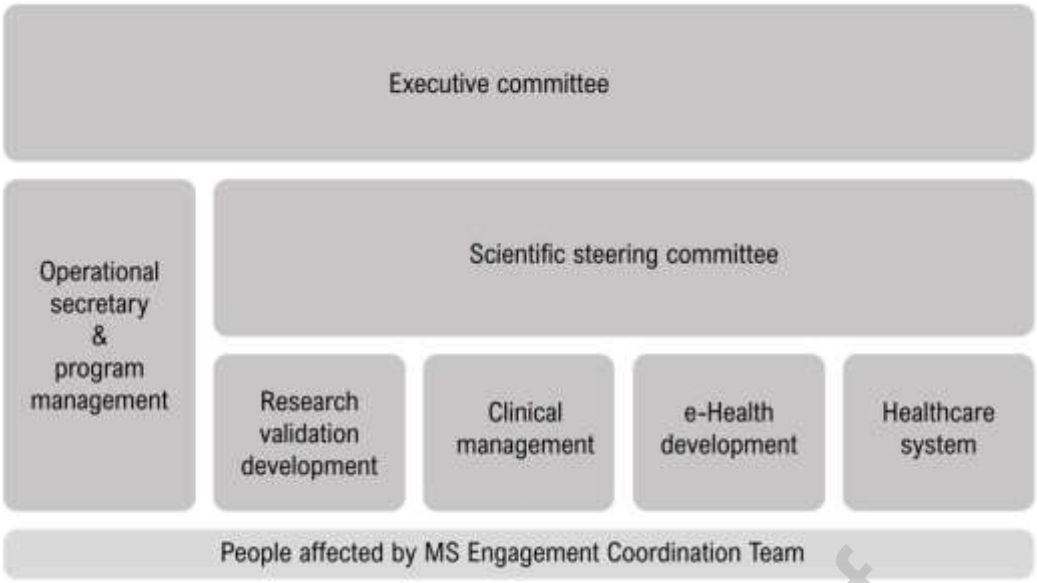

Figure 1 PROMS Governance

The PROMS Initiative: the path forward for setting the agenda

Inspired by the "*Framework To Guide The Collection And Use Of Patient-Reported Outcome Measures In The Learning Health Care System*"[xxii], the PROMS Initiative has currently identified four strategic priorities where the engagement of the MS community through an international and multi-stakeholder effort would provide significant insights to address the research questions presented in the introduction: (i) healthcare system, (ii) research validation and development, (iii) clinical management and (iv) e-Health. Through a series of meetings, working groups developed new multi-stakeholder perspectives on these four proficiency areas and presented key recommendations for setting the agenda at the first PROMS scientific virtual meeting. During 2021, the Strategic Direction has been finalized by the PROMS stakeholders through a co-creation process where the concept of interest of each stakeholder category has been fully discussed and captured:

PROMS Strategic Direction:

Engaging People with MS in providing PROMs that give a picture of their status today and changes over time (re-define MS progression, improvement and worsening), leveraging passive and active monitoring, in a holistic, comprehensive and personalized approach to improve prognosis, prevent progression and improve lives of People with MS.

The PROMS scope of work framework[xxiii] is outlined below (Figure 2) and the document contains goal(s) and concepts of interest of PROMS stakeholders (Figure 3) toward the agenda and objectives, critical actions and deliverables, and synergism with other strategic priorities.

In a first phase, the working groups will work in parallel toward synergizing and capitalizing their results in the PROMS Agenda, that will be the result of a cross-fertilization process among the four strategic priorities.

