

Disability Outcome Measures in Phase III Clinical Trials in Multiple Sclerosis

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Published online: 20 June 2018
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Abstract Accumulating neurological disability has a substantial impact on the lives of patients with multiple sclerosis (MS). As well as the established Expanded Disability Status Scale (EDSS), several other outcome measures are now available for assessing disability progression in MS. This review extends the findings of a previous analysis of relapsing-remitting MS (RRMS) trials published up to 2012, to determine whether there has been a shift in outcome measures used to assess disability in phase III clinical trials in RRMS and progressive MS. Forty relevant trials were identified (RRMS, $n = 16$; progressive MS, $n = 18$; other/mixed phenotypes, $n = 6$). Sustained EDSS worsening, particularly over 3 months, was included as an endpoint in almost all identified trials. Other disability-related endpoints included the Multiple Sclerosis Functional Composite z -score and scores for the physical component summary of the Multiple Sclerosis Impact Scale and Medical Outcomes Study Short-Form (36-item) Health Survey. Tests assessing manual dexterity, ambulation, vision and cognition were also employed, and in some trials, composite endpoints were used. However, there was no obvious trend in choice of disability outcome measures over time. Sustained EDSS worsening over short time periods continues to be the most widely used measure of

disability progression in pivotal MS trials, despite its well-recognised limitations. A new tool set is needed for use in MS clinical trials that detects the benefit of potential treatments that slow (or reverse) progressive disability.

Key Points

Despite its limitations, a short-term sustained increase in the EDSS score continues to be the most widely used disability outcome measure in clinical trials in MS. Other outcome measures have been used, but mainly as secondary endpoints.

There is a need for outcome measures that more accurately reflect irreversible disability progression in MS. This includes not only mobility but also other key symptom domains such as manual dexterity, cognition and visual function.

Ideally, measures used to assess disability progression in MS should reflect outcomes that are important to the patient. They should also be designed to allow their incorporation into busy, everyday clinical practice as well as clinical trials.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40263-018-0530-8>) contains supplementary material, which is available to authorized users.

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1 Introduction

Multiple sclerosis (MS) is an autoimmune disease characterised by clinical neurological relapses and progressive neurological disability [1]. Relapses are thought to reflect acute focal inflammation, while progressive disability

likely represents chronic, diffuse neurodegeneration [2]. According to the classical view of the natural history of MS, focal inflammation is the precursor of neurodegeneration, with successive relapses leading to accumulation of disability [2]. However, the contemporary view of MS is that there is a dissociation between relapses and long-term disability [3].

Not surprisingly, accumulating neurological disability has a substantial impact on the lives of the relatively young population of patients affected by MS. Studies have shown that increasing levels of disability have a negative effect on the quality of life (QoL) of both patients and caregivers [4–6]. Furthermore, overall costs associated with MS increase as disability accumulates [7], with direct medical costs contributing more in the earlier stages of disease and indirect costs (e.g. productivity loss) predominating in the later stages [8]. The main goal of managing MS is therefore to reduce, or preferably prevent, long-term disability progression [9]. Hence, clinicians involved in the management of MS, whether from a clinical or research perspective, need access to specific, reliable, valid and sensitive tools that measure patient disability. This is challenging in view of the highly variable clinical expression and course of the disease [10].

The Expanded Disability Status Scale (EDSS) [11] was introduced in the early 1980s and is the most widely used tool for assessing MS disability in clinical trials [10]. In clinical practice, it is mainly used in specialist MS centres, while non-specialists may use the EDSS as a basis for their assessments. Measured on a scale of 0 (normal neurological function) to 10 (death due to MS), the lower range (up to 4.0) measures impairment in eight functional systems, the mid range (4.0–7.0) focuses on ambulatory function, and the top range (7.0–9.5) largely assesses the ability to carry out activities of daily living [10]. Its main advantage is undoubtedly its widespread use, which fosters familiarity and acceptance among neurologists and permits a degree of comparison between different studies [10, 12]. However, its limitations are well recognised and include high levels of variability, non-linearity (which complicates statistical analysis), limited sensitivity and insufficient assessment of domains such as upper limb function and cognition [10, 12, 13]. A training platform called Neurostatus, which incorporates a standardised neurological examination form, has been developed to reduce variability and improve both inter- and intra-rater reliability of EDSS assessments [14].

Other measures of disability include the timed 25-foot walk (T25FW), which assesses ambulatory function [15], and the 9-hole peg test (9HPT), which measures upper body function and manual dexterity [16]. Both tests, along with the Paced Auditory Serial Addition Task (PASAT), which measures an aspect of cognitive function, are components of the Multiple Sclerosis Functional Composite (MSFC), which was introduced in the late 1990s to address

some of the limitations of the EDSS [17]. To calculate the overall score, results from the three tests are transformed into *z*-scores by standardising to a reference population, then averaged to create the composite MSFC *z*-score [12]. The validity and reliability of the MSFC have been demonstrated [18] and results have been shown to correlate with EDSS scores, changes in magnetic resonance imaging measures, and patients' QoL [18, 19]. Nevertheless, it does have some limitations, including practice effects with the PASAT (improved performance with repeated testing), issues with *z*-scores (lack of intuitiveness; variations in reference populations) and lack of a consensus on the definition of clinically important change [12, 18]. Furthermore, despite acceptance of its component tests, limited clinical interpretability [12] and a lack of familiarity remain major concerns preventing the broader use of the overall MSFC score.

In 2014, Lavery et al. conducted a review of the outcome measures used to assess disability progression in relapsing-remitting MS (RRMS) trials published up to 2012 [20]. Within the 19 trials included in their analysis, the most commonly used measure was sustained worsening of EDSS over a 3-month period. This endpoint was first reported when data from a trial of glatiramer acetate were published in 1995 [21]. A more rigorous measure of disability progression, based on worsening of EDSS over 6 months, was first reported 13 years later in 2008, when data from the REGARD trial (subcutaneous interferon β -1a vs. glatiramer acetate) were published. The first use of MSFC was reported 2 years earlier, when the results of the CHAMPIONS [22], AFFIRM [23] and SENTINEL [24] studies were published.

The aim of this current review was to extend the findings of Lavery et al. [20] to determine whether there has been a shift in the outcome measures used to assess disability in published and ongoing phase III clinical trials, not only in RRMS but also in progressive forms of MS.

2 Methods

Published phase III trials in RRMS and progressive MS were identified via a PubMed search (conducted on 31 May 2017) using appropriate terminology (Online Resource 1a). The results were hand-searched to exclude any non-relevant publications. The bibliographies of relevant review articles were also hand-searched for publications not captured using PubMed. RRMS trials published before 2012 were excluded as this time period was covered in the review by Lavery et al. [20]. Searches for progressive MS trials were limited to the last 20 years.

