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Redefining functionality and treatment efficacy in multiple sclerosis

John F. Foley, MD
David W. Brandes, MD, MS, FAAN

ABSTRACT

Although our understanding of multiple sclerosis (MS) has grown exponentially in the past century and a half, there is still some divergence between physicians’ perceptions of effects of MS on patients and those of the patients themselves. This article examines current practices in MS assessment and clinical trial design, highlighting certain deficiencies associated with commonly used measurement techniques (e.g., the Expanded Disability Status Scale and MRI) that are reflective of these discrepancies. In particular, the authors note that there is only minimal clinical awareness of the effects of MS on patient quality of life (QoL). We posit that QoL elements including impaired cognition, fatigue, pain, a variety of visual disturbances, depression, and degrading social function may have at least as much impact on people with MS as ambulatory issues. And because QoL measures often do not correlate with Expanded Disability Status Scale or MRI findings, we recommend that QoL be assessed independently. Various validated measures do exist to assess QoL elements, which are outlined here, along with thoughts on how to incorporate these into regular patient management visits. Ultimately, we believe that expanding on the traditionally accepted definitions of “functionality” and “efficacy” will allow for the adoption of a more holistic picture of MS and its impact. NEUROLOGY 2009;72 (Suppl 5):S1–S11

Frequently, the physician perception of any given disease state is quite different than the patient-perceived experience of the disease. Physicians tend to focus on the clinical profile, disease mechanism, and therapeutic intervention, whereas the patient experience encompasses complex social, psychological, political, and personal elements as well.

As happens with many chronic diseases, our understanding of exactly what multiple sclerosis (MS) is, including its progression, its impact, and how best to manage it, has changed throughout the history of the disease.1 In early descriptions (cf. Charcot 1868), the disease was defined by autopsy-driven pathophysiology, recognized only late in the disease process, and labeled as incurable.1 Fortunately, years of discovery and clinical and technologic advances have resulted in an evolution in MS diagnosis, most recently represented in the McDonald Criteria, introduced in 2001 and subsequently revised in 2005 to allow for simplified, accelerated diagnosis.2 Similarly, familiarity with the way MS affects its victims has increased over the last 140 years. It is now fully accepted that MS is a complex disease with a relatively unpredictable course that may be different for every patient, affecting multiple domains including physical, cognitive, and psychological function, and requiring both subjective and objective evaluations.

Why, then, do we so often address only limited areas of impact when assessing patient functionality and determining treatment efficacy? In most trials and treatment settings, focus is placed almost exclusively on physician-centered MS-defining parameters. When we assess patient functionality, we tend to look only at limited physical and ambulation parameters. Likewise, our evaluation of treatment efficacy is generally limited to these relatively insensitive met-
support a more holistic picture of the disease and its manifestations. It is our position that in addition to adding QoL considerations to regular patient assessments, future MS clinical trials should include endpoints that encompass multiple domains, expanding on the traditionally accepted definitions of “functionality” and “efficacy” to include the quality of life (QoL). QoL is represented by a multitude of elements including the disease-related presence of comprehensive cognitive issues, fatigue, physical dysfunction, pain, a variety of visual effects, emotional disturbance, and social function. Table 1 presents a list of extra-ambulatory issues reported by many people with MS.

Researchers in many areas are already aware of the importance of QoL. More than 15 years ago, in an early and influential book on the subject, Patrick and Erickson posited that health-related QoL measurement was essential in chronic disease. They noted that physiologic measurements, while informative for clinicians, do not adequately represent patients’ interests, which are often more closely related to functional capacity and a sense of well-being (and which patients can almost “measure” themselves). They also pointed out that a group of patients who all have the same physical manifestations of a chronic disease may well have extremely diverse self-reported psychological responses. This reinforces the belief that physical/neurologic effects may not give a full view of disease impact. It is our position that in addition to adding QoL considerations to regular patient assessments, future MS clinical trials should include endpoints that encompass multiple domains, expanding on the traditionally accepted definitions of “functionality” and “efficacy” to support a more holistic picture of the disease and its impact, and that this evolution can and should take place concurrently in the office setting.