Figure 2 PROMS scope of work cycle

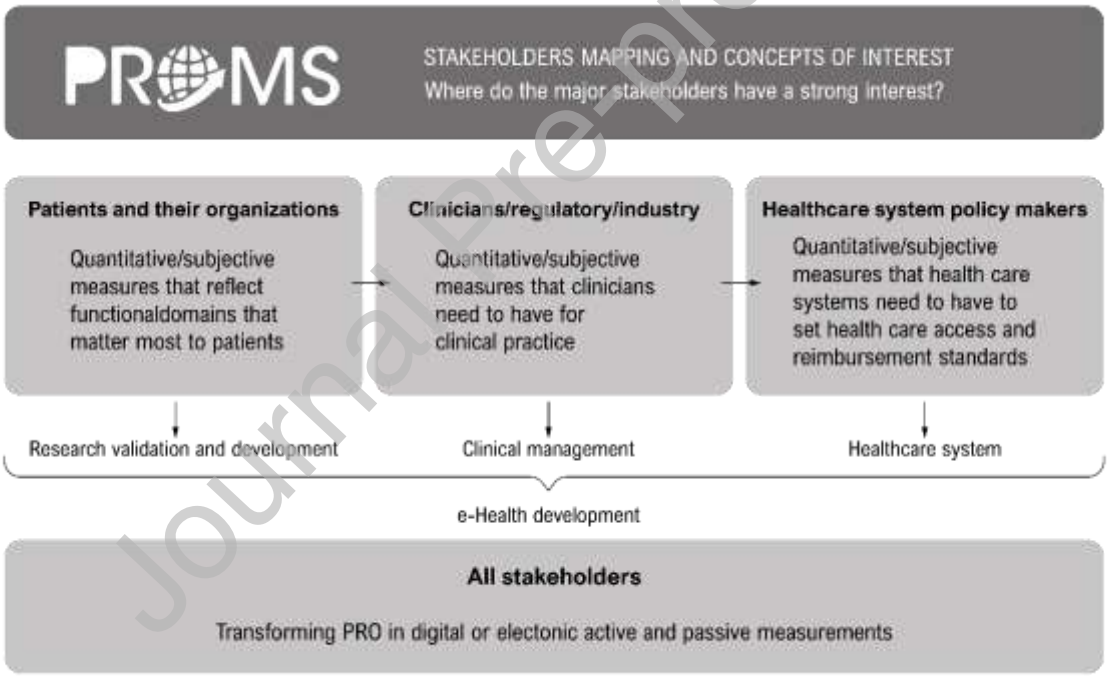

Figure 3 Stakeholders Mapping and Concepts of Interest

"What outcomes matter most to patients?"
Enabling science with and of patient input

The PROMS Initiative aims to provide guidance for identifying gaps in PROMs that reflect functional domains that matter most to patients. A Survey and a Delphi study will be performed to build consensus on the above gaps[xxiv]. In building consensus, the PROMS stakeholders will take into account the evidence collected by other initiatives such as the Progressive MS Alliance[xxv], PROMOPRO-MS[xxvi], iConquerMS[xxvii], the

Critical Path Institute Patient Reported Outcome (PRO) Consortium[xxviii], the Patient Centered Outcomes Research Institute (PCORI)[xxix], the Multiple Sclerosis Data Alliance (MSDA)[xxx] and the MOving eXercise research in multiple sclerosis FOrward (MoXFo) initiative[xxxi].

Following this, a guidance framework for developing new PROMs, co-created with patients, will be set up taking into account the current complexity of measuring functioning across MS disease stages and within individuals along their disease course, but also geographical, social and cultural differences. As for the latter, linguistic validation of PROMs - as well as the concept of electronic PROMs (ePROMs[xxxii]) that can improve usability and interpretability - will be developed, promoting a unifying vision on the shared use of valid and reliable PROMs.