Ongoing or unpublished phase III trials were identified via ClinicalTrials.gov (search conducted 13 June 2017)

using appropriate search terminology (Online Resource 1b). The results were hand-searched to exclude non-relevant trials (e.g. those that evaluated pain, fatigue or immunogenicity). Extension and non-comparative trials, as well as those denoted as ‘withdrawn’ or of ‘unknown status’, were excluded. Trials denoted as ‘completed’ and with linked publications were cross-checked against the list of published trials found using PubMed, and added if necessary.

Searches were not limited to products licensed to treat MS; drugs for which development is ongoing or was subsequently terminated were also included.

3 Results

All data generated or analysed during this study are included in this published article and its supplementary information files.

3.1 Phase III Relapsing or Relapsing-Remitting Multiple Sclerosis Trials

Overall, 16 phase III trials were identified in relapsing MS or RRMS (12 published from 2012 onwards and four unpublished) (Table 1). Three additional articles published before 2012, but not included in the review by Lavery et al., were also identified [37–39]. Two of these trials evaluated disability progression according to sustained (3-month) worsening of EDSS (the other did not include a disability-related outcome), therefore the conclusions from the review by Lavery et al. are not changed by inclusion of the outcomes reported in these additional publications.

The 16 trials identified were initiated between 2005 and 2014. As expected, the primary endpoint in most trials was the annualised relapse rate (ARR). In two trials (CARE MS-I [27] and CARE MS-2 [28]), the primary endpoint was a composite of relapse rate and sustained disability progression; in one unpublished trial, the primary endpoint was sustained worsening of EDSS over 3 months.

Secondary endpoints used to assess disability were sustained worsening of EDSS over 3, 6 and/or 9 months, changes in the EDSS score, changes in the MSFC *z*-score, freedom from disease activity or no evidence of disease activity, the Multiple Sclerosis Impact Scale (MSIS-29) physical component score, the Medical Outcomes Study Short-Form (36-item) Health Survey (SF-36) physical component summary score, a visual function test and a test to assess cognition (Fig. 1).

The latter two were tertiary endpoints in a single trial [35]. Two trials had no specified disability outcome measures [32, 34] and one trial evaluated sustained *improvement* in EDSS (over 3 months) as a tertiary endpoint [35].

There was no obvious trend in the choice of disability outcome measures over time, based on the year in which trials were initiated (Fig. 2).

3.2 Phase III Progressive Multiple Sclerosis Trials

Overall, 15 articles (published in the last 20 years) reporting phase III trials in progressive MS were identified; three ongoing trials were also identified (Table 2). All of these trials used a disability outcome measure as the primary endpoint and the range of disability endpoints was more diverse than those included in RRMS trials (Fig. 3).

The most commonly used primary endpoint was sustained EDSS worsening over 3 or 6 months. These were first used in trials published in 1998 [40] and 2004 [45], respectively, and, most recently, in trials published in 2017 [55] and 2011 [53], respectively (as well as in one ongoing trial [NCT01665144]). In two other trials, one published in 2004 [47] and the other published in 2007 [51], 3-month EDSS worsening was included as a co-primary endpoint. More recent trials (one published in 2016 [54] and two ongoing [NCT02220933 and NCT02936037]) had a primary endpoint that defined progressors as those patients meeting at least one of two or three disability endpoints (deterioration in EDSS, T25FW or 9HPT results).

Among the range of secondary endpoints used, sustained EDSS worsening over 3 or 6 months was the most commonly used (Fig. 3). Two novel EDSS endpoints (area under the EDSS–time curve [46] and slope of the EDSS progression curve [42]) were used, albeit in only one trial each. Additional disability outcomes assessed ambulation [45, 54, 55, 57–59], upper body function [45, 46, 50, 54, 59], cognition [48, 50, 57] and visual function [46, 50]. In one of the ongoing trials, ambulation is being measured remotely [57].

Based on the year in which trials were published, there was no obvious trend in the choice of disability outcome measures over time (Fig. 4).

3.3 Other Phase III Trials

Six additional trials were identified (two published [60, 61] and four ongoing); five of these trials included patients with relapsing or progressive MS, and one included patients at high risk of progression during the initial MS phase (MITOX-REBIF) (Table 3). In the published trials, the primary and secondary endpoints focused on sustained EDSS worsening over 3 months. In the ongoing RRMS/secondary progressive MS trials, the primary endpoint is ARR, and secondary disability endpoints are sustained (3- and 6-month) EDSS worsening and sustained (6-month) EDSS improvement. In the MITOX-REBIF trial, the primary endpoint is a composite measure that accounts for

Table 1 Published and unpublished phase III trials in patients with relapsing MS or RRMS

Trial name/group [registry number]	Trial start date [publication date]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
Combi-Rx [25] [NCT00211887]	Jan 2005 [Mar 2013]	Interferon β -1a IM + glatiramer acetate vs. interferon β -1a IM vs. glatiramer acetate	RRMS [≤ 5.5]	ARR	Sustained (6-month) disability progression on EDSS ^a MSFC score
FREEDOMS II [26] [NCT00355134]	Jun 2006 [Jun 2014]	Fingolimod vs. placebo	RRMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^a Sustained (6-month) disability progression on EDSS ^a Change in MSFC z-score
CARE MS-I [27] [NCT00530348]	Sep 2007 [Nov 2012]	Alemtuzumab vs. interferon β -1a SC	RRMS [≤ 3.0]	Co-primary: relapse rate and sustained (6-month) disability progression ^b	Change in EDSS score Change in MSFC z-score Freedom from disease activity (absence of relapses and sustained accumulation of disability)
CARE MS-II [28] [NCT00548405]	Oct 2007 [Nov 2012]	Alemtuzumab vs. interferon β -1a SC	RRMS [≤ 5.0]	Co-primary: relapse rate and sustained (6-month) disability progression ^b	Change in EDSS score Change in MSFC z-score Freedom from disease activity (absence of relapses and sustained accumulation of disability)
ALLEGRO [29] [NCT00509145]	Nov 2007 [Mar 2012]	Laquinimod vs. placebo	RRMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^a Sustained (6-month) disability progression on EDSS ^a EDSS score and change in EDSS score MSFC z-score
BRAVO [30] [NCT00605215]	Apr 2008 [Apr 2014]	Laquinimod vs. placebo vs. interferon β -1a IM	RRMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^a MSFC z-score <i>Exploratory:</i> Sustained (6-month) disability progression on EDSS
TOWER [31] [NCT00751881]	Sep 2008 [Mar 2014]	Teriflunomide vs. placebo	Relapsing MS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^a Change in EDSS score
TENERE [32] [NCT00883337]	Apr 2009 [May 2014]	Teriflunomide vs. interferon β -1a SC	Relapsing MS [≤ 5.5]	Time to failure (first occurrence of confirmed relapse or permanent treatment discontinuation for any cause)	None
ADVANCE [33] [NCT00906399]	Jun 2009 [Jul 2014]	Peginterferon vs. placebo	RRMS [≤ 5.0]	ARR	Sustained (3-month) disability progression on EDSS ^b
GALA [34] [NCT01067521]	May 2010 [Jun 2013]	Glatiramer acetate vs. placebo	RRMS [≤ 5.5]	Number of relapses	None (disability progression [EDSS score increase ≥ 1] and change in EDSS score were measured, but not specified as endpoints)