Current state of affairs. Many neurologists agree that there are a number of extraphysical elements that should be considered when assessing MS impact and treatment efficacy, including the “hidden reservoir of morbidity” realized in multiple sensory symptoms (pain, fatigue, dizziness, etc), and social/psychological/emotional issues. Nonetheless, standard measurements of MS severity, primarily the Kurtzke Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC), focus almost entirely on physical functionality (although cognitive impairment is partially evaluated as well). Similarly, evaluation of therapeutic effectiveness in MS revolves around decreasing severity and delaying long-term disability using short-term surrogate markers for disease progression via MRI and clinical activity.

Current clinical markers used to assess disease activity include annualized relapse rate, time to first relapse, and probability of freedom from relapse for a specified period of time. MRI markers include gadolinium-enhancing lesions, new T2 lesions, or a combination of the two. Although they have been a valuable element in gold-standard MS diagnosis and monitoring since their use was validated, current MRI metrics are inadequate to fully assess disease progression, especially as it relates to gray-matter disease. An emerging body of research is showing that advancing MS pathology is more comprehensive than typically measured MRI findings indicate; in fact, Daumer et al. conducted a survey of 31 trials in which MRI was used as an outcome. The authors concluded that the existing MRI measures provided little, if any, ancillary value beyond relapse and disability outcomes, and suggested that other surrogate markers should be validated. Other publications support this recommendation, and reinforce the importance of exploring gray-matter and whole-brain atrophy in MS. For example, recent studies have found that gray-matter damage, which is not effectively detected through MRI, may be more pronounced than white-matter damage, especially early in the disease process, and can have considerable impact on clinico-cognitive functioning and neuropsychological deficits. New approaches to MRI assessment are being actively pursued, including MR spectroscopy and quantitative atrophy measures, as well as diffusion tensor imaging.
bral/mental (and “other”)—are rated on a scale of 0 to 5 or 6, with 0 being “normal.”16 These Functional Systems Scores (FSS) are combined with an assessment of mobility, and an EDSS score is assigned. EDSS scores range from 0 to 10 in half-point increments, with 0 representing a normal neurologic examination and 10 indicating death due to MS.16

Many researchers and clinicians are also using the newer MSFC. The MSFC was designed to supplement the EDSS and is growing in popularity as an alternative measure.17–19 This newer assessment tool includes disease-specific, psychometrically sophisticated clinical outcome measures that evaluate both cognitive and physical domains throughout the course of illness. It uses three quantitative tests: the Timed 25-Foot Walk (T25-FW, testing leg function), 9-hole Peg Test (9-HPT, testing arm function), and Paced Auditory Serial Addition Task (PASAT-3, testing cognitive function).17,20 The MSFC, designed to be more patient centered than the EDSS, has greater responsiveness to change than the standard scale, at times even predicting change in the EDSS.21 It has also been shown to have good validity, sensitivity, and inter-rater and test-retest reliability. Some trials have found that the MSFC has better measurement precision than the EDSS and is superior in detecting differences between groups.18

There is a potential for MSFC sensitivity to practice effects, but this can be mitigated by having patients take three or four “practice” tests before baseline measurements are obtained.20,21 The MSFC score is a continuous variable that can have both parametric and nonparametric statistical analysis.20

