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REVIEW

# Functional clinical outcomes in multiple sclerosis: Current status and future prospects



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Received 12 December 2014; received in revised form 23 February 2015; accepted 14 March 2015

**Abbreviations:** BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-Second Edition; DAF, disease activity-free status; EDSS, Expanded Disability Status Scale; MACFIMS, Minimal Assessment of Cognitive Function in MS; MSFC, MS Functional Composite; MusiQoL, MS International Quality of Life; PASAT, Paced Auditory serial Addition test; QoL, quality of life; SDMT, Symbol Digit Modalities Test

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**KEYWORDS**

Multiple sclerosis;  
Clinical outcome  
measures;  
Disease-modifying  
therapies;  
Clinical trials

**Abstract**

For decades, the Expanded Disability Status Scale (EDSS) has been the principal measure of disability in clinical trials in patients with multiple sclerosis (MS) and in clinical practice. However, this test is dominated by effects on ambulation. Composite endpoints may provide a more sensitive measure of MS-related disability through the measurement of additional neurological functions. The MS Functional Composite (MSFC) includes a walking test (25-ft walk) plus tests of upper extremity dexterity (9-hole peg test) and cognitive function (Paced Auditory serial Addition test [PASAT]). Replacing PASAT with the Symbol Digit Modality test, a more sensitive test preferred by patients, may improve the clinical utility of the MSFC. In addition, disease-specific measures of QoL may be used alongside the MSFC (which does not include measurement of QoL). Clinical data suggest that disease-modifying therapies may delay or prevent relapse, and better composite measures will be valuable in the assessment of disease activity-free status in people with MS.

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**1. Introduction**

The number of available options for the medical management of multiple sclerosis (MS) has expanded considerably in recent years, with the introduction of new disease-modifying drug treatments (Damal et al., 2013). However, the design of clinical trials has changed little during this period, and tends to rely on single primary outcome measures based on progression of disability or the frequency of relapses (Rieckmann et al., 2013). Broader and more sensitive outcome measures to evaluate the effects of therapies in patients with multiple sclerosis are needed. For example, recent research has suggested that white matter lesions during the early course of MS may not impair functional capacity due to plasticity and redundancy within neuronal circuits; however, continued damage to white matter due to MS, or normal neuronal loss due to ageing, can subsequently lead to functional or cognitive deficits once the “brain reserve” has been used up (Sumowski et al., 2013a, 2013b). Thus, a more accurate measurement of functional physical and cognitive abilities may broaden the

evidence base for interventions in MS and provide better information on which patients would be likely to benefit from a given treatment at a given stage of the disease. Indeed, the introduction of new endpoints in clinical trials was one of six key priorities for improving the delivery of MS care identified by an international expert consensus process in 2013 (Rieckmann et al., 2013). The purpose of this paper is to discuss the strengths and limitations of available clinical outcome measures in assessing the functional status of patients with MS. The use of emerging MRI endpoints will be mentioned only briefly. We also present recommendations on how such measures may contribute to improved MS care in the future.

**2. Outcomes related to motor impairment****2.1. Expanded Disability Status Scale (EDSS)**

The EDSS has been used to provide an index of functional disability in MS patients from the 1980s (Kurtzke, 1983) to

the present day (National Multiple Sclerosis Society; Wilken et al., 2013). Within a scale of 0-10 (in unit steps of 0.5), EDSS steps 0-3.5 indicate that the patient has good functional status without requiring assistance; steps 4.0-5.5 are based on walking distance, while steps 6.0-9.5 reflect increasing requirements for assistance (step 10 represents death). Accordingly, the problematic end of the EDSS scale (where patients have the most severe disability) is dominated by problems with ambulation to the exclusion of other functional limitations (Cohen et al., 1993).

A study comparing measurements of EDSS with a 42 item assessment of impairment of activities of daily living demonstrated a significant correlation between the results from these instruments; however, this was driven entirely by impairments in mobility (Cohen et al., 1993). Therefore, the EDSS does not provide an adequately sensitive measurement of other important determinants of functional capacity in MS, such as cognition and manual dexterity (arm/hand function). In addition, the EDSS changes little over time in most patients, indicating low sensitivity for detecting treatment-related changes in disability during clinical trials (Rabadi and Vincent, 2013; Zhang et al., 2013), although administering two EDSS tests before treatment has been shown to improve the ability of the EDSS to detect such changes (Zhang et al., 2013). Substantial inter-operator variability in EDSS measurements has also been proposed as an important limitation of this test, with one group suggesting that a change in EDSS score of at least 1 unit (2 scale steps) is required to signify a reliable measurement of change in disability status (Noseworthy et al., 1990).