Table 1 continued

Trial name/group [registry number]	Trial start date [publication date]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
DECIDE [35] [NCT01064401]	May 2010 [Oct 2015]	Daclizumab vs. interferon β -1a IM	RRMS [≤ 5.0]	ARR	Sustained (3-month) disability progression on EDSS ^b Progression of physical disability on MSIS-29 Physical Subscale ^c <i>Tertiary</i> : Sustained (6-month) disability progression on EDSS ^b Change in EDSS score Sustained (3-month) improvement in EDSS ^d Change in MSFC z-score Change in visual function test results Change in cognitive function (SDMT) Change in MSIS-29 Physical Subscale score NEDA (no clinical [relapses and confirmed disability progression] or MRI disease activity)
GATE [36] [NCT01489254]	Dec 2011 [Dec 2015]	Generic vs. branded glatiramer acetate vs. placebo	RRMS [≤ 5.5]	Total number of gadolinium-enhancing lesions	Change in EDSS score Sustained (3-month) disability progression on EDSS ^b Freedom from disease activity (no relapses, sustained change in EDSS score or new or enlarged T2 lesions or gadolinium-enhancing lesions)
OPERA-1 [NCT01247324]	Aug 2011 [NA—ongoing]	Ocrelizumab vs. interferon β -1a SC	Relapsing MS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^e Sustained (6-month) disability progression on EDSS ^e Change in MSFC Change in SF-36 Physical Component Summary score NEDA (neurological symptoms and MRI)
OPERA-2 [NCT01412333]	Sep 2011 [NA—ongoing]	Ocrelizumab vs. interferon β -1a SC	Relapsing MS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^e Sustained (6-month) disability progression on EDSS ^e Change in MSFC Change in SF-36 Physical Component Summary score NEDA (neurological symptoms and MRI)
CONCERTO [NCT01707992]	Feb 2013 [trial completed but not yet published]	Laquinimod vs. placebo	RRMS [not specified]	Sustained (3-month) disability progression on EDSS ^e	Sustained (6-month) disability progression on EDSS ^e Sustained (9-month) disability progression on EDSS ^e

Table 1 continued

Trial name/group [registry number]	Trial start date [publication date]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
RPC1063 [NCT02294058]	Dec 2014 [trial completed but not yet published]	RPC1063 (ozanimod) vs. interferon β -1a IM	Relapsing MS [≤ 5.0]	ARR	Not specified

Endpoints measuring the following parameters are not included as they do not necessarily capture disability: quality of life, fatigue, depression, psychological impairment, social impairment, hospitalisations, interventions for disease-related events and clinical global improvement

Published trials include those published from 2012 onwards, with the exception of the DEFINE and CONFIRM trials, which are included in the review by Lavery et al. [20]; unpublished trials were sourced from ClinicalTrials.gov

ARR annualised relapse rate, EDSS Expanded Disability Status Scale, IM intramuscular, MRI magnetic resonance imaging, MS multiple sclerosis, MSFC Multiple Sclerosis Functional Composite, MSIS Multiple Sclerosis Impact Scale, NA not applicable, NEDA no evidence of disease activity, RRMS relapsing-remitting multiple sclerosis, SC subcutaneous, SDMT Symbol Digit Modalities Test, SF-36 Medical Outcomes Study Short-Form (36-item) Health Survey

^aEDSS score increase ≥ 1.0 if baseline score 0–5, or ≥ 0.5 if baseline score ≥ 5.5

^bEDSS score increase ≥ 1.0 or ≥ 1.5 if baseline score = 0

^cIncrease ≥ 7.5

^dEDSS score decrease ≥ 1 if baseline score ≥ 2.0

^eNo further details given

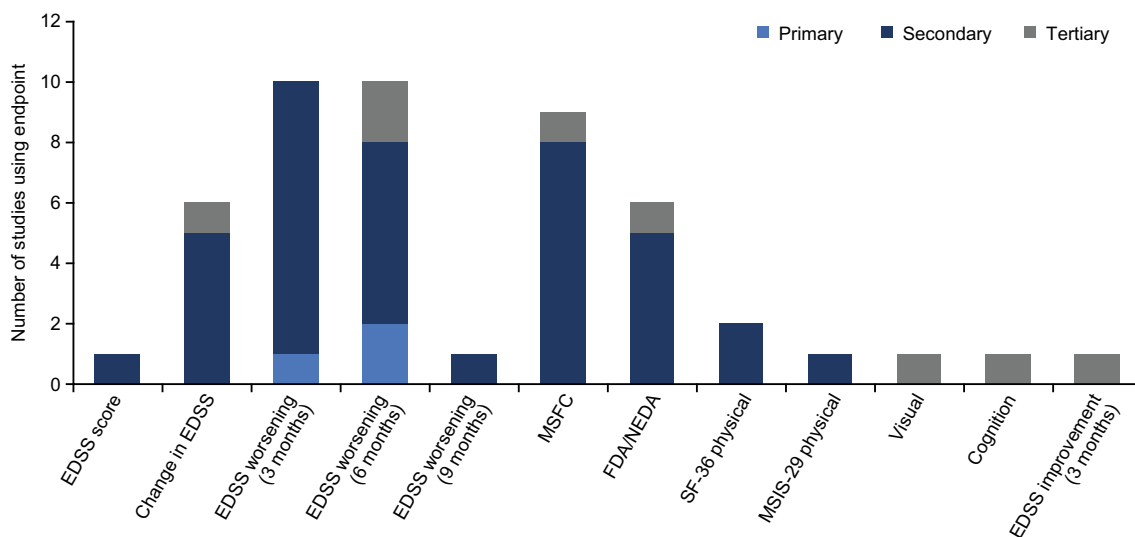


Fig. 1 Disability outcomes measures used in phase III relapsing multiple sclerosis or RRMS trials ($n = 16$). Includes unpublished trials and trials published from 2012 onwards (with the exception of the DEFINE and CONFIRM trials, which are included in the review by Lavery et al. [20]). EDSS Expanded Disability Status Scale, FDA

freedom from disease activity, MSFC Multiple Sclerosis Functional Composite, MSIS Multiple Sclerosis Impact Scale, NEDA no evidence of disease activity, SF-36 Medical Outcomes Study Short-Form (36-item) Health Survey, RRMS relapsing-remitting multiple sclerosis

