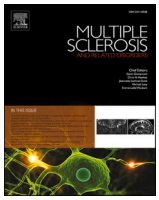
Multiple Sclerosis and Related Disorders 84 (2024) 105501

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Defining a standard set of health outcomes for patients with relapsing-remitting multiple sclerosis

Miguel Llaneza González [a,1], Pedro Carrascal Rueda [b,1,2], Olga Delgado Sánchez [c,1], Mónica Borges Guerra [d,1], Alfredo Rodríguez Antigüedad [e,1], Alberto Morell Baladrón [f,1], Noelia Becerril Ríos [d,1], Àlex Rovira [g,1], Virgina Meca Lallana [h,1], Laura Benedito-Palos [i], Marta Comellas [i], David Vilanova [j], Ainara Echeto [j], Xavier Pérez [j], Celia Oreja-Guevara [k,l,1,*]

[a] Neurology Department, Hospital Universitario Central de Asturias, Av. Roma, s/n, Oviedo 33011, Spain
[b] Esclerosis Múltiple España (EME), Ronda de Segovia, 69, Local Derecha, Madrid 28005, Spain
[c] Pharmacy Department, Hospital Universitario Sos Espases, Carretera de Valldemossa, 79, Palma, Illes Balears 07120, Spain
[d] Multiple Sclerosis Center, Hospital Universitario Virgen de la Macarena, Av. Dr. Fedriani, 3, Sevilla 41009, Spain
[e] Neurology Department, Hospital Universitario Cruces, Cruces Plaza, s/n, Barakaldo, Bizkaia 48903, Spain
[f] Pharmacy Department, Hospital Universitario La Princesa, Calle de Diego de León, 62, Madrid 28006, Spain
[g] Section of Neuroradiology, Department of Radiology, Hospital Universitario Vall d'Hebron, Pg. de la Vall d'Hebron, 119, Barcelona 08035, Spain
[h] Multiple Sclerosis Center, Hospital Universitario La Princesa, Calle de Diego de León, 62, Madrid 28006, Spain
[i] Outcomes'10, Avda. Sos Baynat s/n, Ed Espaitec 2, Castellón de la Plana 12071, Spain
[j] Bristol-Myers Squibb, C. de Quintanadueñas, 6, Madrid 28050, Spain
[k] Neurology Department, Hospital Clinico San Carlos, IdISSC, C/ Profesor Martin Lagos s/n, Madrid 28040, Spain
[l] Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid (UCM), Madrid, Spain

ARTICLE INFO

Keywords:
Relapsing-remitting multiple sclerosis
Patient-centred care
Outcome measurement
Patient-reported outcomes
Patient centricity
Quality of life

ABSTRACT

Background: Standardizing health outcomes is challenging in clinical management, but it also holds the potential for creating a healthcare system that is both more effective and efficient. The aim of the present study is to define a standardized set of health outcomes for managing Relapsing-Remitting Multiple Sclerosis (RRMS).
Methods: The project was led and coordinated by a multidisciplinary scientific committee (SC), which included a literature review, a patient-focused group, three nominal group meetings, and two SC meetings.
Results: 36 outcome variables were included in the standard set: 24 clinical (including weight, smoking habit, comorbidities, disability, mobility, diagnosis of secondary progressive multiple sclerosis, relapsed-related variables, radiological variables, cognitive status and disease-related symptoms), nine treatment-related (pharmacological and non-pharmacological information), and 3 related to the impact of RRMS on the patient's life (quality of life, pregnancy desire, work-related difficulties). In addition, experts also agreed to collect 10 case-mix variables that may affect but cannot be controlled as part of the management of the condition: 4 sociodemographic (age, sex, race, and employment status) and 6 clinical (height, date of diagnosis and first episode, serological status, early symptoms, and number of relapses pre-diagnosis).
Conclusion: The information provided through the present standard set of outcome variables can improve the management of RRMS and promote patient-centred quality care.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EDSS, Expanded Disability Status Scale; EMA, European Medicines Agency; EQ-5D-VAS, visual analogical scale of the EuroQol questionnaire; HRQoL, Health-Related Quality of Life; ICHOM, International Consortium for Health Outcomes Measurement; MFIS, Modified Fatigue Impact Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life; NG, nominal group; PRO, patient-reported outcome; PROM, patient-reported outcome measure; RRMS, relapsing-remitting multiple sclerosis; SC, scientific committee; SDMT, Symbol Digit Modality Test; SPMS, secondary progressive multiple sclerosis.

* Corresponding author at: Neurology Department, Hospital Clinico San Carlos, IdISSC, C/ Profesor Martin Lagos s/n, Madrid 28040, Spain.
E-mail address: orejacbn@gmail.com (C. Oreja-Guevara).

[1] All authors have contributed equally.

[2] Present address: Plataforma de Organizaciones de Pacientes (POP), www.plataformadepacientes.org. direccion@plataformadepacientes.org.

https://doi.org/10.1016/j.msard.2024.105501
Received 30 November 2023; Received in revised form 1 February 2024; Accepted 11 February 2024
Available online 13 February 2024

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system that is the most common cause of non-traumatic neurologic disability in young adults (Río and Montalbán, 2014). Approximately 2.5 million people live with MS worldwide (36 affected per 100,000), with a higher prevalence in countries at higher latitudes (Browne et al., 2014). Globally, females are twice as likely to suffer from MS as males, although the ratio of women to men is as high as 4:1 in some countries (Walton et al., 2020).

In most cases, the disease course begins as relapsing-remitting MS (RRMS), characterized by discrete periods of neurological symptoms that coincide with the appearance of inflammatory lesions. Over time, most patients convert to a progressive stage called secondary progressive MS (SPMS), with a decreased or complete cessation of relapses and contrast-enhancing lesions on magnetic resonance imaging (MRI) and a gradual accumulation of disability associated with brain and spinal cord atrophy. A small subset of patients debuts with primary progressive MS not preceded by a relapsing-remitting phase (Lublin et al., 2014).