**Issues with current measurement modalities.** Although the physician-reported EDSS has numerous strengths and addresses shortcomings of earlier clinical measures,16,22 it does have a number of limitations. One of these is the fact that EDSS scoring is not linear, meaning that parametric statistical analysis cannot be used. In addition, certain function- or domain-specific, as well as psychometric, deficiencies have been identified.22 Function- or domain-specific limitations include being weighted too heavily toward lower-extremity disability with poor measurement of upper limb function;17 poor measurement of cognitive function;17 limited ability to discriminate disability vs QoL;22 and lack of attention to common symptoms such as pain and fatigue in patients with less disability.23 Psychometric deficiencies include poor validity, responsiveness, and intra-rater reproducibility.22,24 Perhaps, most important is the limited utility of the measure at the bedside, with poor sensitivity to clinical change not associated with impaired gait and in patients with milder disease.25,26 As previously suggested, the areas not adequately addressed by the EDSS are vital to patient experience and QoL. Cognitive function, fatigue, pain, visual issues, depression, and social function may be at least as important to understanding outcomes of therapy as measures of neurologic function and mobility. Studies have already shown that the broad area of overall health-related quality of life (HRQoL), including physical, psychological, social, and environmental aspects of health, has important ramifications in patients with MS.27,28 In one study, multivariate analysis of contributors to HRQoL in patients with MS showed that impairment in mental function (including cognitive, emotional, and sleep functions) was most closely related of all domains to decreased QoL. Limitations in basic movement activity, conversely, were less related than anticipated.27 In another study, health-related QoL was shown to be a strong predictor of disability measured by the EDSS 1 year later. HRQoL measurements may, therefore, be useful in decision making when deciding on a patient’s course of treatment.29 The following paragraphs will examine the impact of a number of factors that affect QoL.

One area crucial to QoL, and addressed in only a limited way with the EDSS, is cognition. This is an important oversight, as cognitive deficits are present in up to about 70% of people with MS, although intelligence appears to remain relatively intact and dementia is rare.30 “Cognitive deficit” is a broad category, encompassing recent memory recall, attention and concentration, information processing speed, executive functions including multitasking, reasoning, problem solving, and visuospatial perception.30–32 Not surprisingly, then, compromise in cognition has the potential for vast effects on patients’ lives, relationships, and ability to function in society. Notably, there appears to be little correlation between conventional measurements of disease burden and cognitive deficit in MS.33 However, relatively recent advances in imaging have revealed some correlation between cognitive loss and cerebral damage (including lesion volume, third ventricle size, and overall cerebral atrophy).31 And newer information suggests that tissue destruction, tissue repair, and adaptive functional reorganization are all elements of cognitive impairment, which may be associated with damage to normal-appearing brain tissue.33,34 This implies that assessing cognitive impairment may give important clues to the severity of disease. It is also important to be aware of the possibility that people with MS are using cognitive reserves, as defined by Stern35 for some time in the early and middle stages of the disease, and that damage may be more extensive than is apparent before measurable cognitive deficits appear.
Table 2 presents a summary of the impact of cognitive impairment.

Fatigue, another major factor in QoL, ultimately occurs in almost 75% of people with MS—on a daily basis in at least 65%—and is one of the most disabling symptoms of the disease, interfering with and considerably limiting daily activities and communication (table 3). Nonetheless, it is only minimally included in the EDSS, where it is usually considered in either the “sensory” or “other” functional system. Fatigue, which has been identified by many patients as one of the worst symptoms of MS, tends to increase in the earlier stages of decreasing functional ability, but remains stable once “abnormal gait” is reached. Hence, worsening fatigue may be a good indicator of early disease progression.

Another factor not considered in the EDSS is pain. Pain is increasingly recognized as a major aspect of MS, occurring in up to 86% of patients. Like fatigue, pain is often described as one of the worst symptoms of MS. Chronic pain, including lumbar and dysesthetic extremity pain, is most commonly reported, and may have a range of causes, including neuropathic demyelinated lesions, spasticity, and poor posture. See table 4 for a summary of the impact of pain. Although it may occur at any stage of the disease, the presence of pain appears to be correlated to greater age, higher EDSS, longer duration of disease, and the presence of primary or secondary progressive MS.

The impact of impaired vision is summarized in table 5. Although “visual” is one of the functional systems considered in the EDSS, its scope is overly broad. Visual disturbances such as optic neuritis are usually herald the onset of MS, and may affect as many as 80% of patients at some time in the course of the disease. Notably, monosymptomatic optic neuritis can be a predictor of MS even in patients with normal MRI findings. Optic neuritis has many presentations and a variable course: vision loss is usually unilateral but may sequentially involve the other eye. In other patients, optic neuropathy may be present but asymptomatic. Other common MS-related ophthalmologic issues are movement abnormalities, including nystagmus, oscillopsia, diplopia, internuclear ophthalmoplegia, and ocular inflammation. Recent studies suggest that visual acuity may be a reflection of CNS status, and that visualizing the retina through imaging studies such as optical coherence tomography may help model the course of disease.