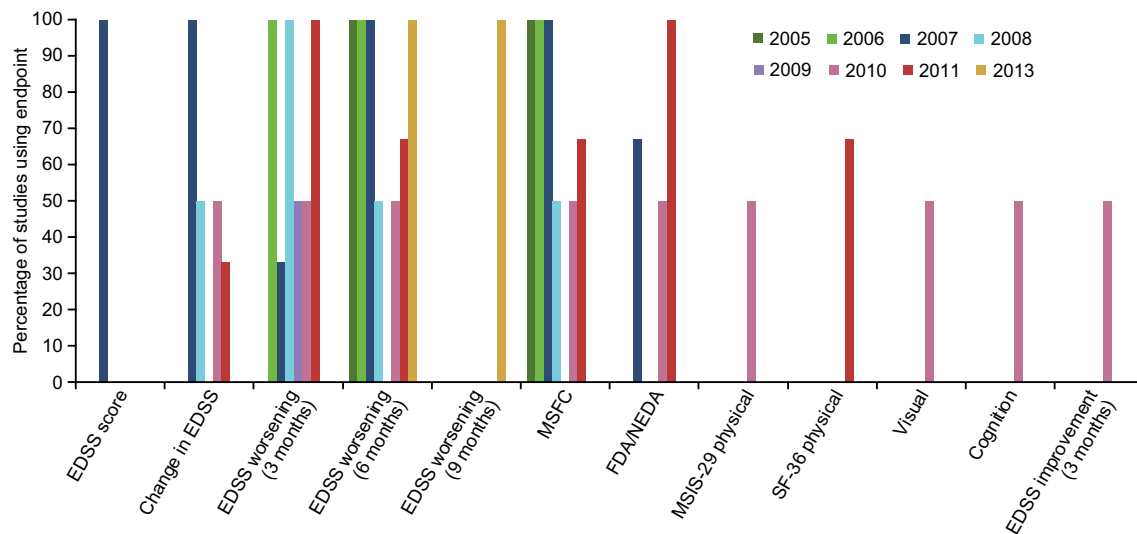


Fig. 2 Disability outcome measures used over time in phase III relapsing multiple sclerosis or RRMS trials ($n = 16$). Includes unpublished trials and trials published from 2012 onwards (with the exception of the DEFINE and CONFIRM trials, which are included in the review by Lavery et al. [20]); ongoing trials were sourced from ClinicalTrials.gov; dates refer to study initiation. EDSS Expanded

relapses and EDSS progression, and the secondary endpoints are the EDSS score and rate of progression to clinically definite MS (in those with a single clinical event before initiation of treatment).

4 Discussion

The current evaluation highlights the wide range of endpoints that have been used to evaluate disability in phase III clinical trials in MS, particularly in progressive forms of the disease. As one might expect, disability measures were assessed as both primary and secondary endpoints in progressive MS trials, whereas the primary endpoint in most RRMS trials was based on the relapse rate. While entirely rational, this in itself presents a challenge in assessing treatment differences in disability progression in RRMS as trials are powered to detect differences in primary, but not secondary, endpoints. Trials including relapsing and progressive MS phenotypes have either relapses or disability progression as the primary endpoint, although one ongoing study has a composite endpoint (absence of relapses and an increase in EDSS ≤ 1) [NCT02937285].

Based on the current analysis, it is difficult to discern any evolution over time in the primary or secondary disability outcome measures used in these trials. As found in the previous review by Lavery et al. [20], sustained EDSS worsening, particularly over 3 months, is widely used and was included as an endpoint in almost all of the trials identified, including those that are ongoing. This is

Disability Status Scale, FDA freedom from disease activity, MSFC Multiple Sclerosis Functional Composite, MSIS Multiple Sclerosis Impact Scale, NEDA no evidence of disease activity, SF-36 Medical Outcomes Study Short-Form (36-item) Health Survey, RRMS relapsing-remitting multiple sclerosis. There was one trial published in 2014, which did not include any disability outcome measures

interesting as it has been shown that short-term changes in EDSS do not correctly identify patients with truly irreversible disability progression. For example, in a trial of 929 patients with RRMS or clinically isolated syndrome, sustained progression was maintained (over a mean follow-up of 45 months) in fewer than 50% of those meeting the initial criteria for EDSS progression (mainly over 6 months) [62]. In another trial, which included data from over 16,000 patients, approximately 70% of patients with EDSS worsening over 3 or 6 months had sustained disability over 5 years; this increased to 80 and 89% when the criteria were changed to EDSS worsening over 12 and 24 months, respectively [63]. In this context, it is interesting that in the CONCERTO trial [64], one of the endpoints was the EDSS progression over 9 months, the longest time period reported in any of the trials included in the current evaluation. Although the issue of using short-term EDSS changes is particularly pertinent to relapsing MS (in view of the potential confounding effects of transient, relapse-related neurological impairment), it is also recognised that the EDSS has limited ability to detect clinically relevant disability progression in progressive MS [65]. In a recent analysis of data from the placebo arm of the PROMiSe trial, which was conducted in patients with primary progressive MS [49], sustained (3-month) worsening of the EDSS was less sensitive to disability progression than sustained (3-month) changes in the T25FW ($\geq 20\%$ increase) or composite measures (EDSS or T25FW; EDSS or 9HPT $\geq 20\%$ increase; EDSS, T25FW or 9HPT). The authors concluded that T25FW or