EDSS remains popular among neurologists and is still accepted by regulatory authorities as definitive evidence of disease progression (Bevan and Cree, 2014). A recent study described a benefit for alemtuzumab versus interferon- $\beta$ 1a with regard to a composite measure described as “Sustained Accumulation of Disability”, which was defined in terms of an increase in EDSS score of 1.0 or 1.5 units, depending on baseline score (Coles et al., 2012), information which is presented in the draft EU labelling for this treatment, which was approved in Europe during the latter part of 2013 (see its current Prescribing Information).

## 2.2. Timed 25-ft walk

A timed walk over a distance of 25 ft (about 8 m) has emerged as a sensitive and meaningful test, as shown by a cross-sectional study in 169 patients with MS (Goldman et al., 2013). In this study, a cut-off value of 6 s for completing the walk was predictive of significant disability due to MS (inability to continue in original occupation, use of cane while walking, and requirement for some degree of assistance with activities of daily living), while a time of at least 8 s to complete the course was associated with increased risk of receipt of disability benefits, use of a walking frame and inability to pursue usual daily activities. Further development of this test shows that there is some training effect, with a reduced time for a second versus a first attempt, but that it has low intra-subject variation if second and subsequent attempts are considered (Larson et al., 2013). Alternatively, taking the fastest two of three

walks restricted the variability in walking time to 10% or less (Kaufman et al., 2000).

A longer walking distance may be required to estimate patients' maximal walking speed, as patients with MS achieved higher peak walking speeds over a 100 m walk compared with a 25-ft walk (Phan-Ba et al., 2011). An amended version of the 25-ft walk has been described in which patients take a 3-m run-up before the clock is started, which appeared to allow a more reliable measurement of maximal walking speed (Phan-Ba et al., 2012). This test is a component of the MS Functional Composite (MSFC; see below).

## 2.3. Nine-hole peg test

This measure of upper extremity function requires the patient to take each of nine pegs from a shallow container, place them into holes a block, and then remove them and place them back in the container (one at a time, in each case). Scores are derived from the time taken to complete the task using the dominant and non-dominant hand (two trials for each hand). Reproducibility is high within subjects and between test operators (National Multiple Sclerosis Society). Adverse changes in the score for this test are associated with greater levels of long-term disability (Kragt et al., 2006). This test is also a component of the MSFC (see below). The “squares test”, a measure of dexterity performed using a paper and pencil, has been proposed as an alternative to the 9-hole peg test for this purpose (Gielen et al., 2014).

## 3. Cognitive outcomes

The Symbol Digit Modalities Test (SDMT) is a sensitive and robust assessment of cognitive status, across domains including divided attention, visual scanning, tracking and motor speed in adults (Strauss et al., 2006). The person taking the test is provided with a set of symbols, each corresponding to a number. He or she is required to write down the symbols corresponding to a series of numbers within a short space of time. The SDMT is quick (~5 min) and straightforward to administer, provides a clear test score that is not influenced by subjective interpretations on the part of the healthcare professional who administers the test, and is little affected by patients' age, gender or educational status (Sheridan et al., 2006; Sonder et al., 2014).

A study in 485 patients with MS found that the SDMT was a more robust and reliable measure of cognitive impairment than a version of the Paced Auditory Serial Addition test (PASAT3) during long-term follow-up; PASAT is alternative test of cognitive function that requires patients to hear a number every three seconds and add it to the number they heard previously, thus testing working memory and attention (Strauss et al., 2006; Sonder et al., 2014). White matter lesions on MRI have been shown to be more strongly associated with SDMT than PASAT in patients with MS (Papadopoulou et al., 2013; Yu et al., 2012). In addition, patients and physicians prefer the SDMT to PASAT (Walker et al., 2012). Multiple forms of the SDMT are available however, although there is clinical evidence that at least three of these are effectively clinically equivalent for

assessing cognitive deficit in MS (Benedict et al., 2012a). A low SDMT score is significantly associated with impaired visual function due to MS lesions (see below) (Wieder et al., 2013).