Another area of impact, which is often interconnected with a number of others, is depression (table 6). In the functional systems used by the EDSS, the only assessment that hints at depression is in the “cerebral functions” section, where it is virtually dismissed—a score of 1 (almost normal) is indicative of “mood alteration only,” and does not affect the EDSS score. However, studies have found depression to be more common in MS than in some other chronic or fatal diseases, with a lifetime prevalence...
that may be as high as 50% (compared with rates of 9% to 11% in people with amyotrophic lateral sclerosis). Much research has centered on the interaction of depression with disease progression, as well as signs and symptoms that might be expected to go hand in hand with depression, like physical disability, cognitive dysfunction, fatigue, and pain. Notably, there is some disagreement about the relationship between depression and disease progression: one study found no close relationship, and earlier research suggests only limited relationships between depression and the signs and symptoms listed earlier. However, recent findings do indicate that depression may be correlated with fatigue, anxiety, and functional limitation. Research continues in this area, and it has recently been suggested that four variables—social support, coping, conceptions of the self and illness, and stress—could further explain the relationship between depression and common MS sequelae like fatigue, physical disability, cognitive dysfunction, and pain. This suggestion may help lead to more effective recognition and treatment of depression.

Although more women than men with MS—as in the general population—may experience depression, clinicians should be aware that men with MS are also fairly likely to experience depression at some point in the course of the disease; in fact, one study of 607 people with MS determined that gender was not a significant predictor of depression. Clinicians should be aware of this potential, as well as the fact that, based on our sociological views on gender roles, men may be less likely to self-identify depression, or may be less forthcoming about the presence of depressive symptoms. Given the high prevalence of depression in MS, all patients should be educated that certain apparently somatic symptoms, like sleep disturbances, fatigue, or slowing in behavior, may in fact be related to depression.

Finally, strongly connected to physical signs but largely ignored in the EDSS, degrading social function can be a major factor in the lives of patients with MS. Indeed, many psychosocial factors are far more closely tied to QoL than physical aspects like number or extent of MRI lesions. Under the umbrella of social functioning are a number of subcategories, including coping, self-efficacy, ability to work or carry out normal tasks, and ability to participate in daily activities.

Toward a new definition of functionality. No single tool is adequate for comprehensive functionality assessment. Historically, patient’s experience has not always been a fundamental element in assessment. Rather, the construct of “functionality” has traditionally addressed investigators’ needs (i.e., concrete, quantifiable, objective measures). Moving forward, it is essential that we redefine functionality to include the aspects of QoL that are at least as vital to the patient as the neurologist-defined measures of disease severity and progression.

Toward a new definition of efficacy. The ultimate goal of every practitioner treating people with MS is to minimize disability progression and maximize QoL. Having redefined functionality to include QoL, it is likewise time to redefine our concept of “effectiveness” of disease treatment to reflect this evolution in understanding, moving beyond the domains of relapse and mobility and including serial measurements of functional domains in context throughout the course of the disease. It is also important to recognize that additional domains may change more rapidly than standard measurements. This means that testing should be performed at regular intervals to ensure that management strategies are meeting patients’ needs, and to make therapeutic alterations as necessary—even in the absence of relapse or loss of mobility.

As an example, efficacy assessments in clinical trials should include both neurologist-derived and patient-derived measures to provide results that may better translate into the practice setting. Likewise, in practice, measures of efficacy should expand beyond the disease metrics currently generally used by investigators, like relapse rate and quantified neurologic impairment; they should also include domains that are maximally meaningful to patients, like QoL or social functioning measures.