Within this framework, the PROMS Initiative will validate MS specific PROMs, co-created with people with MS, by testing them in proof-of-concept clinical trials. This will improve clinical trial design aiming at measuring the impact of treatments on outcome that matter most to people with MS[28]. Existing PROMs are increasingly used as secondary or tertiary outcomes in MS clinical trials on disease-modifying therapies and symptomatic treatments, whereas in rehabilitation trials are used as primary outcomes[33]. Although some clinical trials show promising results, there are limitations to the use of current PROMs that do not cover the full extent of MS activity and progression[xxxiii] and are not considered by regulatory agencies enough clinically meaningful[xxxiv]. The lack of a set of standard measures has significant disadvantages and some available measures are of uncertain validity. Different generic PROMs have been developed. Among these, the US National Institute of Health (NIH) supported the creation of 2 standard sets of PROMs: one for use across neurological conditions (Neuro-QoL[xxxv)]) and one for use across a broad range of chronic health conditions (PROMIS[xxxvi]). The Critical Path PRO Consortium is working in collaboration with FDA on the qualification of two PROMs for people living with MS, one to measure fatigue (PROMIS FatigueMS-8a[xxxvii]) and the other to measure physical function (PROMISnq PFMS-15a). The 'SymptoMScreen' tool is another example of valuable addition to existing PROMs in MS and could be highly useful in studies of large populations seeking to reduce respondent burden[xxxviii].
However, many of the existing PROMs were not developed in partnership with MS patients nor with sufficient understanding about what matters to them, and most of them have not gone through a complete validation process.

The PROMS Initiative will approach relevant agencies and groups, such as the EMA Innovation Task Force, the Critical Path PRO Consortium/Food and Drug Administration (FDA), for a cross fertilization among the initiatives, and in particular to establish a collaboration toward the path forward for validation and regulatory approval of a PROMs selected as case study.

"Which existing PROMs should clinicians use to have impact on clinical practice?"

PROMs that work at population level in clinical trials and that can be customized for 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 clinical practice. The PROMS Initiative aims to provide guidance for the incorporation of PROMs into the MS clinical practice workflow based on input from MS stakeholders. The collection and use of PROs covering symptoms, (dis)abilities and quality of life issues will contribute to improve outcomes in areas that matter to people living with the disease.

The PROMS Initiative will identify and catalogue existing PROMs used in clinical practice and collected in core PROMs data registries. PROMs will be categorized in relation to their fitness for specific purposes. However, the incorporation/introduction of PROMs into clinical practice should not be considered a substitute for the patient-clinician interaction, it should enhance that interaction. Clear goals for the

incorporation of PROMs into the MS clinical workflow will be established based on input from the following stakeholders: MS patients, care/support partners and clinicians (through surveys, focus groups, etc.). The challenge in this area is the selection of PRO instruments for specific MS purposes from many available, in addition to overcoming logistical and cultural barriers to the adoption and effective routine use by different stakeholders of these PROMs into clinical practice. The challenge, ultimately, will be to demonstrate the value of collecting and using PROs in practice. The PROMS Initiative will work on a standardized core data set from practice to care, easy to use and able to capture the right outcomes, looking at sensitivity, specificity, and validity. The Initiative will propose this core data set to be used in clinical trials, collected into registries, translated into digital (active and passive), and proposed for the healthcare setting. Overall to fulfil the Initiative's mission, recommendations will be developed to provide a unified view on the use of PROMs and e-PROMs in clinical practice to people affected by MS, healthcare providers, regulatory agencies and HTAs.

Ideally, this would be a happy medium between PROMs that work at population level in clinical trials[xxxix] and PROMs that can be customized for use in clinical practice. Electronic health technologies (e-Health) and medical device (m-Health) could help meeting this challenge and could play an increased role in filling the gaps between use of PROMs in clinical trials versus clinical practice in MS[xl].

"How could the use of PROMs be improved to inform health policy and models of assistance to drive meaningful changes for patients' quality of life?"

Design with the end in mind: health ecosystem that is on the path for PRO/PROMs to impact MS care

The use of systematic and integrated measurements of PROs, in addition to clinical outcomes for MS, over an adequate observation period would provide the information needed to enable the positive loop that drives outcomes, practice improvement and cost optimization toward a personalized approach[xli].