The last two decades have witnessed the development of new therapies for RRMS that demonstrate increased efficacy relative to previous treatments. Many new drugs target the inflammatory phase of disease by manipulating different aspects of the immune system (Wagner and Goverman, 2015). Nevertheless, the multiple related symptoms and the unpredictable prognosis considerably impact patients' Health-Related Quality of Life (HRQoL) (Gil-González et al., 2020). In this sense, an early and individualized therapeutic approach and an accurate clinical and radiological follow-up are essential for adequately managing the disease (Comi et al., 2017).

Due to the heterogeneous nature of the disease, developing reliable and valid measures to assess disease characteristics from the patient's perspective has become a significant task to achieve more efficient and holistic management of MS (Nowinski et al., 2017). Consequently, growing evidence supports the systematic collection of patient-reported outcomes (PROs) to improve patient-centred care (Rudick and Miller, 2008). PROs quantify and monitor MS impacts longitudinally, determine costs and therapeutic effectiveness, and interpret the clinical meaningfulness of changes in objective measures (Bharadia et al., 2022).

Moving towards an effective and efficient patient-centred approach requires a standardized data capture system, integrating evidence from clinical outcomes and PROs. Assessing these outcomes is a means to compare performance between institutions and can be used to improve healthcare delivery. To answer the need for standardized and internationally accepted outcome measures, pioneer initiatives such as the International Consortium for Health Outcomes Measurement (ICHOM) (International Consortium for Health Outcomes Measurement (ICHOM), 2021) developed a set of recommendations for several diseases, among which RRMS is not included. They are elaborated to cover the full patient care cycle, can be applied in different healthcare settings and recommend a minimum time point for patient data collection (Ackerman et al., 2017). In this scenario, this project aimed to define a standard set of health outcomes and the most appropriate instruments to measure them for managing patients diagnosed with RRMS as the first step to standardizing the collection of health outcomes in this MS form.

2. Material and methods

The project was led and coordinated by a scientific committee (SC) of healthcare professionals experts in the management of RRMS (four neurologists, one neuroradiologist, two hospital pharmacists, one neuropsychologist, and one nurse) and one representative of a Spanish patient advocacy group (*Esclerosis Múltiple España*, EME). It comprised the five phases (January–September 2022) outlined below.

2.1. Literature review

To identify health outcomes (clinical and PROs) and instruments of measurement to be used during RRMS patient follow-up, a systematic literature review, according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) was carried out in Medline/PubMed (Supplementary Table S1). In addition, the main Clinic Practice Guidelines and recommendations on managing RRMS were consulted, as well as the European Medicines Agency (EMA) guidelines for clinical research with medicines for treating MS.

2.2. Focus group

An online focus group was conducted with RRMS patients identified and invited to participate voluntarily through EME to achieve a heterogeneous group representing both sexes, different ages and times of diagnosis. The focus group aimed to gain patients' perspectives on the impact of the disease and its treatment on their day-to-day lives.

2.3. First scientific committee meeting

The first meeting with the SC aimed to discuss and select the health outcome variables for managing RRMS to be included in the standardized set for further assessment in the nominal groups (NG) based on the literature results and patient input in the focus group.

During the discussion group, the SC screened health outcomes (variable/instrument/frequency of measurement) and selected them according to their relevance for patient follow-up and availability in Spanish. Moreover, the SC proposed new health outcomes not previously identified in the literature review but relevant from their perspective.

2.4. Nominal group meetings

Three multidisciplinary NG were conducted to reach a consensus on the health outcomes for inclusion in the standard set. The NG is a qualitative methodology that allows for reaching a consensus and ensuring balanced participation among group members, giving them equal opportunities to share their opinions (Gallagher et al., 1993; Moore, 1987). The consensus was established when $\geq$ 75 % of participants agreed.

2.5. Final scientific committee meeting

The main objective of the last SC meeting was to define the health outcomes for inclusion in the standard set for RRMS. For this purpose, the SC reviewed the results of the three NGs, ensuring consensus on the health outcomes for which no overall agreement was reached. Based on their discussion and conclusions, the health outcomes for inclusion in the standard set for RRMS were defined.

3. Results

3.1. Literature review

A total of 77 health outcomes were identified in the literature review (Fig. 1). They were categorized into case-mix variables (baseline factors that may affect the health outcomes but cannot be controlled as part of the management of the condition and enable patient characterization) ($n = 27$) and outcomes variables (variables for patient follow-up that allow determining the impact of healthcare service or intervention on the health status of patients) ($n = 50$) (Supplementary Table S2).

3.2. Focus group

The focus group included 6 RRMS patients (83.3 % women) ranging

in age from 32 to 59 years and with the time since diagnosis from 1 to 35 years. Results from the meeting showed that the PROs related to symptoms that had the most impact on daily life were, in order of importance: fatigue, cognitive disturbances, muscle weakness, spasticity, mood disturbances, visual disturbances, mobility problems, body pain, sleep disturbances, swallowing difficulties, sensory disorders, bowel and urinary problems, and sexual problems. In terms of global PROs, those with the most significant impact on patient's daily life were (also in order of importance): HRQoL, limitations in daily activities, restrictions in family/social life, limitations in work, social support and, lastly, satisfaction with treatment and care received and treatment adherence. In general, patients in the focus group agreed that most of the symptoms affecting their daily lives and impacting their quality of life were not routinely explored in clinical practice.

3.3. First scientific committee meeting

The SC considered the relevance of 18 out of 27 case-mix and 29 out of 50 outcome variables previously identified in the literature. Moreover, 6 new additional case-mix and 11 outcome variables were proposed. In the same way, the variable related to MRI was split into 5 independent variables, and spasticity and muscle tone were grouped. Thus, the SC selected 25 case-mix and 46 outcome variables for presentation and evaluation during the NGs (Supplementary Table S3).