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is also used to evaluate cognitive function in MS. BICAMS involves use of the SDMT if only five minutes is available, with the addition of the California Verbal Learning Test-Second Edition (CVLT-II) and the Brief Visuospatial Memory Test-Revised (BVMT-R) if 15 min was available for each patient (BICAMS, 2013). Thus, BICAMS was designed to provide flexibility for small centres where staff administering the test may have limited training in neuropsychology. Standards for establishing cultural validity and for the demonstration of local reference populations for BICAMS have been published (Benedict et al., 2012b). The Minimal Assessment of Cognitive Function in MS (MACFIMS) includes PASAT, SDMT, CVLT-II, BVMT-R, Delis-Kaplan executive function scale sorting test, judgment of line orientation test, and controlled oral word association test (Grazioli et al., 2008). MACFIMS has been shown to reproduce common manifestations of cognitive impairment revealed by other tests, and can distinguish cognitive deficits found in relapsing-remitting versus secondary progressive MS (Benedict et al., 2006).

#### 4. Visual outcomes

Diminished low-contrast visual acuity correlates significantly with loss of retinal nerve fibre layer thickness in MS (Fisher et al., 2006). Low-contrast visual acuity testing is particularly suited for use in MS, as subtle disturbances of visual function may not be apparent with high-contrast

letter charts (Balcer and Frohman, 2010). Axonal loss in the retinal nerve fibre layer was as severe for patients with so-called “benign” MS (EDSS < 3 over 15 years) compared with the general population of patients with MS, and loss of low-contrast visual acuity was marked and similar in each group (however, loss of retinal ganglion cells is also an important source of impaired visual function in MS) (Galetta et al., 2012; Saidha et al., 2011; Walter et al., 2012).

Impaired low-contrast acuity is associated significantly with cognitive impairment (particularly information processing speed and memory) (Wieder et al., 2013), quality of life (QoL) (Mowry et al. 2009; Galetta et al., 2012) and the burden of brain MRI lesions (Wu et al., 2007). Low-contrast visual acuity testing appears to be sufficiently sensitive to detect treatment-related improvements in visual function in clinical trials (Balcer et al., 2012). Sloan charts are suitable for binocular testing, thus reflecting patients' usual daily activities (Balcer et al., 2003). The King-Devick rapid eye movement test (Moster et al., 2014), based on rapid naming of numbers, takes less than two minutes to perform and has been proposed as a practical measure of visual function and vision-related quality of life (see below for discussion of measures of quality of life).

#### 5. Quality of life

MS exerts a marked negative impact on QoL (Miller and Allen, 2010), and maintaining QoL is an important goal within the overall management of the disease (Al-Tahan et al., 2011). Numerous generic and MS-specific measures of quality of life have been described (Table 1). A detailed comparison of their properties is beyond the scope of this review and this section will focus mainly on two instruments

**Table 1** Examples of instruments for measuring quality of life in patients with multiple sclerosis.

Generic	<ul style="list-style-type: none"> <li>• General Health Survey of the Medical Outcomes Study [usually applied in its abbreviated form, the Short Form-36 (SF-36) questionnaire]</li> <li>• World Health Organization Quality of Life Brief Form (WHO-QoL-BREF)</li> <li>• EuroQol EQ-5D</li> <li>• Sickness Impact Profile (SIP)</li> <li>• Life Satisfaction Questionnaire (LSQ)</li> <li>• Quality of Well-Being Scale (QWBS)</li> </ul>
MS-specific	<ul style="list-style-type: none"> <li>• Multiple Sclerosis Quality of Life questionnaire (MSQOL54)</li> <li>• Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)</li> <li>• Quality of Life Index-Multiple Sclerosis (QLI-MS)</li> <li>• Leeds Multiple Sclerosis Quality Of Life scale</li> <li>• MS Impact Scale (MSIS-29)</li> <li>• Disability and Impact Profile (DIP)</li> <li>• Extension of Quality-adjusted Time without Symptoms of Disease and Toxicity of Treatment</li> <li>• Multiple Sclerosis Quality of Life Inventory<sup>a</sup></li> <li>• Functional Assessment of Multiple Sclerosis (FAMS)</li> <li>• Quality of Life Index (QLI)<sup>b</sup></li> <li>• Multiple Sclerosis Impact Scale (MSIS-29)</li> </ul>