Whereas substantial consensus is available on clinical outcomes, consensus on PROMs remains elusive. Healthcare System-PROMs are often used to assess quality and value of clinical services and not that of individual patients. Therefore, the hurdles for adoption of Healthcare System-PROMs will have to take the above aspect into consideration.

The global PROMS Initiative aims to define a set of standardized PROMs relevant to Healthcare System and that capture changes in the real life of people with MS and are most important for improving their long-term wellbeing. PROMS Initiative will explore this concept by designing and implementing a "Policy Advocacy Plan", with the aim: i. to understand how PROMs are currently incorporated into health policy and practice, ii. to develop recommendations which gives an evidenced outline of how PROMs can be incorporated into health policy and management and the value to be realized from doing so., iii. to increase awareness of the value of PROMs in health policy and practice, iv to facilitate the incorporation of PROMS into relevant aspects of health policy relating to the treatment and care of individuals living with MS.

A Proof of Concept Baseline Study will be conducted in eight different countries, balancing from high income countries (i.e. Belgium, Canada, Denmark, Italy, UK, US) and middle and low income countries (i.e. regions of Latin America and Middle East and North Africa), with the intent to verify what is the scope for the PROMS Initiative to innovate and what is going to be acceptable for policy makers. The pilot will also serve to explore how PROs for MS can be used to increase access to rehabilitation, disease modifying treatment, and reimbursement. The first action of the baseline study is to interview national MS Societies

and experts of public healthcare systems in the related country, to assess the level of patient engagement in the different healthcare systems. A structured topic guide has been produced for the scope.

The outcome of the baseline study will inform a plan to identify the core set of quality metrics that will need to be collected to assess the value of MS interventions and to allow comparisons of MS interventions/services at different levels of complexity and across healthcare systems in different parts of the world. The PROMS Initiative will build on the experience of other relevant initiatives[xlii,xliii]. The adoption of international quality standards will be a complex process if the PROMS initiative goal is to achieve at least a common denominator across many cultures and healthcare systems. Any attempt to get healthcare managers to adopt and mandate the collection of PROs as part of routine MS care needs to be part of a strategy that can be applied also across the major neurological diseases. For example, depression screening is a recommended quality measure for patients with several neurologic conditions, including dementia, MS, stroke, epilepsy and Parkinson disease[xliv,xlv,xlvi,xlvii,xlviii].

The baseline study will also identify which PROMs are already in use to assess quality, cost-effectiveness and value of interventions in MS as well as interventions in other chronic diseases, for example, rheumatoid arthritis and type 1 diabetes mellitus. This evaluation needs to cut across other disease areas as health economists need PROMs, for example the widely used health scale EQ-5D[xlix], that allow them to make comparisons with other chronic diseases. However, the use of this scale in MS has major limitations because it fails to capture with adequate granularity the often dynamic and variable nature of the disease and its impact on patients, i.e., the challenge is not only about 'what is measured' but also relates to 'how it is measured'. In addition, case studies in other diseases of how PROMs are successfully being used in healthcare could serve as a model for adoption and/or improvement for application to MS services. To achieve this, the PROMS Initiative will explore the use of PROs at different levels[l]: (1) micro level where PROs can influence the patient-centered care and individual clinical encounter (patient-physician relationship, screening/early identification, individual prognosis); (2) meso level where PROs can be used for benchmarking, performance monitoring and quality improvement; and (3) macro level where PROs can be used for regulatory approval, post-marketing surveillance, coverage and reimbursement, and clinical guidelines. Cost-utility analysis measures health effects in terms of both quantity and quality of life, and explicitly drives reimbursement decisions in several jurisdictions.

Barriers to adoption of Healthcare System-PROMs will also be analyzed. The PROMS Initiative acknowledges that Healthcare Systems' contexts are unique to each country and that a global strategy for implementation in every country is neither possible nor appropriate[li]. We will opt for standards adaptable to local cultural, political and economic contexts. In particular, the PROMS's recommendations will foresee different level of standards: from minimum standards (e.g. information, education) to gold standards (e.g. PROMs used as impact indicators).