Although MS HRQoL may not directly map to disease activity or progression, physical scales, or MRI findings, QoL measures can be complementary to neurologist-derived disease measures assessing neurologic disability or impairment. Elements of QoL are important determinants of overall health status and, because they measure the impact of disease on the patient, they allow for a new, “net” assessment of the effectiveness of therapy. Adding measures such as general well-being and social and

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**Table 6** Impact of depression

<table>
<thead>
<tr>
<th>Lifetime prevalence</th>
<th>Up to 50% of people with MS</th>
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<tr>
<td>Effects</td>
<td>May present with confounding MS symptoms including</td>
</tr>
<tr>
<td>- Fatigue</td>
<td></td>
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<tr>
<td>- Sleep disturbances</td>
<td></td>
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<td>- Slowed movement</td>
<td></td>
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<tr>
<td>- Weight loss</td>
<td></td>
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<td>- Negative self image</td>
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<tr>
<td>Testing modalities</td>
<td>BDI; SF-36; MSNQ</td>
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</table>

MS = multiple sclerosis; BDI = Beck Depression Inventory; SF-36 = Short Form-36; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire.
Researchers in MS are already exploring the importance of QoL. Although some may believe QoL to be an amorphous measurement not suited to clinical study, this is not the case. In fact, general QoL and even MS-specific QoL are quantifiable through the use of existing, validated scales, making it a clinically viable efficacy measure. Indeed, between 1992 and 2002, 83 MS studies were conducted using QoL questionnaires. Twenty-seven of these were focused on the use of QoL scales in MS; 37 actually assessed QoL in patients with MS, attempting to relate it to various other measurements and factors, and 19 examined QoL as an outcome measure. Despite this consideration, QoL measurements are almost never fully integrated into clinical study methodology. In fact, very few phase 3 MS trials have integrated HRQoL measures into their outcomes. One of the reasons for this may be the challenges inherent in developing and validating QoL scales. However, there are already a number of validated options, and expansion of the assessment methodology may very well lead to improved disease management practices, increased disease stability, and better QoL.

Some of the scales that have been introduced relatively recently to assess the impact of MS on patients’ QoL include:

- The Multiple Sclerosis Impact Scale-29 (MSIS-29), introduced in response to a need for patient-based measures of outcome that maintained the scientific viability of accepted efficacy scales. Created for use in both clinical trials and in practice, this 29-item scale was developed with the assistance of patients with MS, and measures both physical and psychological impacts of MS. The MSIS-29 appears to have good responsiveness and sensitivity to patient-defined important changes.

- The 36-item Medical Outcomes Survey Short Form (SF-36), which is one of the components of the Multiple Sclerosis Quality of Life Inventory. The SF-36 includes eight health-concept scales with 2–10 items each (physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and two summary measures (physical health, encompassing the first four measures, and mental health, encompassing the latter four). The SF-36 provides a more differentiated picture than the EDSS, and may be used as complement to the EDSS. Nortvedt and Riise reported 53 MS studies published between 1995 and 2001 that used the SF-36, and noted that the questionnaire is generally valid for MS, although the physical functioning scale has a potentially obviating floor effect in severely disabled patients, and some researchers have noted that the utility of the SF-36 might be limited by not having questions specific to MS. Because of the wide confidence intervals surrounding individual scores, the SF-36 is most appropriately used for group comparisons, not individual treatment decisions; clinicians should bear this last consideration in mind when structuring clinical trials or examining clinical trial reports.

Other scales used in MS clinical studies that include QoL components include the Health Utilities Index Mark III, the EQ-5D, the WHOOQL-BREF, the Disability and Impact Profile, and others. In addition to these broader scales, several specialized instruments are available that may help capture treatment efficacy in other specific MS areas of concern beyond the reach of the EDSS. These areas include the following:

- Cognitive function, which is often measured through the Paced Auditory Serial Addition Test (PASAT-3 or PASAT-2). The PASAT-3, which is the third component of the MSFC, assesses working memory, processing speed and flexibility, and simple calculation ability. Different neuropsychological elements of cognitive impairment can be measured using the Symbol Digit Modalities Test, in which patients look at a list of symbol/number combinations and then, when shown a random symbol, identify the correct corresponding number, or the Multiple Sclerosis Neuropsychological Questionnaire, a self-administered questionnaire for patients and caregivers that assesses cognitive and neuropsychiatric issues.