<sup>a</sup>Made up of modules from: SF-36; Modified Fatigue Impact Scale (MFIS); MOS Pain Effects Scale (PES); Sexual Satisfaction Scale (SSS); Bladder Control Scale (BLCS); Bowel Control Scale (BWCS); Impact of Visual Impairment Scale (IVIS); Perceived Deficits Questionnaire (PDQ); Mental Health Inventory (MHI); MOS Modified Social Support Survey (MSSS).

<sup>b</sup>A generic version and versions specific for MS and other diseases are available. Compiled from information presented by Baumstarck et al. (2013d), Fischer et al. (1999b) and World Health Organisation (2015).

which have been validated extensively in patients with MS in many countries.

The MS International Quality of Life (MusiQoL) questionnaire is a disease-specific, multi-dimensional, self-administered questionnaire for assessing QoL that has been validated in 14 languages (Simeoni et al., 2008; Baumstarck et al., 2013a). Thirty-one items explore nine dimensions of QoL that reflect closely patients' day-to-day experiences (activities of daily living; psychological well-being; symptoms; relationships with friends; relationships with family; sentimental and sexual life; coping; rejection; relationships with the healthcare system) (Baumstarck et al., 2013a). MusiQoL retains its validity in patients with MS and impairment of cognition, attention or memory and some subscores (but not the overall MusiQoL index) were sensitive to decreased quality of life due to worsening disability (EDSS), compared with changes in physical dimensions of the generic SF-36 QoL questionnaire (Baumstarck et al., 2012a, 2012b, 2013a, 2013b). Elsewhere, MusiQoL predicted adverse changes in the EDSS (Baumstarck et al., 2013c; Ertekin et al., 2014).

The MSQoL-54 instrument, like MusiQoL, has been extensively validated in a number of countries and is available in a number of languages (Vickrey et al., 1995). A recent study has compared the use of MSQoL-54 and MusiQoL in a 2-year study in 334 patients with relapsing-remitting MS managed with interferon- $\beta_{1a}$  (Moore et al., 2015). The instruments demonstrated similar responsiveness to change and correlated particularly strongly with feelings of anxiety or depression, compared with physical signs and symptoms or the occurrence of relapse. One notable difference between them was that MusiQoL was faster to complete than MSQoL54: while patients appreciated the apparently greater "thoroughness" of MSQoL54. The authors noted that MusiQoL may be a more pragmatic choice given their similar clinical utility.

The Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) has also been shown to be sensitive to changes in overall health status in three cohorts of MS patients in different clinical settings (patients whose health status deteriorated, patients in a neurorehabilitation programme and patients in an aerobic fitness programme; Gold et al., 2010). HAQUAMS may also be appropriate for use in a clinical trial setting. Further head-to-head comparisons between different quality of life instruments would be useful to assist clinicians in choosing the most appropriate one for the needs of their patients.

## 6. Composite outcomes evaluating aspects of functional status in addition to ambulation in MS

### 6.1. MS Functional Composite

The MSFC was developed following a task force set up by the US National Multiple Sclerosis Society specifically to address the limitations of the EDSS, as described above (Rudick et al., 1997, 2002; Cutter et al., 1999; Fischer et al., 1999a). It provides a composite score from the timed 25-ft walk, PASAT and the 9-hole peg test (in addition to individual scores from each individual domain), which have been described separately above and typically takes a tra-

ined operator 25-30 min to administer to a patient (National Multiple Sclerosis Society).

The MSFC is multidimensional in nature, and extends measures of functional status beyond the ambulation-driven output from the EDSS (Hoogervorst et al., 2002). MSFC scores correlate closely with EDSS scores in patients with MS (Miller et al., 2000) and changes in the MSFC paralleled changes in grey matter volume (Hofstetter et al., 2014). A 2-year study in patients with relapsing-remitting or secondary progressive MS showed that EDSS scores, unsurprisingly, correlated tightly with the results of the 25-ft walk test, but that the MSFC provided additional correlations with other measures of neurological function (Ozakbas et al., 2005). MSFC scores have also been shown to correlate significantly with other measures of disability, including relapse rates, changes in MRI lesion burden and patient-reported outcomes, including QoL (Miller et al., 2000; Kalkers et al., 2001; Rudick et al., 2002, 2009; Polman and Rudick, 2010). In one study (Miller et al., 2000), correlations between MSFC scores and a series of patient reported outcomes (Total, Physical and Psychosocial dimensions of the Sickness Impact Profile, and employment status) remained significant after controlling for EDSS, although correlations with SF-36 scores were generally weaker in this study for both EDSS and MSFC. Thus, changes in the MSFC predict patient-reported outcomes independently of changes in the EDSS, to some extent.