"How could the use of PROMs be improved in medicine life cycle management and decision-making approval processes?"

Rethinking trials, real-world research and ultimately practice via e-PROMs

Clinic-based performance measures, such as EDSS and Multiple Sclerosis Functional Composite (MSFC), provide informative snapshots about disability and specific neurological functions in an artificial environmental context, but do not capture performance fluctuations in the natural environment. Questionnaires provide valuable insights but are subject to recall bias and may be associated with variable perception of similar deficits. The complementary clinical assessments of patients' functions, abilities or disabilities are currently undertaken by tools that are predominantly subjective and not quantitative. Therefore, more objective and ecologically valid outcome measures are needed to advance MS research

and help make clinical trials and subsequently clinical care more efficient, by having more sensitive outcome measures to improve their power and demonstrate added value[lii]. Digital technology has the potential to bring measures of the individual's perception and feelings, as well as objective performance tests and measures, to the point of research and care.

The COVID-19 pandemic has accelerated the need to be able to evaluate and manage patients remotely, however, validated available tools and assessments are limited at best. It has already been shown that data from wearables and mobile technologies could be used to rapidly quantify and provide a holistic view of behavioral changes in response to public health interventions as a result of infectious outbreaks such as COVID-19[liii].

Adding remote continuous digital self-monitoring measures (mobile health apps, wearables) may result in a closer and more precise look at the reality of MS, and will favor the shift from center-based to a personalized patient-centered care[32,liv]: e.g. reduce observer-dependency, reduce measurement errors/complications, enhance sensitivity, and importantly, improve patients' coping and attitudes towards their disease.

The current knowledge on the role of digital technology in MS is however fragmented, limiting the possibility to standardize its use in clinical practice. Moreover, technical requirements to obtain optimal outcomes from sensors need an increase in research efforts in order to reach uniformity. Another factor that may limit the application and use of wearable biosensors in MS is patient adherence[32].

The PROMS Initiative has acknowledged that direct patient input into clinical trials and practice is limited but emerging. Therefore, the PROMS Initiative aims to enable patients to receive long-term benefits from e-Health and m-Health, through the application of patient reported and patient provided active and passive measures in clinical research, and ultimately, in clinical practice. MS relevant domains and hence the performance measures to collect data both passively and actively will be identified.

A Learning Health Care System construct may help integrate multiple established and new measures into advances for clinical development, measures in real-world research and ultimately knowledge at the point of care. However, ways to control medical technology and engineering to advance measures, advanced analytics (machine learning and artificial intelligence) and data sharing and collaborative research are needed at all times.

Another goal is to map out a regulatory plan for e-Health outcomes for application in research and clinical practice specific to e-Health measures (patient reported and patient provided active and passive measures) and m-Health devices (medical devices or repurposed commercial devices). Digital health technology can move drug development forward; however, coordination and early interaction between stakeholders are key to reach a consensus on the quality and quantity of digital evidence needed and on the methods to collect that evidence[lv]. Regulatory approval to advance measures in MS for clinical research and care will take some time and may be a constraint to broad adoption.

There are several challenges related to the uptake of e-Health from research to care in MS (e.g. harmonization across different systems and devices; privacy/data security and data regulation; accuracy of devices in measuring the actual symptom/action you want; achieving sustained patient engagement with the technology; engagement from clinicians; different regulatory pathways to validate outcomes from digital technology; role of reimbursement). These barriers will be even more difficult to be managed in Low-Middle Income Countries. However, the PROMS Initiative, thanks to its global and multi-stakeholder nature, will promote collaboration and ensure access across the global continuum on selected standardized e-Health approaches[lvi].

Finally, this research will lead to building recommendations of candidate measures and clinical digital biomarkers of MS for potential application. The PROMS Initiatives will develop case studies across different disease domains and geography to prove meaningfulness and clinical relevance, toward digital endpoints that can be accepted by regulators.