3.4. Nominal group meetings

A total of 29 experts on RRMS from different specialities ($n = 9$ neurologists, $n = 6$ hospital pharmacists, $n = 3$ neuroradiologists, $n = 2$ nurses, $n = 2$ neuropsychologists, $n = 2$ physiotherapists, $n = 1$ clinical psychologist, $n = 1$ rehabilitation physician, $n = 1$ speech therapist, $n = 1$ social worker, and $n = 1$ primary care specialist) and Spanish regions participated in three NG meetings.

The three NGs agreed on 7 case-mix and 23 outcome variables proposed by the SC in the standard set. Additionally, during the meetings, 3 new case-mix variables and 1 outcome variable were presented in some NGs (Supplementary Table S4).

3.5. Final scientific committee meeting

Based on the consensus reached among NGs, the SC assessed the inclusion or exclusion of the new health outcomes proposed and those for which the NGs did not get a consensus.

3.5.1. Case-mix

The SC agreed to collect at baseline (at diagnosis/before initiating treatment) the main sociodemographic (age, sex, race, and work situation) and clinical factors (date of diagnosis, serological status, list of initial symptoms, height, date of the first MS episode, and the number of episodes before diagnosis) as case-mix variables (Table 1).

3.5.2. Outcome variables

The SC agreed to collect a series of outcome variables during follow-up. These variables were classified as clinical, treatment-related, and disease impact-related on patients' lives (Table 2).

3.5.2.1. Clinical follow-up variables. It was agreed to record: weight, smoking habit, comorbidities, degree of disability, mobility, MRI dates, number and topography of new/enlarging T2 lesions and gadolinium-enhanced lesions, degree of brain atrophy, cognitive status, visual symptoms, spasticity, bowel/bladder dysfunction, fatigue, sexual dysfunction, emotional disturbances, sleep disorders and if this applies: relapse dates, the severity of relapses, symptoms of relapses, recovery from relapses, and clinical diagnosis of secondary progressive multiple sclerosis (in which case this standardized set will no longer apply).

The instrument selected for the semestral assessment of the degree of

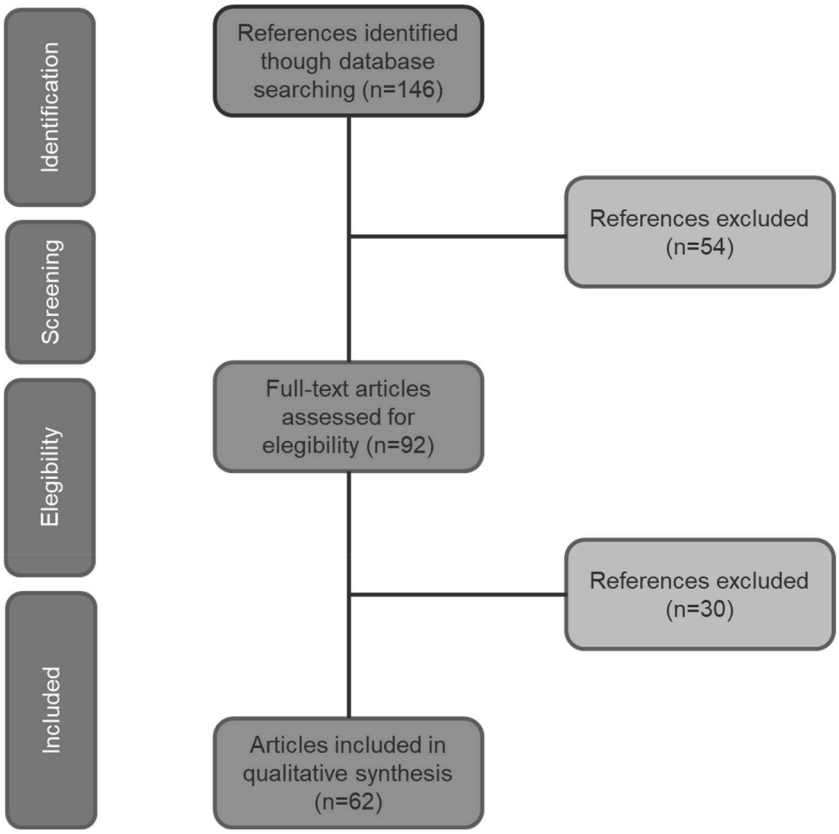


Fig. 1. Prisma flow diagram.

Table 1
Standard set of patient-centered outcomes in RRMS. Case-mix variables.

Patient profile	Variable	Supporting information	Measurement instrument	Timing	Data sources
Sociodemographic factors					
All patients	Age		Date of birth	Baseline (at diagnosis)	Clinical report
	Sex	Biological gender	F: female; M: male		
	Race		(1) White; (2) Black; (3) Asian; (4) Latin American; (5) Multiracial; (6) Other (specify)		
	Employment status		(1) Worker: Type of work (specify) and type of working day (full/part-time); (2) Student (type of studies); (3) Unemployed; (4) Household work; (5) Retired (working age: Yes/No); (6) Other situations (specify)		Patient-reported
Baseline clinical factors					
All patients	Diagnosis date		dd/mm/yyyy	Baseline (at diagnosis/ before treatment begins)	Clinical report
	Serological status		- Hepatitis A, B and C - Varicella-zoster - Measles - Syphilis (VDRL) - HIV - Other (specify if applicable)		
	Initial symptoms	Including the topography of the event	List of symptoms		
	Date of the first episode		dd/mm/yyyy		
	Num of episodes before diagnosis		N.A.		
	Height	Measurement BMI calculation (kg/m2)	cm		

BMI: body mass index; HIV: human immunodeficiency virus; N.A.; non applicable; VDRL: Venereal Disease Research Laboratory.

disability, severity and recovery from relapses, visual symptoms, cognitive status, spasticity, bowel/bladder dysfunction, and fatigue was the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The severity and recovery from relapses should also be assessed at relapse and three months later based on the requirement and response to corticosteroids. In addition, on an annual basis, some symptoms such as vision, cognitive status, sexual dysfunction, emotional disturbances and fatigue should be assessed through the specific items of the Multiple Sclerosis International Quality of Life (MusiQoL) questionnaire (Simeoni et al., 2008). It was also proposed to evaluate fatigue through the Modified Fatigue Impact Scale (MFIS) (Kos et al., 2005), cognitive status through the Symbol Digit Modality Test (SDMT) (Benedict et al., 2017), and sexual dysfunction and sleep disorders through anamnesis.