Inability to work is a common fear among patients with MS and the MSFC has been shown to predict employment status better than the EDSS in patients with MS (Miller et al., 2000; Honarmand et al., 2011). In addition, the MSFC has been shown to be a better predictor than the EDSS of changes in functional status during and following MS relapses (Patzold et al., 2002). Analysis of data from a 2-year intervention trial in patients with MS showed that changes in the MSFC correlated significantly with changes in 6/11 scales of the MS Quality of Life Inventory, while changes in the EDSS correlated with changes in only 2/11 scales (Miller et al., 2006). The close association between MSFC and QoL scores in patients with MS has prompted identification of MSFC scores with the severity of MS as perceived by the patient (Ozakbas et al., 2004); other data have shown that MSFC scores are sensitive predictors of impairment of activities of daily living such as driving (Shawaryn et al., 2002).

A cut-off value for clinical significance of changes of at least 15% for each MSFC component has been proposed. However, one study showed cut-offs of 20% for the 25-ft walk and 9-hole peg test to more effectively identify patients with progressive disability (no satisfactory cut-off for PASAT could be determined) (Bosma et al., 2010). A second study found the 15% cut-offs to provide a more sensitive evaluation of disability progression (Rudick et al., 2009). These data are consistent with the results of a further study that demonstrated day-to-day variability of less than 20% in scores for the 25-ft walk and 9-hole peg test in patients with MS (Schwid et al., 2002). Practice effects (changes in test performance unrelated to disease progression) may limit evaluation of the 9-hole peg test and PASAT (Solari et al., 2005; Rosti-Otajärvi et al., 2008). However, three practice sessions before the recorded measurements have been shown to be sufficient to establish a stable baseline for the MSFC (Cohen et al., 2001).

## 6.2. Relapse-related outcomes

Improved treatment of MS has led to increasing emphasis on prolonged periods of remission. Disease activity-free (DAF) status is a relatively recent outcome measure that is increasingly used to assess functional status in evaluating novel pharmacologic agents (Bevan and Cree, 2014). Increased DAF duration has been observed in patients with MS after treatment with cladribine (in the CLARITY study; Giovannoni et al., 2010, 2011) or natalizumab (the AFFIRM study; Havrdova et al., 2009), each versus placebo. DAF is a composite measure based on the absence of relapses, absence of increased disability lasting for more than three months and absence of disease activity on MRI (gadolinium-enhanced lesions on T1-weighted scans and new or enlarged lesions on T2-weighted scans). The debate on how to define DAF is still continuing and a consensus on what individual endpoints to be included (and how to measure them) may emerge in the near future (Bevan and Cree, 2014).

## 6.3. Annual relapse rate

The percentage of patients relapsed, the time to first relapse, the severity of a relapse, and requirement for steroid use or hospitalisation are other potential secondary outcome measures in MS. However, the frequency of relapses in interventional trials in MS has fallen since the 1990s: apparently due to changes in selection criteria of patients and a reduced relapse rate due to earlier allocation of patients to rescue therapies. This phenomenon complicates comparisons of relapse rates between clinical trials conducted at different time points (Inusah et al., 2010).

## 6.4. Other composite outcomes

A recent study from the Czech Republic supported the use of a composite evaluation consisting of a battery of validated tests (low-contrast letter acuity; Motricity Index; Modified Ashworth Scale; Berg Balance Scale; tests of postural reaction, tremor, dysdiadochokinesia, and dysmetria; Nine-hole peg test; timed 25-ft walk; and the 3-min version of the Paced Auditory Serial Addition test), plus a further test of knee hyper-extension of their own design (Rasova et al., 2012). The authors describe this panel of tests as repeatable and suitable for demonstrating treatment-related changes in functional status for either research or routine clinical management of patients with MS.