The PROMS Initiative has launched a survey about the use of digital tools and conducted a landscape analysis with the aim to develop a catalogue collecting e-Health solutions on domains relevant for MS, but not necessary disease-specific. Building on results from the working groups, the PROMS initiative will propose core e-Health tools to facilitate the adoption of PROs in MS research, clinical trials and clinical management toward capturing People with MS status today and changes over time.

Conclusions

The PROMS Initiative is the first example of a multi-stakeholder initiative jointly led and coordinated by an academic/clinical organization (ECF) and patient organizations (MSIF/AISM). The PROMS governance recognizes the crucial importance of a framework to guide effective participatory governance and an impact assessment system to align the results to the PROMS mission and agenda. PROs are of utmost importance to assess RRI impact. There is still much room for improvement towards a truly participatory approach in the design of the measures themselves, which are right now settled mainly in a top-down approach by clinicians. A new approach based on co-accountability[lvii], in which conventional metrics related to the excellence dimension are integrated with new measures related to the economic (efficiency), social, efficacy (achieving the mission), and patient-reported dimensions, seems to be more appropriate. In this approach, the patient-reported dimension is a transversal dimension applied throughout the four dimensions of the MULTI-ACT[19] model for enabling the science of patient input, where PROs are investigated as metrics able to measure the impact of Research & Innovation on outcomes that matter most to patients. People with MS are engaged as key stakeholders (science with patient) together with their care/support partners in measuring the impact of research on outcomes that matter to them (science of patient); they are the explicit drivers to bridge excellence with validity and relevance. The PROMS Initiative intends to move from the tokenistic concept of “patient-centricity” to the concept of “effective patient engagement” via an increased uptake of PRO measurements from research to care. To meet the challenge, members from different stakeholder categories presented a framework for, and first steps toward, addressing four key strategic priorities, key success indicators and expected impact (Figure 4).