Ambulation, manual dexterity, and balance were determined to be evaluated independently of the patient's mobility annually. The selection of specific evaluation tests will depend on the degree of disability of the patients at the time of the assessment.

The frequency of measurement of radiological variables was established as a first assessment no more than 3 months after disease onset (number and topography of T2 lesions, number and topography of contrast-enhancing lesions, degree of brain atrophy), and then no more than 3 months before starting or modifying treatment, a "rebase" assessment 3–6 months after treatment initiation and then every 12 months during follow-up. Follow-up may be spaced out to 2–3 years in clinically stable patients with treatment that does not require safety monitoring. Gadolinium-based contrast agents will only be used in those patients who required it, according to recent guidelines (Wattjes et al., 2021). On the other hand, the SC proposed using the simplified Pasquier scale (Pasquier et al., 1996) to assess brain atrophy at baseline and every 5 years during follow-up.

3.5.2.2. Treatment-related variables. Both pharmacological and non-pharmacological treatments were considered. First, the experts agreed to report the persistence of disease-modifying therapies and symptomatic and comorbidity medications. Additionally, it was decided to record adverse and severe adverse events using Common Terminology Criteria for Adverse Events (CTCAE) and reasons for discontinuation. Finally, it was agreed to assess drug adherence through anamnesis and hospital pharmacy dispensing records. Concerning non-pharmacological treatment, it was considered to collect the patient's physical activity and rehabilitation.

3.5.2.3. Impact of the disease on patients' life variables. It was decided to evaluate HRQoL annually using the MusiQoL questionnaire (Simeoni et al., 2008) and the visual analogical scale of the EuroQol questionnaire (EQ-5D-VAS) (EuroQol Group, 2022). In the same way, conducting an annual work status follow-up and consulting the gestational desire were also considered relevant. In the case of HRQoL and gestational desire, it was deemed that the baseline measure would be taken three months after diagnosis (the timeframe in which it was considered that patients might have accepted the diagnosis).

4. Discussion

The RRMS standard set herein is a starting point for the standardized measurement of health outcomes, which can help to improve disease management and promote patient-centred care.

The present standard set includes 36 outcome variables classified as clinical, treatment-related, and disease impact-related on patients' lives. In addition to traditional clinical variables related to patient characteristics, relapses and MRI, eight are related to symptoms that the condition can produce (cognitive status, visual symptoms, spasticity, bowel/bladder dysfunction, fatigue, sexual dysfunction, emotional disturbances, and sleep disorders). The instrument to evaluate a large number of proposed variables is the EDSS (Kurtzke, 1983). The EDSS is one of the most widely used instruments to assess disease progression. Several studies have been conducted to analyze the usefulness of the EDSS scale for quantifying disability in multiple sclerosis and recording changes in disability over time (Meyer-Moock et al., 2014). However, some symptoms are also proposed for tracking *via* PRO measurements (PROM).

Different PROMs validated in the Spanish population were identified and proposed during the project's development (see Supplementary Material). The participating experts selected the most suitable and feasible ones to be used systematically in Spanish clinical practice. Thus, in line with the National MS Society (Kalb et al., 2018), early baseline

Table 2
Standard set of patient-centered outcomes in RRMS. Outcome variables.

Patient profile	Measure	Supporting information	Measurement instrument	Timing	Data sources
Clinical variables					
All patients	Weight	Weight control for BMI calculation (kg/m^2)	kg	Baseline and follow-up visits: every 6 months	Clinical report
	Smoking habit	Tobacco cessation monitoring	(1) Non-smoker; (2) Ex-smoker (≥ 1 year), (3) Active smoker		Patient-reported
	Comorbidities		List of comorbidities		Clinical report
	Disability		EDSS		
	Mobility[1]	Ability to walk	Any of the following tests: - T25FW - Timed 10 m walk test - 6′ test - Step counters - Tinetti scale	Baseline and follow-up visits: every 12 months	
		Manual dexterity	9HPT		
		Equilibrium and coordination	Tinetti Scale (or another validated scale)		
Patients who develop SPMS	SPMS	The set of variables for RRMS would not apply to those patients who develop SPMS	(1) Yes: approximate start date (year, retrospective); (2) No	N.A.	
Patients who suffer a relapse	Relapse date		dd/mm/yyyy	N.A.	
	Severity of relapse		- EDSS Scale - Steroid treatment: (1) Yes; (2) No		
	Symptoms of relapse	Symptomatology associated with relapses, including topography	List of symptoms		
	Recovery from relapse		- EDSS Scale - Response to steroid treatment: (1)Yes; (2) No	3 months after relapse	
All patients	MRI date		dd/mm/yyyy	N.A.	Clinical report
	Number of T2 lesions	Number of T2 lesions at diagnosis	Cerebral: - if ≤20 lesions, indicate the exact number. - if >20 lesions make an estimate (20–50; 50–100;>100 or uncountable (confluent) Spinal cord: (1) Yes: - if ≤ 10 lesions, indicate the exact number - if > 10 lesions	Baseline (maximum 3 months before starting or modifying a treatment).	