Table 2 Published and ongoing phase III trials in patients with progressive MS

Trial name/group [registry number ^a]	Publication date [start date ^a]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
Published studies					
European Trial Group [40]	Nov 1998 [1994]	Interferon β -1b vs. placebo	SPMS [3.0–6.5]	Time to sustained (3-month) disability progression on EDSS ^b	Time to/proportion of patients becoming wheelchair-bound (EDSS \geq 7) Sustained (3-month) disability progression on EDSS (proportion of patients) ^b Change in EDSS EDSS score at endpoint
Cladribine Clinical Trial Group [41]	Mar 2000 [Dec 1994]	Cladribine vs. placebo	Progressive MS [3.0–6.5]	Change in EDSS	Change in SNRS Time to sustained (2-month) progression on EDSS ^d
SPECTRIMS [42] ^c	Jun 2001	Interferon β -1a SC vs. placebo	SPMS [3.0–6.5]	Time to sustained (3-month) disability progression on EDSS ^d	Sustained (3-month) disability progression on EDSS (proportion of patients) ^d Area under the EDSS–time curve
IMPACT [43] ^c	Sep 2002	Interferon β -1a IM vs. placebo	SPMS [3.5–6.5]	Change in MSFC z-score	Sustained (3-month) disability progression on EDSS ^b Change in EDSS score Proportion of patients categorised as stable, worse or better based on EDSS change
MIMS [44]	Dec 2002	Mitoxantrone vs. placebo	Progressive MS (progressive-relapsing MS or SPMS) [3.0–6.0]	Five clinical measures: change in EDSS, change in ambulation index, number of corticosteroid-treated relapses, time to first treated relapse, change in standardised neurological status	Disability progression on EDSS (proportion of patients) ^c Sustained (3- and 6-month) disability progression on EDSS (proportion of patients) ^c Time to first sustained EDSS deterioration Use of wheelchair assistance
Andersen et al. [45]	May 2004	Interferon β -1a SC vs. placebo	SPMS [$<$ 7.0]	Time to sustained (6-month) disability progression on EDSS ^d	Progression in RFSS ^f <i>Tertiary</i> : Proportion of progression-free patients Ambulation index Arm index
ESIMS [46, 47]	Sep 2004	IVIG vs. placebo	SPMS [3.0–6.5]	Co-primary: Treatment failure (sustained [3-month] disability progression on EDSS) ^d Deterioration of EDSS and/or confirmed 20% worsening in 9HPT	Treatment failure after 3 and 6 months Difference in mean slope of progression Confirmed 20% worsening in 9HPT Change in EDSS score Time to deterioration in EDSS, 9HPT, pyramidal, visual and brainstem function scales and composite outcome scores Change in visual function Change in 9HPT results

Table 2 continued

Trial name/group [registry number ^a]	Publication date [start date ^a]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
North American Trial Group [48] ^c	Nov 2004	Interferon β -1b vs. placebo	SPMS [3.0–6.5]	Sustained (6-month) disability progression on EDSS ^b	Change in EDSS score Cognition (change in composite neuropsychological test score)
PROMISE [49] ^c	Jan 2007	Glatiramer acetate vs. placebo	PPMS [3.0–6.5]	Time to sustained (3-month) disability progression on EDSS ^d	Sustained (3-month) disability progression on EDSS (proportion of patients) ^d Change in EDSS score Change in MSFC score
Poehlau et al. [50, 51]	Nov 2007	IVIG vs. placebo	PPMS or SPMS [3.0–7.0]	Sustained (3-month) improvement in disability on EDSS ^e Sustained (3-month) disability progression on EDSS ^d	Visual function Upper extremity function (box and block test; 9HPT) Cognitive function (neuropsychological battery)
OLYMPUS [52] [NCT00087529] Note that this is a phase II/III trial	Oct 2009 [Jun 2004]	Rituximab vs. placebo	PPMS [2.0–6.5]	Sustained (3-month) disability progression on EDSS ^b	None <i>Exploratory:</i> Sustained (6-month) improvement in disability on EDSS Change in MSFC total and component scale scores
MAESTRO [53] [NCT00869726]	Oct 2011 [Dec 2004]	MBP8298 (dirucotide) vs. placebo	SPMS [3.5–6.5]	Sustained (6-month) disability progression on EDSS ^d	Change in MSFC z-scores
INFORMS [54] [NCT00731692]	Mar 2016 [Jul 2008]	Fingolimod vs. placebo	PPMS [3.5–6]	Clinical disease progression (at least one of the following): sustained [3-month] disability progression on EDSS ^d ; $\geq 20\%$ increase on T25FW; or $\geq 20\%$ increase in time taken to complete 9HPT	Sustained [3-month] disability progression on EDSS ^d Clinical disease progression according to T25FW and 9HPT
ORTARIO [55] [NCT01194570]	Jan 2017 [Mar 2011]	Ocrelizumab vs. placebo	PPMS [3.0–6.5]	Sustained (3-month) disability progression on EDSS ^b	Ambulation (MSWS-12) Sustained (6-month) disability progression on EDSS Change in performance on T25FW Change in Physical Component Summary score of SF-36
PROMESS [56] [NCT00241254]	Jan 2017 [Dec 2005]	Cyclophosphamide vs. methylprednisolone	SPMS [4.0–6.5]	Time to sustained (4-month) disability progression on EDSS ^h	Sustained (4-month) disability progression on EDSS (proportion of patients) ^h Progression of MSFC z-scores
Ongoing studies					
EXPAND [NCT01665144]	NA [Dec 2012]	Siponimod vs. placebo	SPMS [3.0–6.5]	Sustained (3-month) disability progression on EDSS ^d	Sustained (3-month) deterioration $\geq 20\%$ on T25FW Sustained (6-month) disability progression on EDSS ^d
MS-SPI [NCT02220933]	NA [Oct 2013]	MD1003 (biotin) vs. placebo	Spinal progressive MS [4.5–7.0]	Sustained (3-month) improvement in disability on EDSS ^j or T25FW ($\geq 20\%$) [proportion of patients]	MSWS-12 response rate MSWS CGI-/PGI-improvement 9HPT

Table 2 continued

Trial name/group [registry number ^a]	Publication date [start date ^a]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
MS-SPI2 [NCT02936037]	NA [Dec 2016]	MD1003 (biotin) vs. placebo	PPMS or SPMS [3.5–6.5]	Sustained (3-month) improvement in disability on EDSS ⁱ or T25FW ($\geq 20\%$) [proportion of patients]	Time to sustained (3-month) disability progression on EDSS ⁱ CGI-Improvement Change in T25FW <i>Other</i> : Remote monitoring of ambulation Kurtzke functional subscores Cognition (SDMT)

Endpoints measuring the following parameters are not included as they do not necessarily capture disability: quality of life, fatigue, depression, psychological impairment, social impairment, hospitalisations and interventions for disease-related events

Trials published from 1997 to 2017; ongoing trials were sourced from ClinicalTrials.gov

9HPT 9-hole peg test, CGI Clinical Global Impression, EDSS Expanded Disability Status Scale, IM intramuscular, IVIG intravenous immunoglobulin, MS multiple sclerosis, MSFC Multiple Sclerosis Functional Composite, MSWS Multiple Sclerosis Walking Scale, NA not applicable, PGI Patient Global Impression, PPMS primary progressive multiple sclerosis, RFSS Regional Functional System Score, SC subcutaneous, SDMT, Symbol Digit Modalities Test, SF-36 Medical Outcomes Study Short-Form (36-item) Health Survey, SNRS Scripps Neurological Rating Scale, SPMS secondary progressive multiple sclerosis, T25FW timed 25-foot walk