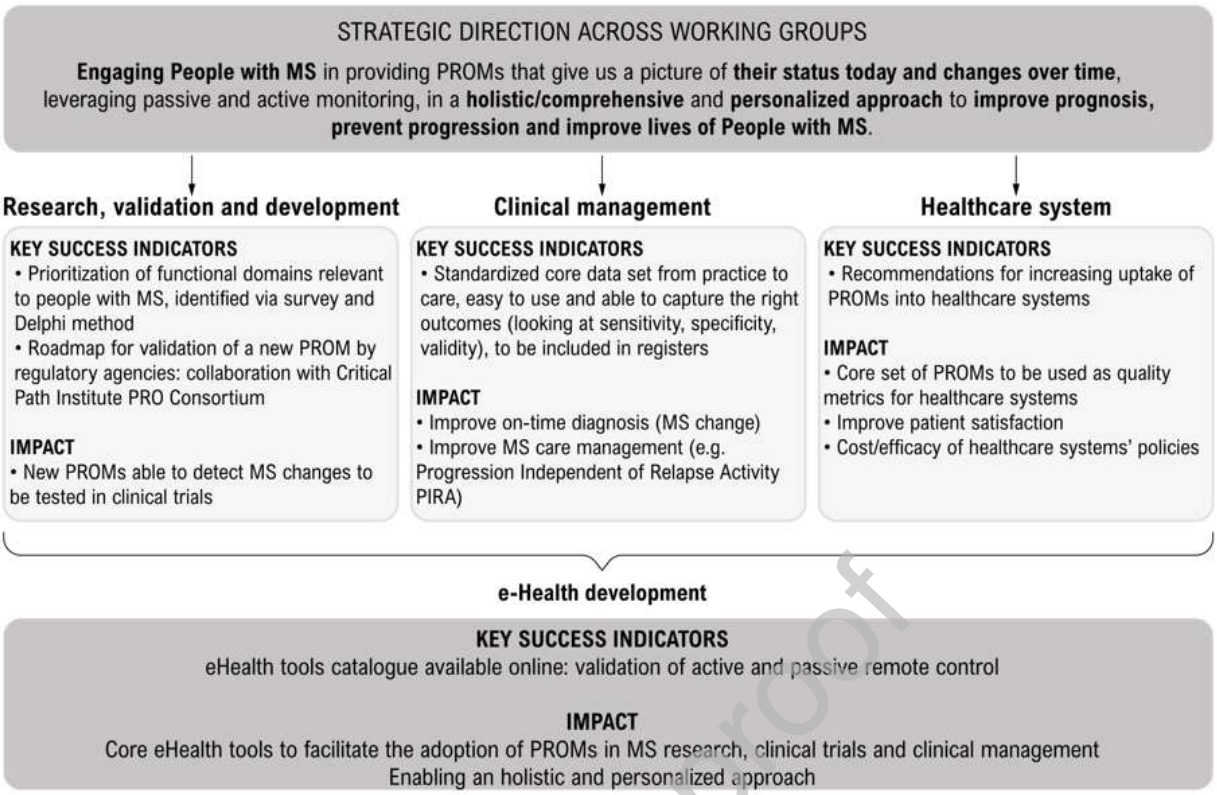

Figure 4 PROMS Key Success Indicators and impact

Transversal primary research outcome will include knowledge transfer and dissemination toward the development of a PROMS academy.

Following the international meeting in 2021, we anticipate that the final PROMS agenda will be realized and a call to action will be issued to sustain the agenda. Potential sources of funding for this call include the existing research funding mechanisms of the member organizations of the PROMS Initiative as well as international public funding.

Fostering multi-stakeholder participatory governance is a bold ambition, and potentially fraught with many challenges. More than ever, the COVID-19 pandemic calls for a shift of RRI from a cross-cutting issue to a strategic concern[lviii], and highlights the importance of promoting an effective co-creation approach with solid scientific bases. The PROMS Initiative has the potential to help meet the challenge by guiding future breakthroughs in MS patient-reported research and care, and beyond.

The guiding principle of the global PROMS Initiative will be at all times to engage all parties from across the globe that have an interest in furthering the mission of the PROMS Initiative. The PROMS Initiative aims to learn from their expertise, giving them opportunity to shape the overall scientific agenda, safeguarding that all stakeholders, including people with and affected by MS, have an equal voice, and ensuring that, when relevant, people with or affected by other conditions and diseases are also involved.

Engaging people with MS in providing PROMs that give us a picture of their status today and changes over time, leveraging passive and active monitoring, in a holistic/comprehensive and personalized approach will be instrumental to define MS improvement and worsening and to unmask the hidden part of the MS treatment iceberg. This might also contribute to re-define MS progression[lix], toward improving prognosis, preventing progression and improving lives of people with MS.

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PZ, GB, DB, EG, UK, HW, MAB: These authors have no relevant individual conflicts of interest to declare. PVe received honoraria and consulting fees from Biogen, Sanofi-Genzyme, Novartis, Teva, Merck, Roche, Imcyse, AB Science and Celgene; Research supports from Novartis, Sanofi-Genzyme and Roche.

MPA has served on Scientific Advisory Boards for Biogen, Novartis, Roche, Merck, Sanofi Genzyme and Teva; has received speaker honoraria from Biogen, Merck, Sanofi Genzyme, Roche, Novartis and Teva; has received research grants or her Institution from Biogen, Merck, Sanofi Genzyme, Novartis and Roche. She is co-Editor of the Multiple Sclerosis Journal and Associate Editor of Frontiers in Neurology.

TC is an employee of the National Multiple Sclerosis Society USA. His organization is a member of the MS International Federation – one of the sponsors of the PROMS initiative.

GCu is member of Data and Safety Monitoring Boards: AMO Pharma, Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Mitsubishi Tanabe Pharma Holdings, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc, , NHLBI (Protocol Review Committee), NICHD (OPRU oversight

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