(*continued on next page*)

Table 2 (*continued*)

Patient profile	Measure	Supporting information	Measurement instrument	Timing	Data sources
			indicate: more than 10 lesions or diffuse pattern; (2) No		
		Number of new/enlarging T2 lesions at follow-up	Brain: exact number. Spinal cord (if performed): exact number	At 3–6 months after starting treatment) and follow-up visits: every 12 months (it may be spaced 2–3 years in clinically stable patients on drug treatment with no safety concerns).	
	Topography of T2 lesions	Topography of T2 lesions at diagnosis	- Periventricular: (1)Yes; (2) No - Leukocortical: (1) Yes; (2) No - Subcortical: (1) Yes; (2) No - Brainstem: (1)Yes; (2) No - Cerebellum: (1) Yes; (2) No - Spinal Cord: (1) Yes; (2) No (if spinal cord MRI is performed)	Baseline (maximum 3 months before starting or modifying a treatment).	
		Topography of new/ enlarged T2 lesions at follow-up	- Brain hemispheres: (1) Yes; (2) No - Brainstem: (1)Yes; (2) No - Cerebellum: (1) Yes; (2) No - Spinal Cord: (1) Yes; (2) No (if spinal cord MRI is performed)	At 3–6 months after starting treatment) and follow-up visits: every 12 months (it may be spaced 2–3 years in clinically stable patients on drug treatment with no safety concerns).	
Patients requiring the use of gadolinium	Number of contrast-enhancing lesions		Brain - if ≤10 lesions, indicate the exact number - if >10 lesions, indicate >10 lesions Spinal cord: (1) Yes: - if ≤10 lesions, indicate the exact number - if >10 injuries, indicate >10 injuries; (2) No	Baseline (maximum 3 months before starting or modifying a treatment), at 3–6 months after starting treatment) and follow-up visits: every 12 months (it may be spaced 2–3 years in clinically stable patients on drug treatment with no safety concerns).	
	Topography of contrast-enhancing lesions	At diagnosis	- Leukocortical: (1) Yes; (2) No - Periventricular: (1)Yes; (2) No - Subcortical: (1) Yes; (2) No - Brainstem: (1)Yes;	Baseline (maximum 3 months before starting or modifying a treatment).	

(*continued on next page*)

Table 2 (*continued*)

Patient profile	Measure	Supporting information	Measurement instrument	Timing	Data sources
			(2) No - Cerebellum: (1) Yes; (2) No - Spinal Cord: (1) Yes; (2) No (if spinal cord MRI is performed)		
		Follow-up	- Brain hemispheres: (1) Yes; (2) No - Brainstem: (1)Yes; (2) No - Cerebellum: (1) Yes; (2) No - Spinal Cord: (1) Yes; (2) No (if spinal cord MRI is performed)	At 3–6 months after starting treatment) and follow-up visits: every 12 months (it may be spaced 2–3 years in clinically stable patients on drug treatment with no safety concerns).	
All patients	Degree of brain atrophy		GCA-scale for global cortical atrophy on MRI	Baseline and follow-up visits: every 5 years	
	Cognitive status		- EDSS Scale - SDMT - MusiQoL: items 13, 14	Baseline and follow-up visits: - EDSS: every 6 months - SDMT: every 12 months (or earlier if clinically indicated) - MusiQoL: every 12 months	Clinical report / Patient-reported
	Visual symptoms	If there is a suspicion of impairment, more specific tests will be carried out and/or the patient will be referred to a health professional specialised in the symptoms reported by the patient	- EDSS - MusiQoL: ítem 15	Baseline and at follow-up visits: - EDSS: every 6 months - MusiQoL: every 12 months	
	Spasticity		EDSS	Baseline and follow-up visits: every 6 months	Clinical report
	Bowel/bladder dysfunction		EDSS		
	Fatigue		- EDSS Scale - MFIS Scale - MusiQoL: items 7, 8	Baseline and at follow-up visits: - EDSS: every 6 months - MFIS and MusiQoL: every 12 months	Clinical report / Patient-reported
	Sexual dysfunction		- Anamnesis: (1) Yes; (2) No. - MusiQoL: item 24	At follow-up visits: every 12 months (or sooner if clinically indicated)	Physician-reported / Patient-reported
	Emotional disturbances		- Anamnesis: (1) Yes; (2) No. - MusiQoL (items 9–12)	Baseline and at follow-up visits: - Every 6 months - MusiQoL: every 12 months	Physician-reported / Patient-reported
	Sleep disorders		Anamnesis: (1) Yes; (2) No	At follow-up visits: every 6 months	Physician-reported
Treatment variables					
All patients	DMTs		Drug: Start date and end date	N.A.	Clinical report
Patients with symptomatology	Symptomatic treatment				
Patients with comorbidities	Comorbidity treatment	Concomitant treatment			
All patients	Adherence	The assessment of adherence will be conditioned by the type of drug	- Anamnesis: (1) Yes; (2) No - Dispensing record at Hospital Pharmacy	At follow-up visits: every 6 months after the start of treatment	Clinical report / Physician-reported
	Adverse events Severe adverse events		CTCAE		Clinical report

(*continued on next page*)

Table 2 (*continued*)

Patient profile	Measure	Supporting information	Measurement instrument	Timing	Data sources
Patients who have discontinued treatment	Reasons fir discontinuation		- Intolerance - Lack of effectiveness - Progression - Patient decision - Pregnancy/ lactation - Safety (AEs) - Other (specify)	N.A.	
All patients	Rehabilitation		(1) Yes: discipline and number of sessions; (2) No	At follow-up visits: every 6 months after the rehabilitation recommendation has been made	Patient-reported
	Physical activity	Exercising as part of healthy lifestyle habits	(1) Yes: type of exercise and frequency; (2) No	Baseline and follow-up: every 6 months (if there have been changes)	
Variables related to the impact of the disease on the patient's life					
All patients	HRQoL	Impact of the disease on patient quality of life and overall health	- MusiQoL: overall score - EQ-5D-VAS	Baseline (3 months after diagnosis) and at follow-up visits: every 12 months	Patient-reported
	Gestational desire		Anamnesis: (1) Yes; (2) No		
	Work status	If changes occur during monitoring, specify	- Change in work activity: (1) Yes; (2) No - MusiQoL: item 6	At follow-up visits: every 12 months	

AE: adverse event; BMI: body mass index; CTCAE: Common Terminology Criteria for Adverse Events; DMTs: disease-modifying therapies; EDSS: Expanded Disability Status Scale; EQ-5D-VAS: Visual analogical scale of EuroQol-5D; GCA: Global Cortical Atrophy; 9HPT: Nine-Hole Peg Test; MFIS, Modified Fatigue Impact Scale; MRI: magnetic resonance image; MusiQol: Multiple Sclerosis International Quality of Life; N.A.; non applicable; RRMS: relapsed-remitting multiple sclerosis; SDMT: Symbol Digit Modality Test; SPMS: secondary progressive multiple sclerosis; T25FW: Timed 25-Foot Walk test.