^aIf available

^bEDSS score increase ≥ 1.0 if baseline score ≤ 5.5 , or ≥ 0.5 if baseline score ≥ 6.0

^cPublication does not specify that trial is phase III (assumption based on trial design [randomised, controlled and double-blind] and sample size [$n > 400$])

^dEDSS score increase ≥ 1.0 if baseline score ≤ 5.0 , or ≥ 0.5 if baseline score ≥ 5.5

^eIncrease ≥ 1.0

^fIncrease $\geq 2\%$

^gEDSS score decrease ≥ 1.0 if baseline score ≤ 5.0 , or ≥ 0.5 if baseline score ≥ 5.5

^hEDSS score increase ≥ 1 if baseline score 4.0 or 4.5, or ≥ 0.5 if baseline score ≥ 5.0

ⁱEDSS score decrease ≥ 1.0 if baseline score ≤ 5.5 , or ≥ 0.5 if baseline score ≥ 6.0

composite measures should be considered as the primary endpoint for future studies of new disease-modifying therapies [66].

Despite its limitations, the EDSS is the only disability outcome measure currently advocated by the European Medicines Agency (EMA) for trials in MS [67]. More specifically, the EMA advises that the mean change in EDSS score from baseline is not appropriate and that sustained worsening of a relevant magnitude over a pre-specified timeframe should be used. This undoubtedly explains, at least in part, the persistent use of sustained EDSS worsening over 3 or 6 months in the trials identified as part of the current evaluation. However, the EMA does acknowledge that there is a need for alternative measures (see below for information on the Multiple Sclerosis Outcome Assessments Consortium [68, 69]), and research in this area has been active for many years. The MSFC was first introduced almost 20 years ago to address some of the limitations of the EDSS [17], and a recent meta-analysis has shown it to be more sensitive than the EDSS for detecting progression of MS [70]. The MSFC was included in over half (9/16) of the phase III RRMS trials identified in

the current evaluation, although it was a primary endpoint in only one [43]. Perhaps surprisingly, the MSFC was used in only 5/20 phase III trials (25%) in progressive MS. Two factors that may have limited the use of the MSFC are lack of clarity (until relatively recently, at least [15, 16]) on the magnitude of clinically significant changes for the three component tests [12] and patients' dislike of the PASAT (used to assess cognition) [15, 16]. The major issue is probably the lack of acceptance by regulatory agencies, which is most likely driven by the poor clinical interpretability of the overall score [12]. Other approaches taken to improve on disability assessment include development of the EDSS-Plus, which includes the EDSS and the 9HPT and T25FW [71], and use of a roving versus fixed reference value [72].

Among the trials identified in the current evaluation, some included secondary outcomes to assess manual dexterity and cognition, aspects of disability progression that are not evaluated by the EDSS. Some also included separate measures of ambulation, one of the most valued functions for patients with MS [15]. Although the data obtained for these endpoints are informative, as discussed

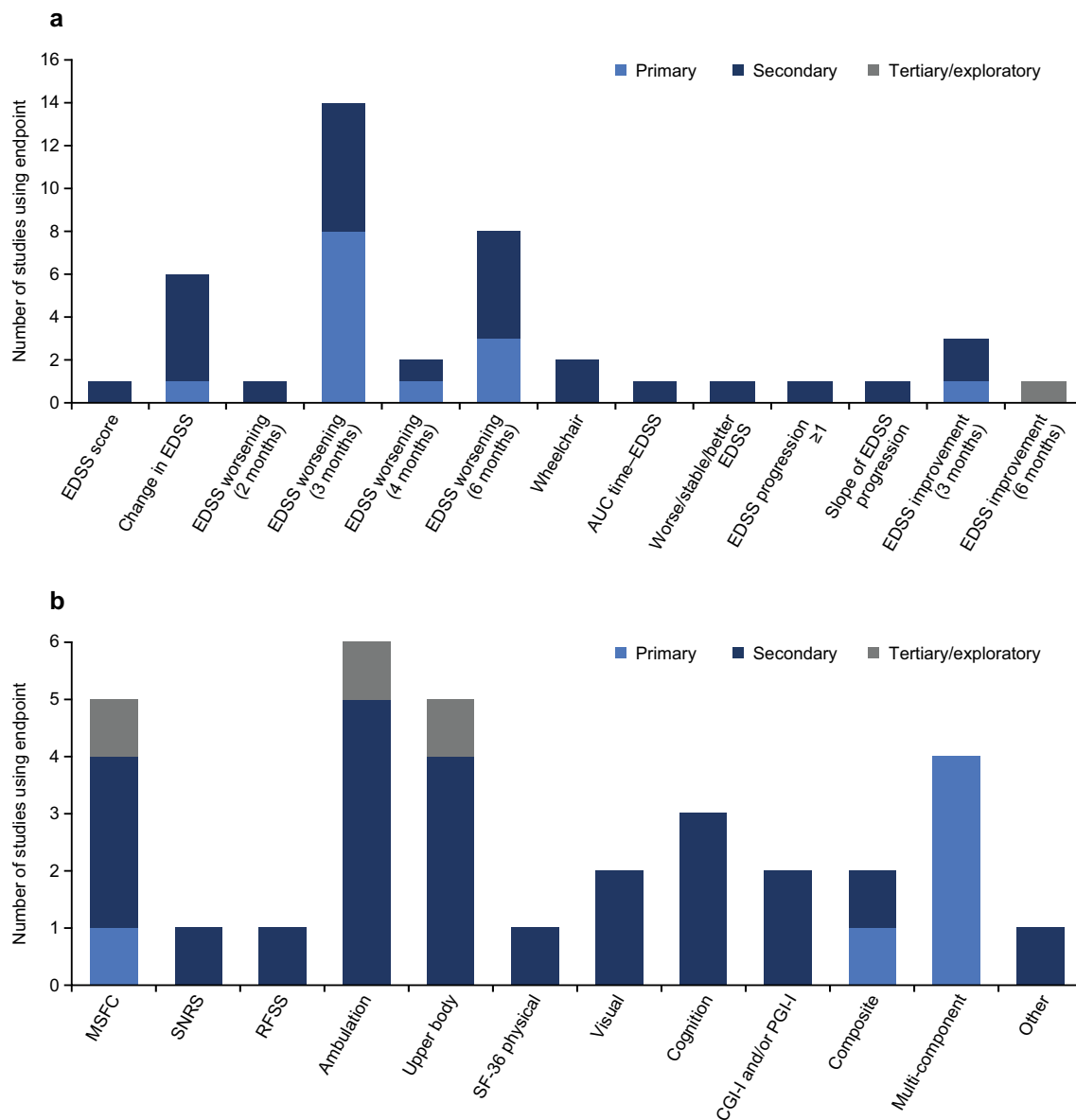


Fig. 3 Disability outcome measures used in phase III progressive MS trials ($n = 18$): **a** EDSS-related measures; **b** other outcome measures. Includes unpublished trials and trials published from 1997 onwards; note that in some trials, endpoints relating to the same measure were included as both primary and secondary endpoints (e.g. time to 3-month worsening of EDSS and the proportion of patients with 3-month worsening of EDSS). *AUC* area under the curve, *CGI-I*