- Fatigue, which can be assessed using the 9-item Fatigue Severity Scale (FSS), the 21-item Modified Fatigue Impact Scale, or Simple Visual Analogue Scales (VAS) depending on the ultimate purpose of the results.

- Physical disability. Mobility, the most commonly assessed element of physical disability, can be measured with the Patient-Determined Disease Steps, a patient-reported tool that defines midrange mobility more precisely than the EDSS, or with the T25-FW, an element of the MSFC that can also be used independently. It is important to remember that disability is not limited to ambulatory issues, and may affect the upper body as well. The finger-tapping test is one relatively sim-
ple way of assessing psychomotor dysfunction in the upper body.55,56

- Pain. Although few relevant pain instruments exist for testing in patients with MS (apart from the bodily pain component of the SF-36), standardized questionnaires with visual analogues can help determine type and severity. Mechanical measurement, as with an algometer, has been used in some studies.39

- Visual acuity, which has been assessed by measures including the Optic Neuritis Treatment Trial Patient Questionnaire, the 25-Item National Eye Institute Visual Function Questionnaire-25, and the 7-item MS Vision Questionnaire-7.42 Sloan low-contrast letter acuity charts have also proved a valid measure in clinical trials of MS therapies that reflect sustained visual change and underlying function.43

- Emotional state, which in MS is often manifested as depression. Clinical assessment tools used in recent trials include the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression (HRSD or HAM-D), the SF-36, and the single-item Subject Global VAS.47,51,57 The Multiple Sclerosis Neuropsychological Questionnaire, discussed earlier, also has some utility in this area.36

Given the number of areas affected by MS, as well as the number of scales available to test for various aspects of disease impact, it seems clear that measurement of clinical efficacy cannot be considered complete unless all areas that affect patient QoL are addressed.

Practical considerations. Knowing, then, that functionality in MS means far more to patients than simple mobility, and that assessment of disease impact and therapeutic effectiveness must include functional, imaging, and psychosocial modalities, how can clinicians make sure that appropriate steps are being taken to maximize their patients' QoL? First and foremost, by including broader measurements than the EDSS. One of these, which is in the process of validation, is the Patient-Determined Disease Steps, a surrogate measure of the EDSS.4,58 A similar tool, the Performance Scales, include subscales addressing mobility, hand function, bladder and bowel control, fatigue, vision, cognition, and sensory affects, and spasticity.58 Measures like these may provide a broader range of data and possibly a more informative understanding of treatment efficacy than previous scales and measures, because they rely on patients' views and can correlate to more standard objective scales.

Office-based clinical management can also benefit from a multidisciplinary approach to functionality assessment. For example, when monitoring disease progression, clinicians should consider periodic quantitative assessment of such areas as functional status, health-related and other quality-of-life issues, and cognitive function, along with traditional assessments of disease progress and severity, including...
tracking MRI findings over time and measuring relapse rates. Similarly, the approach to therapeutic interventions should include consideration of multiple efficacy outcomes.\textsuperscript{59} It is only based on this overall assessment of disease status that appropriate judgments regarding treatment choices can be made.

To these ends, Frohman et al.\textsuperscript{59} suggest using a specific recording instrument to be integrated into the medical record, that includes fields for many patient- and investigator-implemented measures. These measures comprise not only fully objective entries: disease-modifying agent information, MS subtype, EDSS score, T25-FW, 9-HPT, PASAT, and MRI findings but also more subjective ones: patient’s examination, QoL information via VAS or QOL-54, fatigue scale, depression scale, and Activities of Daily Living. Notably, not every test needs to be conducted at every visit, and using this simple instrument allows a series of records to be easily compared serially across visits to allow objective examination of subjective opinions about disease stability or breakthrough.

Figure 1 provides an example of what this type of recording instrument might look like for practices that use electronic medical records (EMR).