[1] The selection of specific tests to assess mobility will depend on the degree of disability of the patients at the time of the assessment.

screening with SDMT and annual re-assessment are proposed to screen cognitive problems. Likewise, the MFIS test is suggested to evaluate fatigue. Severe fatigue frequently occurs in MS patients, and an early diagnosis is mandatory since that can be as disabling as objective neurological deficits (Tur, 2016). Since MFIS is more oriented to tackle specific fatigue domains than other instruments, it may help monitor therapeutic interventions (Fisk et al., 1994). Finally, five symptoms can also be assessed through related items included in the specific MS-HRQoL questionnaire, MusiQoL (Simeoni et al., 2008). In additionally to the parts that evaluate the relationship with friends, relationship with family, coping, rejection and relationship with the health care system, MusiQoL allow to assess of the following domains: daily activities (where fatigue is considered), symptoms (including cognitive status and vision problems), psychological well-being, and sentimental and sexual life (Fernández et al., 2011). Affect in separate items or domains can serve as a warning system to address specific symptoms more specifically.

Variables related to pharmacological treatment will provide information on adherence and persistence to medication and the presence of adverse events. In MS, non-adherence/non-persistence is associated with suboptimal response to treatment, including disease relapses and the need for more expensive healthcare (Lizán et al., 2014; Mardan et al., 2021). Consequently, proper monitoring can contribute to better clinical outcomes. In the same way, the standard set also includes variables related to non-pharmacological treatment. Indeed, rehabilitation, which integrates psychotherapy and symptomatic therapy, is regarded as the best non-pharmacological treatment for MS (Kubsik-Gidlewska et al., 2017). In addition, many studies indicate that exercise is safe and effective in improving symptoms (Motl, 2020). Also, exercise training may be necessary to slow the progression of the disease. Therefore, specialists treating the disease are encouraged to prescribe, promote and monitor exercise at the diagnosis and all stages of the disease trajectory (Learmonth and Motl, 2021).

Regarding the impact of the disease on the patients' lives, although other valid instruments were contemplated during the project phases (see Supplementary Material), MusiQoL is the instrument of choice for assessing HRQoL. It is recommended that this variable be baseline assessed three months after diagnosis to allow for a margin of acceptance after the initial shock in which patients may experience various emotions such as fear, loss of control and hopelessness (Carey et al., 2022). Although clinical assessment of patients with MS tends to focus on physical disability, the importance of monitoring HRQoL is increasingly recognised (Solari, 2005). Thus, HRQoL instruments can provide additional information on disease impact that would not be evaluated using observer-based measures focusing on physical disability (Nortvedt and Riise, 2003). In addition to HRQoL, gestational desire and possible changes in work activity are also considered. Although the collection of HRQoL and other PROs is scarce in clinical practice, including these variables in the standard set was considered key to establishing the impact of disease from the patient's perspective (Nowinski et al., 2017). Therefore, implementing PROs in clinical practice will allow clinicians to focus on the aspects of the disease that most matter to the patient, encouraging better patient engagement in disease management.

As with the essential variables for disease follow-up, the experts agreed on those case-mix necessary to characterize the patient. Including standardized case-mix variables is beneficial for benchmarking and comparing results based on patient profiles (International Consortium for Health Outcomes Measurement (ICHOM), 2021). In addition, their use allows the classification of individuals into subpopulations that differ in prognosis and response to a specific treatment, which can help clinicians to individualize the follow-up and therapeutic approaches. Furthermore, both clinical and demographic characteristics can influence ensuing cognitive difficulties (Jacobsen et al., 2021).

This project has some inherent limitations to its design. First, the systematic literature review only covered the last three years. However, it aimed to identify the variables used at that time and the results obtained were considered sufficient to serve as a starting point for the subsequent phases of the project. Secondly, this standard set reflects the opinion of a group of 38 experts on RRMS management and seven patient representatives. Although no significant differences are expected, a different group of experts and patients could have agreed on various other recommendations. Thirdly, some health outcomes proposed during the project were finally excluded from achieving a minimum standard set. In this regard, it is necessary to bear in mind that additional information can be registered in the clinical report according to the patient's characteristics or follow-up needs. Finally, some relevant variables, such as biomarkers or novel endpoints, may not have been considered when elaborating on the standard set. To minimize this limitation, and due to the continuing advances in disease knowledge and treatment, we recommend periodically updating the list of biomarkers for evaluation during patient follow-up. We also suggest that the present standard set be regularly updated.

This standard set for RRMS marks a starting point to move toward patient-centred care. However, several barriers must be overcome on the road to its successful implementation. Health professional-related barriers include lack of consultation time, lack of support staff, the need for specific MS units in most hospitals, lack of habit of using questionnaires for PRO collection and lack of space for PROMs administration. Newer platforms for data collection, based on information and communication technologies, may reduce the burden on patient and clinician and data processing time, thus facilitating the use of PROs in clinical practice. Other limitations analyzed by the SC were those related to the Spanish healthcare system. The experts noted the heterogeneity among the healthcare regions regarding the lack of equity in access to specialized services and treatments. That could lead to difficulties in implementing a standardized system for collecting variables in hospitals with fewer healthcare resources. At the same time, however, these systems can detect differences and possible areas for improvement in hospitals or health systems.

This project, whose results are presented here, has provided an opportunity to pool different stakeholders' perspectives (including patients) involved in disease management. Therefore, the herein standard set may pave the way to promoting patient-centred quality care and standardizing the collection of variables in RRMS. In turn, the information provided through the systematic compilation of these health outcomes may allow clinicians and health policymakers to define strategies to achieve high-quality, value-based care.