Clinical Global Impression of Improvement, *EDSS* Expanded Disability Status Scale, *MSFC* Multiple Sclerosis Functional Composite, *MS* multiple sclerosis, *PGI-I* Patient Global Impression of Improvement, *RFSS* Regional Functional System Score, *SF-36* Medical Outcomes Study Short-Form (36-item) Health Survey, *SNRS* Scripps Neurologic Rating Scale

above, trials are designed and specifically powered to detect statistical treatment differences in primary endpoints, but not necessarily in secondary endpoints.

Other pertinent observations include the use, in some trials, of composite endpoints to assess disability progression. These include a single composite score of five component measures [44], as well as endpoints for which patients only had to satisfy one of two or more criteria to be classified as progressors (e.g. increase in EDSS score or

$\geq 20\%$ worsening on the 9HPT) [46, 54]. Interestingly, when testing the EDSS-Plus (see above), it was observed that defining progression on at least one of three components (EDSS, T25FW or 9HPT) identified 60% of patients as progressors, compared with 25, 42 and 34%, respectively, when using the individual tests alone [71].

The inclusion of endpoints to evaluate disability *improvement* is also pivotal as it marks the start of a shift in the goals for treating MS, from limiting disability

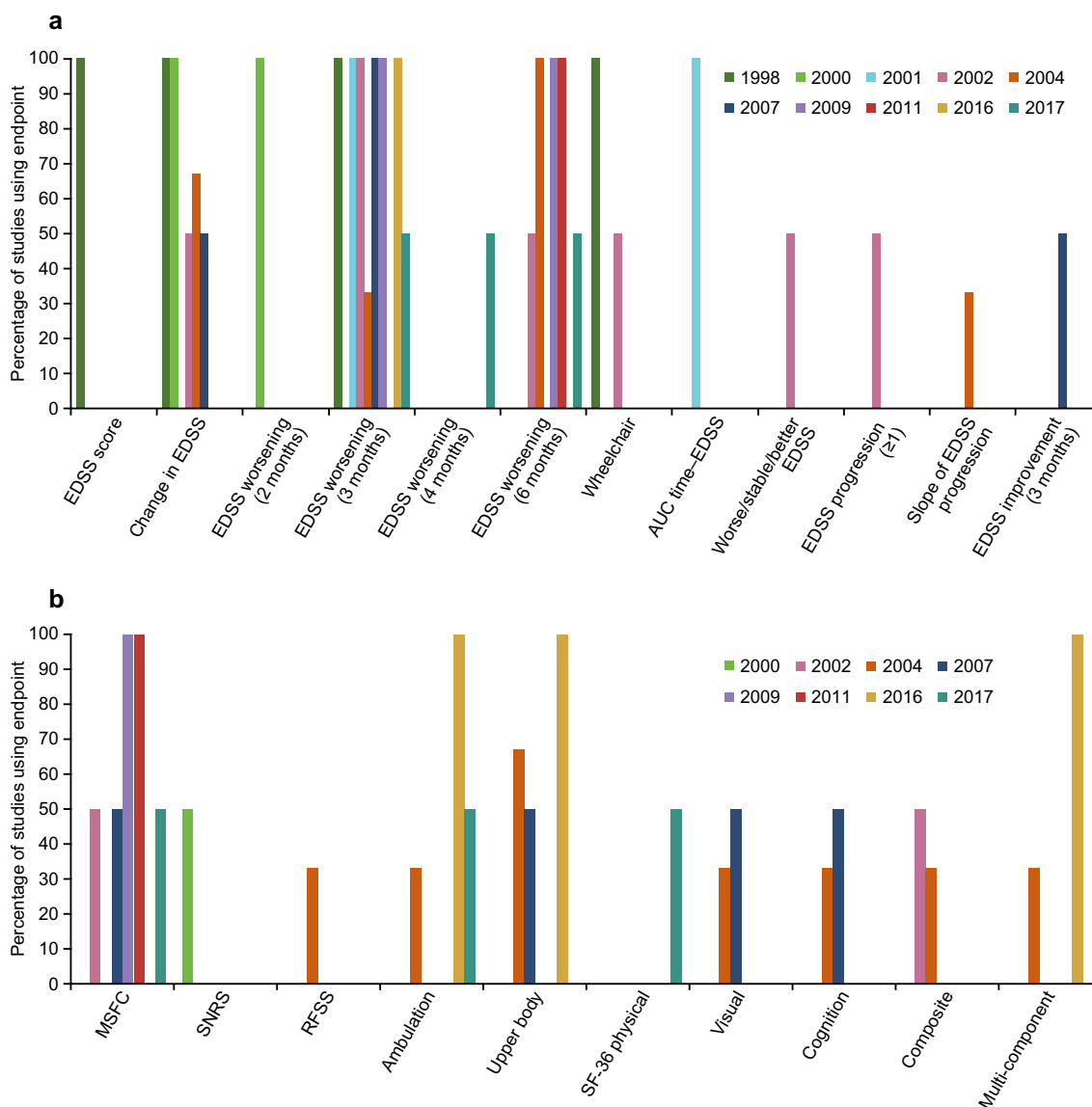


Fig. 4 Disability outcome measures used over time in phase III progressive MS trials published since 2007 ($n = 18$): **a** EDSS-related measures; **b** other outcome measures. Published trials only (trials could not be assessed according to start date, as this was not available for all published trials). *EDSS* Expanded Disability Status Scale, *MS*

multiple sclerosis, *MSFC* Multiple Sclerosis Functional Composite, *RFSS* Regional Functional Scoring Scale, *SF-36* Medical Outcomes Study Short-Form (36-item) Health Survey, *SNRS* Scripps Neurologic Rating Scale

progression to reversing it, using not only agents aimed at halting disease activity but also interventions intended to repair and remyelinate [73]. However, use of the EDSS to assess disability improvement is subject to the same limitations as its use to assess disability progression, and discussions regarding more appropriate endpoints to measure improvement have already started [74]. Another advance in the assessment of disability in MS is the possibility of measuring physical activity and ambulation remotely [75, 76]. The feasibility of remote evaluation of cognitive and patient-reported outcomes in MS has also been assessed [77–79].