Using this type of recording tool across patient visits provides a good visual representation of changing patient status. In this case, we can see, graphically, how this hypothetical patient’s condition is deteriorating, particularly between the second and third visits (figure 2).

Alternatively, it is possible to track each measurement separately.

Practitioners who do not have access to EMR can still use similar tools. It is simple to set up a spreadsheet and print it out for office-visit use. Figure 3 presents an example, using the same categories as the EMR shown in figure 1 and adding finger tapping and visual acuity.

Using this type of recording tool, although it will not automatically generate progress graphs, will allow you to track patients’ disease progression at a glance.

Another benefit to this type of instrument is its flexibility: it can be easily adapted for individual practices.

### Table 1: Example of Recording Instrument

<table>
<thead>
<tr>
<th>Date</th>
<th>ARR</th>
<th>Exam Worsening</th>
<th>MRI GD Status</th>
<th>Lesion Burden Increase</th>
<th>FSS</th>
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Figure 2: Hypothetical patient progress tracking with EMR

Key Performance Indicators

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different scales may be used at different visits to meet time constraints, and many measurements can be made by ancillary personnel. And quite a few of these tests—especially the self-administered measures—can be easily and relatively quickly undertaken during routine visits, providing a useful, well-rounded picture of the patient’s status over time. For example:

- The MSFC, comprising the T25-FW, the 9-HPT, and the PASAT-3 take only about 20 minutes in total, with minimal special equipment required. These tests should be conducted on an annual basis. More information about the MSFC, including equipment descriptions and test directions, can be viewed on the National MS Society’s Web site, www.nationalmssociety.org. The researchers’ section of this site also includes information about a number of other measures used for MS assessment.
- The Fatigue Severity Scale (FSS) consists of nine quantitative questions about fatigue, which patients rate on a scale of 1 (strongly disagree) to 7 (strongly agree) with higher cumulative scores indicating higher levels of fatigue. This test can be self-administered without clinician or staff assistance as patients are in the waiting room, and should be administered at every visit. The full scale can be seen in the article by Krupp et al.
- The BDI and the HAM-D consist of 21 and 17 multiple-choice questions, respectively. Like the FSS, these tests can be self-administered as patients are in the waiting room, and should be administered at every visit. Copies of the BDI can be ordered from Pearson, online at http://pearsonassess.com. The HAM-D can be found in Hamilton.
- The Lawton Activities of Daily Living is another quantitative scale that involves asking patients to identify their abilities relative to everyday activities including using the telephone, shopping, food preparation, housekeeping, laundry, transportation, medication management, and ability to handle finances, and scoring the responses. This test can be administered by office staff with minimal training, and should be administered twice annually. The full scale is available in Lawton and Brody.
Other validated patient-reported scales, such as the Performance Scales and the MS Symptom Inventory, discussed earlier, might also be considered to offer insight into efficacy of therapy and patients’ functioning. In addition, important insights may be gained by inviting caregivers and/or family members to provide their assessments of changes in a patient’s condition or functionality.

**CONCLUSION** We are entering a new era of increasingly complex MS therapeutics, many of which are associated with significant risk and potentially greater efficacy. This milieu demands accurate diagnosis and thorough, comprehensive evaluation across all clinically germane domains performed in a reproducible fashion over multiple time points. Breakthrough disease is optimally rapidly recognized and assessed for potential therapeutic agent crossover. Well-validated, effective tools have been developed, which have greatly expanded our ability to assess global functionality. Time constraint during patient visits is a well-recognized issue in routine clinical practice. Our challenge at this point, then, is to optimize the efficiency with which we can gather this information in a way that can be practically pursued with each office visit. Ultimately, global functionality is really what matters to both patients and their healthcare providers. And with true functionality information in hand, healthcare providers can assess treatment efficacy more accurately and thus modify treatment regimens with greater success.

**REFERENCES**

Redefining functionality and treatment efficacy in multiple sclerosis
John F. Foley and David W. Brandes
*Neurology* 2009;72;S1-S11
DOI: 10.1212/WNL.0b013e3181a99bc2

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