Funding

This project was supported by Bristol Myers Squibb.

CRediT authorship contribution statement

Miguel Llaneza González: Writing – review & editing, Validation, Supervision, Investigation. **Pedro Carrascal Rueda:** Writing – review & editing, Validation, Supervision, Investigation. **Olga Delgado Sánchez:** Writing – review & editing, Validation, Supervision, Investigation. **Mónica Borges Guerra:** Writing – review & editing, Validation, Supervision, Investigation. **Alfredo Rodríguez Antigüedad:** Writing – review & editing, Validation, Supervision, Investigation. **Alberto Morell Baladrón:** Writing – review & editing, Validation, Supervision, Investigation. **Noelia Becerril Ríos:** Writing – review & editing, Validation, Supervision, Investigation. **Àlex Rovira:** Writing – review & editing, Validation, Supervision, Investigation. **Virgina Meca Lallana:** . **Laura Benedito-Palos:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Marta Comellas:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **David Vilanova:** Funding acquisition, Conceptualization. **Ainara Echeto:** Funding acquisition, Conceptualization. **Xavier Pérez:** Funding acquisition, Conceptualization. **Celia Oreja-Guevara:** Writing – review & editing,

Validation, Supervision, Investigation.

Declaration of competing interest

MLG has received fees from the following pharmaceutical companies for his participation in advisory groups, talks, workshops, seminars, conferences, studies or clinical trials: Bayer, Biogen, Teva, Novartis, Sanofi-Genzyme, Almirall, Roche, Bristol Myers Squibb, Merk and Janssen. PCR has served as a speaker for several pharmaceutical companies. ODS reports fees as a study investigator with Pfizer and Bristol Myers Squibb. MB declares relationships with Bristol Myers Squibb, Roche and Biogen. ARA has participated in scientific consultancies and has been a speaker at scientific meetings organized by Merk, Biogen, Novartis, Sanofi, Teva and Bristol Myers Squibb. AMB has no conflicts of interest to disclose. NBR declares relationships with Roche, Merck, Biogen, Sanofi, Janssen and Bristol Myers Squibb. AR serves on scientific advisory boards for Bristol Myers Squibb, Novartis, Sanofi-Genzyme, Synthetic MR, Tensor Medical, Roche, Biogen, and OLEA Medical and has received speaker honoraria from Bayer, Sanofi-Genzyme, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche, Bristol Myers Squibb, and Biogen. AR is also a member of the editorial boards of Neurology and Neuroradiology and the executive committee of MAGNIMS. VML has not declared conflicts of interest. LBP and MC are employees of Outcomes 10, an independent research entity that has received fees from Bristol Myers Squibb for conducting this research. DV and AE are employees and may be shareholders of Bristol Myers Squibb. CO-G has received speaker and consultation fees from Alexion, Biogen Idec, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva.

Acknowledgments

The authors would like to thank all participants in the nominal groups and the following Spanish Scientific Societies for endorsing the project: Sociedad Española de Neurología (SEN), Sociedad Española de Farmacia Hospitalaria (SEFH), Sociedad Española de Enfermería Neurológica (SEDENE), Sociedad Española de Nurorradiología (SENR), and to Spanish patient advocacy group Esclerosis Múltiple España (EME).

Role of funding source

This project was supported by Bristol Myers Squibb (BMS). BMS has been responsible for the conception and design of the study but did not participate in the voting, or the discussions and agreements reached by the clinicians.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105501.

References

Ackerman, I.N., Cavka, B., Lippa, J., et al., 2017. The feasibility of implementing the ICHOM standard set for hip and knee osteoarthritis: a mixed-methods evaluation in public and private hospital settings. J. Patient. Rep. Outcomes. 2, 32. https://doi.org/10.1186/s41687-018-0062-5, 2018/08/28.

Benedict, R.H., DeLuca, J., Phillips, G., et al., 2017. Validity of the symbol digit modalities test as a cognition performance outcome measure for multiple sclerosis. Mult. Scler. 23, 721–733. https://doi.org/10.1177/1352458517690821, 2017/02/17.

Bharadia, T., Vandercappellen, J., Chitnis, T., et al., 2022. Patient-reported outcome measures in MS: do development processes and patient involvement support valid quantification of clinically important variables? Mult. Scler. J. Exp. Transl. Clin. 8, 20552173221105642 https://doi.org/10.1177/20552173221105642, 2022/06/28.

Browne, P., Chandraratna, D., Angood, C., et al., 2014. Atlas of Multiple Sclerosis 2013: a growing global problem with widespread inequity. Neurology 83, 1022–1024. https://doi.org/10.1212/wnl.0000000000000768. Neurology2014/09/10.

Carey, G., Wilson, N., Janssen, J., et al., 2022. I'm walking into the unknown": qualitative insights into how emotions and lived experience related to multiple sclerosis diagnosis impact on decisions to pursue disease modifying treatment. Mult. Scler. Relat. Disord. 58, 103464 https://doi.org/10.1016/j.msard.2021.103464, 2021/12/25.

Comi, G., Radaelli, M., Soelberg Sørensen, P., 2017. Evolving concepts in the treatment of relapsing multiple sclerosis. Lancet 389, 1347–1356. https://doi.org/10.1016/s0140-6736(16)32388-1, 2016/11/28.

EuroQol Group. EQ-5D-5L, https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/(accessed 07/12/ 2022).

Fernández, O., Fernández, V., Baumstarck-Barrau, K., et al., 2011. Validation of the Spanish version of the Multiple Sclerosis International Quality of Life (Musiqol) questionnaire. BMC. Neurol. 11, 127. https://doi.org/10.1186/1471-2377-11-127, 2011/10/22.

Fisk, J.D., Pontefract, A., Ritvo, P.G., et al., 1994. The impact of fatigue on patients with multiple sclerosis. Can. J. Neurol. Sci. 21, 9–14, 1994/02/01.