## 7. Looking ahead

### 7.1. Changes in the use of composite outcomes

The clinical studies summarised above identify composite endpoints as superior to single outcome measures in measuring and predicting disability due to MS. In particular, the MSFC has emerged as superior to the EDSS in this regard (see Section 6.1), though the EDSS is likely to remain widely used in routine clinical practice. The National Multiple Sclerosis Society Task Force on Clinical Disability Measures, the original proponents of the MSFC, is currently re-evaluating this test, and propose

analysis of new datasets in order to better define the clinical meaning of each MSFC component and to adjust its scoring system to make it more straightforward to interpret (Ontaneda et al., 2012). Nevertheless, there may be room for further improvement beyond the current manifestation of the MSFC. In a study of employment status among patients with MS, the SDMT was a better predictor of MS-related retirement than PASAT among these patients (Strober et al., 2014). The SDMT is also easier to administer than PASAT and patients prefer it (Drake et al., 2010; Walker et al., 2012). Alternatively, longitudinal data suggested that SDMT may be useful as a substitute for PASAT in the MSFC (Brochet et al., 2008). Validation of a single form of the SDMT for universal use is needed, as described above, if SDMT is to replace PASAT within the MSFC.

Expert opinion published elsewhere suggests that additional tests beyond the MSFC may be needed for the management of MS (Cohen et al., 2012). The lack of a sensitive measure of visual disability is another important limitation of the MSFC and the measurement of low-contrast letter acuity scores has been shown to add important clinical information beyond that measured by the MSFC (Baier et al., 2005). Accordingly, experts have also called for inclusion of a visual acuity test (e.g. low-contrast visual acuity) to the MSFC (Balcer et al., 2003; Polman and Rudick, 2010; Schinzel et al., 2014). As in other fields of medicine, patient-reported outcomes are increasingly important considerations in MS and the use of an internationally validated, MS-specific instrument for measuring QOL within the MSFC may provide a more complete assessment compared with the use of the MSFC as it stands currently.

DAF status, as an alternative composite outcome, may also have an important role in determining the effectiveness of disease-modifying therapies for MS. Recent intervention trials have used this measure as an index of the protective effect of disease-modifying therapies (Giovannoni et al., 2011; Havrdova et al., 2014).

## 8. Conclusions

The measurement of functional outcome measures in people with MS has been dominated by the measurement of disability, particularly ambulation, as assessed by the EDSS. The widespread adoption of the MSFC has broadened the assessment of functional outcomes to include a measure of cognitive function (PASAT), in addition to upper limb dexterity (9-hole peg test). However, growing evidence suggests potential benefit from replacing PASAT with the SDMT. In addition, maintaining quality of life is an important goal of treatment for patients with MS, as with other conditions, and the addition of a quality of life instrument specific for MS would improve the utility of the MSFC further. Other functional outcome measures relating to visual acuity (e.g. low-contrast visual acuity testing) or relapse rates may also have a role in future.

Measuring and maintaining quality of life is a particularly important goal, not only for patients with MS but also for the evaluating physician, who needs to be able to assess the impact of disease progression and therapeutic interventions on the patient as a whole. We recommend that the additional time needed to apply a validated multi-dimensional Qol instrument during a consultation is a worthwhile

investment that will yield important information on the real clinical status of our patients.

### Conflict of interest statement

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

- We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.
- We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

### Role of funding source

The expert group described here met during a meeting organised by and funded by Merck Serono. Accordingly, all co-authors have acted as honorary consultants to Merck Serono. Dr Amer Amous is an employee of Merck Serono. A medical writer (Dr Mike Gwilt GT Communications, funded by Merck Serono) provided editorial assistance in the development of the manuscript.

- This is a review manuscript and therefore no work covered has involved either experimental animals or human patients
- We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.
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### Acknowledgements

The expert group described here met during a meeting organised by and funded by Merck Serono. Accordingly, all co-authors have acted as honorary consultants to Merck Serono. Dr. Amer Amous is an employee of Merck Serono. A medical writer (Dr. Mike Gwilt, GT Communications, funded by Merck Serono) provided editorial assistance in the development of the manuscript. The authors retained full control over the content of the manuscript.

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