One of the potential limitations of the current evaluation was the use of PubMed to identify phase III MS trials, thus relying on inclusion of the term ‘phase 3’ (or ‘phase III’) in the abstract or Medical Subject Heading (MeSH) terms; however, the bibliographies of review articles on the treatment of MS were also screened to address this. Another limitation, in the context of assessing the evolution of disability outcome measures over time, is that it was not possible to ascertain the start date for all of the trials in progressive MS. The evaluation was therefore conducted according to the trial publication date, which may not truly reflect the chronology of the trials. Nevertheless, it gives a

Table 3 Published and ongoing phase III trials in other MS phenotypes

Trial name/group [registry number ^a]	Publication date [start date ^a]	Treatment	MS phenotype [EDSS inclusion criterion]	Primary outcome measure(s)	Secondary and other outcome measures (disability-related)
Relapsing or progressive MS					
Mayo Clinic–Canadian Cooperative trial [60]	Nov 1998	Sulfasalazine vs. placebo	Active RRMS or progressive MS [1.0–4.0]	Time to sustained (3-month) disability progression (EDSS increase ≥ 1)	Sustained (3-month) disability progression (EDSS increase ≥ 0.5) Treatment failure (sustained [3-month] disability progression [EDSS ≥ 2])
Noseworthy et al. [61]	May 2000	Roquinimex vs. placebo	Active RRMS or SPMS [3.0–6.5]	Time to sustained (3-month) disability progression on EDSS ^b	Sustained (3-month) disability progression on EDSS (proportion of patients) ^b
OPTIMUM [NCT02425644]	NA—study ongoing [Apr 2015]	Ponesimod vs. teriflunomide	RRMS or SPMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^c
ASCLEPIOS II [NCT02792231]	NA—study ongoing [Aug 2016]	Ofatumumab vs. teriflunomide	RRMS or SPMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^c Sustained (6-month) disability progression on EDSS Sustained (6-month) improvement in disability on EDSS ^c
ASCLEPIOS I [NCT02792218]	NA—study ongoing [Sep 2016]	Ofatumumab vs. teriflunomide	RRMS or SPMS [≤ 5.5]	ARR	Sustained (3-month) disability progression on EDSS ^c Sustained (6-month) disability progression on EDSS ^c Sustained (6-month) improvement in disability on EDSS ^c
Other					
MITOX-REBIF [NCT02937285]	NA—study ongoing [Nov 2010]	Mitoxantrone + interferon β -1a SC vs. interferon β -1a SC	Patients with a strong risk of progression in the initial phase of MS [> 3.5]	Absence of relapse and EDSS increase ≤ 1	Change in EDSS score Rate of progression to clinically definite MS (in patients with one clinical event)

Endpoints measuring the following parameters are not included as they do not necessarily capture disability: quality of life, fatigue, depression, psychological impairment, social impairment, hospitalisations and interventions for disease-related events; clinical global improvement was included as it is likely to capture disability in the progressive MS population

ARR annualised relapse rate, EDSS Expanded Disability Status Scale, MS multiple sclerosis, NA not applicable, RRMS relapsing-remitting multiple sclerosis, SC subcutaneous, SPMS secondary progressive multiple sclerosis

^aIf available

^bEDSS score increase ≥ 1.0 if baseline score ≤ 5.0 , or ≥ 0.5 if ≥ 5.5

^cNo further details given

general overview of disability-related outcomes assessed in phase III trials, adding to that provided by Lavery et al. in trials of RRMS [20], and providing useful information on progressive MS trials conducted over the last 20 years.

The need for improved disability outcome measures is recognised by the wider MS community. The international MS Outcome Assessments Consortium was set up to develop a tool set for use in MS clinical trials that can detect

the benefit of potential treatments that slow or reverse progressive disability, and is recognised as a primary outcome measure by regulatory authorities [68, 69, 80]. The consortium, which includes representatives from academic institutions, pharmaceutical companies, the EMA, US FDA and National Institutes for Health, recently published four papers reviewing the evidence for the validity of four outcome measures: the T25FW, the 9HPT, the Symbol Digit Modalities Test (SDMT) and the Low-Contrast Visual Acuity Test (LCVA), suggesting that these scales will be included in the final tool set [15, 16, 81, 82]. These scales assess ambulation, manual dexterity, cognition and vision, respectively, as impairments to these functions represent core symptoms in MS [81]. The SDMT was selected to measure cognition rather than the PASAT (which is part of the MSFC) as it has shown superior reliability and sensitivity and greater patient acceptability [82]. With regard to visual function, which is not captured by the MSFC, LCVA was selected as it captures visual loss not identified using high-contrast visual acuity tests [81]. The four manuscripts also include information on the magnitude of clinically meaningful changes (T25FW, $\geq 20\%$; 9HPT, $\geq 20\%$; SDMT, ≥ 4 points or $\geq 10\%$; LCVA, $\geq 7\%$) based on published data [15, 16, 81, 82].

5 Conclusions

The current evaluation indicates that despite its serious and well-recognised limitations, sustained EDSS worsening continues to be widely used as an endpoint in phase III trials in MS. As such, disability progression has tended to focus on the assessment of mobility. Although mobility is important, there are other domains of MS that are relevant to the detection of progression. Additional outcome measures that assess these domains have been available for many years, but there is now renewed focus on their psychometric and regulatory validation, which should facilitate their more extensive use in the future. Combination endpoints (whereby efficacy is measured according to whether a patient meets one or more of multiple prespecified outcomes) have been used in a small number of recent trials and may improve sensitivity in terms of detecting a change in disability; however, the effect size expected in future trials is unknown and the most appropriate combination of outcome measures may be difficult to predict in a specific population treated with specific therapies with differing mechanisms of action [83]. Ideally, a multifaceted approach should

be adopted that explores aspects of the disease that are directly relevant to patients, and patient involvement should be considered when developing new outcomes to assess disability progression in MS. Another challenge is to ensure that outcome measures developed in the context of clinical trial conduct are suitable for use in busy, everyday clinical practice.

Compliance with Ethical Standards

Funding Nicky French, PhD, of Anthemis Consulting Ltd provided editorial support, funded by Teva Pharmaceutical Industries, Frazer, PA, USA. Teva provided a single medical-accuracy review of the final draft. The author was not compensated and retained full editorial control over the content of the paper. Open access was funded by VU University Medical Center, as part of the Springer Compact agreement.

Conflict of interest The author has received consultancy fees from Genzyme, Biogen Idec, Teva, Merck Serono and Roche.

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