Gallagher, M., Hares, T., Spencer, J., et al., 1993. The nominal group technique: a research tool for general practice? Fam. Pract. 10, 76–81. https://doi.org/10.1093/fampra/10.1.76, 1993/03/01.

Gil-González, I., Martín-Rodríguez, A., Conrad, R., et al., 2020. Quality of life in adults with multiple sclerosis: a systematic review. BMJ Open 10, e041249. https://doi.org/10.1136/bmjopen-2020-041249, 2020/12/02.

Higgins, J., Green, S, 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochra.

International Consortium for Health Outcomes Measurement (ICHOM), https://www.ichom.org/standard-sets/(accessed 26/10/ 2021).

Jacobsen, C., Zivadinov, R., Myhr, K.M., et al., 2021. Brain atrophy and clinical characteristics predicting SDMT performance in multiple sclerosis: a 10-year follow-up study. Mult. Scler. J. Exp. Transl. Clin. 7, 2055217321992394 https://doi.org/10.1177/2055217321992394, 2021/02/25.

Kalb, R., Beier, M., Benedict, R.H., et al., 2018. Recommendations for cognitive screening and management in multiple sclerosis care. Mult. Scler. 24, 1665–1680. https://doi.org/10.1177/1352458518803785, 2018/10/12.

Kos, D., Kerckhofs, E., Carrea, I., et al., 2005. Evaluation of the Modified Fatigue Impact Scale in four different European countries. Mult. Scler. 11, 76–80. https://doi.org/10.1191/1352458505ms1117oa, 2005/03/01.

Kubsik-Gidlewska, A.M., Klimkiewicz, P., Klimkiewicz, R., et al., 2017. Rehabilitation in multiple sclerosis. Adv. Clin. Exp. Med. 26, 709–715. https://doi.org/10.17219/acem/62329, 2017/07/12.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452. https://doi.org/10.1212/wnl.33.11.1444. Neurology1983/11/01.

Learmonth, Y.C., Motl, R.W., 2021. Exercise training for multiple sclerosis: a narrative review of history, benefits, safety, guidelines, and promotion. Int. J. Environ. Res. Public Health 18. https://doi.org/10.3390/ijerph182413245, 2021/12/25.

Lizán, L., Comellas, M., Paz, S., et al., 2014. Treatment adherence and other patient-reported outcomes as cost determinants in multiple sclerosis: a review of the literature. Patient. Prefer. Adher. 8, 1653–1664. https://doi.org/10.2147/ppa.S67253, 2014/12/20.

Lublin, F.D., Reingold, S.C., Cohen, J.A., et al., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 83, 278–286. https://doi.org/10.1212/wnl.0000000000000560, 2014/05/30.

Mardan, J., Hussain, M.A., Allan, M., et al., 2021. Objective medication adherence and persistence in people with multiple sclerosis: a systematic review, meta-analysis, and meta-regression. J. Manage Care Spec. Pharm. 27, 1273–1295. https://doi.org/10.18553/jmcp.2021.27.9.1273, 2021/09/01.

Meyer-Moock, S., Feng, Y.S., Maeurer, M., et al., 2014. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC. Neurol. 14, 58. https://doi.org/10.1186/1471-2377-14-58, 2014/03/29.

Moore, C., 1987. Applied Social Research Methods Series. Group Techniques For Idea Building. Sage Publ. Thousand Oaks, CA.

Motl, R.W., 2020. Exercise and multiple sclerosis. Adv. Exp. Med. Biol. 1228, 333–343. https://doi.org/10.1007/978-981-15-1792-1_22, 2020/04/29.

Nortvedt, M.W., Riise, T., 2003. The use of quality of life measures in multiple sclerosis research. Mult. Scler. 9, 63–72. https://doi.org/10.1191/1352458503ms871oa, 2003/03/06.

Nowinski, C.J., Miller, D.M., Cella, D., 2017. Evolution of patient-reported outcomes and their role in multiple sclerosis clinical trials. Neurotherapeutics 14, 934–944. https://doi.org/10.1007/s13311-017-0571-6, 2017/09/16.

Pasquier, F., Leys, D., Weerts, J.G., et al., 1996. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur. Neurol. 36, 268–272. https://doi.org/10.1159/000117270, 1996/01/01.

Río, J., Montalbán, X., 2014. Descripción actual de la esclerosis múltiple. Medicina Clínica 143, 3–6. https://doi.org/10.1016/s0025-7753(15)30002-6.

Rudick, R.A., Miller, D.M., 2008. Health-related quality of life in multiple sclerosis: current evidence, measurement and effects of disease severity and treatment. CNS Drugs 22, 827–839. https://doi.org/10.2165/00023210-200822100-00004, 2008/09/16.

Simeoni, M., Auquier, P., Fernandez, O., et al., 2008. Validation of the multiple sclerosis international quality of life questionnaire. Mult. Scler. 14, 219–230. https://doi.org/10.1177/1352458507080733, 2007/10/19.

Solari, A., 2005. Role of health-related quality of life measures in the routine care of people with multiple sclerosis. Health Qual. Life Outcomes 3, 16. https://doi.org/10.1186/1477-7525-3-16, 2005/03/22.

Tur, C., 2016. Fatigue management in multiple sclerosis. Curr. Treat. Options. Neurol. 18, 26. https://doi.org/10.1007/s11940-016-0411-8, 2016/04/19.

Wagner, C.A., Goverman, J.M., 2015. Novel insights and therapeutics in multiple sclerosis. F1000Res. 4, 517. https://doi.org/10.12688/f1000research.6378.1, 2015/09/05.

Walton, C., King, R., Rechtman, L., et al., 2020. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult. Scler. 26, 1816–1821. https://doi.org/10.1177/1352458520970841, 2020/11/12.

Wattjes, M.P., Ciccarelli, O., Reich, D.S., et al., 2021. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. 20, 653–670. https://doi.org/10.1016/s1474-4422(21)00095-8, 2021/06/18.