Assessing Quality of Life in Patients with Multiple Sclerosis

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Health-related quality of life (HRQOL) is an important consideration for patients with a chronic disease such as multiple sclerosis (MS). We conducted a review of published articles and conference proceedings to evaluate the use of patient-reported measures of HRQOL in MS. A variety of HRQOL measures are used in MS research and clinical practice settings. Generic HRQOL instruments lack domains considered important to MS patients and are subject to significant floor and ceiling effects when used in MS patients. MS-specific instruments, including the Multiple Sclerosis Quality of Life–54, Multiple Sclerosis Quality of Life Inventory, and Multiple Sclerosis International Quality of Life, offer both advantages and limitations in assessing HRQOL in MS patients. Only a few reports on the use of these instruments to assess HRQOL outcomes in clinical studies have been published. MS-specific instruments hold the most promise in the assessment of the relationship between disease-modifying drug treatment and HRQOL in MS patients. Further research is needed to better understand the limitations of MS-specific HRQOL instruments in assessing HRQOL outcomes in clinical studies. Future MS drug therapy trials should include the use of MS-specific instruments to prospectively assess HRQOL as a study outcome. Int J MS Care. 2010;12:34–41.

The consideration of patient health-related quality of life (HRQOL) is intrinsic to the practice of medicine, particularly when evaluating different therapeutic approaches to chronic disease. Relapsing-remitting multiple sclerosis (RRMS) is a chronic disease that over time negatively affects HRQOL. In chronic debilitating diseases such as MS, long-term preservation of HRQOL should be regarded as a critical marker of therapeutic success. HRQOL is the distillation of almost every aspect of the patient’s existence, including perception of treatment benefit and functional decrements of disease progression. Clearly, then, the utility of HRQOL measurement tools depends on their ability to accurately and consistently quantify quality of life (QOL) over the course of the disease. This difficult endeavor is further complicated by therapeutic options that may themselves significantly affect HRQOL, necessitating consideration of both positive and negative effects on quality of life.

In clinical practice, communication between patients and health-care providers is enhanced through HRQOL assessment. This has been demonstrated in research involving oncology patients. Like MS, oncologic conditions may worsen over time despite appropriate management. In one study, most patients (87%) and all oncologists (100%) believed that the use of HRQOL instruments enhanced patient-physician communication and was beneficial. Oncologists who administered HRQOL tests were more likely than those who did not to identify moderate-to-severe health problems and to provide suggestions for managing them. Although, to our knowledge, a similar study has not been performed involving MS patients, the same benefits could apply. Unfortunately, researchers have found that MS patients and neurologists do not agree on which aspects of MS have the most impact on HRQOL. Yet agreement is critical because health-care provider awareness of patients’ HRQOL may indicate which patients may benefit most from treatment. In fact, some data indicate that patients with the poorest HRQOL may respond better to MS therapies than patients with relatively high...
HRQOL. Therefore, HRQOL measures could be used in the consideration of treatment strategies.

As important as HRQOL measurement is in clinical practice, it is equally critical to the study of MS therapies. These trials reveal the therapeutic effect on objective measures of disease as well as on the quality of patients’ lives. Therefore, this article surveys current efforts to measure HRQOL in patients with RRMS, with an emphasis on three promising MS-specific instruments: the Multiple Sclerosis Quality of Life–54 (MSQOL-54), the Multiple Sclerosis Quality of Life Inventory (MSQLI), and the Multiple Sclerosis International Quality of Life (MusiQOL).

Methods

We performed a search of the published English-language literature (May 1, 1990, to May 15, 2008) in Ovid (EMBASE and MEDLINE), PubMed, and online proceedings of MS conferences in 2007 and 2008 using the keywords “multiple sclerosis” and “quality of life, health-related quality of life, disability, MSQOL-54, MSQLI, or MusiQOL.” Articles and conference proceedings were reviewed for relevance to HRQOL in MS patients; we specifically looked for research that assessed instrument development or validation (ie, HRQOL instruments used in MS populations) and disease-modifying drug trials that measured HRQOL as an end point.

Measuring Quality of Life in MS

Objective measures of the effectiveness of MS therapies used in clinical practice, including the Kurtzke Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) score, magnetic resonance imaging (MRI), and relapse rates, provide important information regarding disability and clinical disease activity in patients with MS but generally exclude several factors important to patients’ HRQOL. For example, the MSFC is a composite measure that assesses MS-related disability; although it indirectly helps to measure facets of MS that often affect HRQOL, it is not an HRQOL instrument. As a result, instruments have been developed to help health-care providers accurately and completely assess MS patients’ HRQOL, particularly when determining disease-related aspects likely to affect patients’ lives.

Several generic and disease-specific instruments have been used to assess HRQOL in patients with MS (Table 1). Most generic instruments assess basic HRQOL issues that may be applicable to all diseases and allow cross-comparisons between disease states, whereas disease-specific HRQOL instruments are designed to address particular health-related effects for the disease being studied. Generic instruments are limited in their ability to discern HRQOL differences in MS patients. For example, the Medical Outcomes Study 36-item Short Form Health Status Survey (SF-36) is a popular HRQOL instrument used in research because of its simple format and comprehensive measures. It is a multi-item scale that assesses eight domains: role limitations (both physical and emotional), functioning (both social and physical), pain, mental health, vitality, and general health perspectives. Although it is useful in capturing the overall impact of disease, it has limited ability to detect subtle disease-specific changes and may not be appropriate for MS patients. In MS clinical studies that used the SF-36 in a patient population with a narrow range of disease severity, the utility of the instrument was diminished because of significant floor (physical function, emotional and physical role limitations) or ceiling (pain, emotional role limitations) effects.

According to accepted criteria, floor and ceiling effects occur when more than 20% of respondents designate their answer as the highest or lowest value on the scale. Thus, disease-specific HRQOL instruments are needed that minimize floor and ceiling effects.

Identification of a reliable, accurate, and accepted instrument for measuring HRQOL in MS has been difficult for several reasons. Lack of standardization in the choice of HRQOL instruments used for clinical studies has led to inconsistent findings, making interpretation and comparison between studies and MS therapies difficult. Use in the clinical setting has been difficult because most established HRQOL instruments were designed for use in clinical studies and are often time-consuming to complete, may require trained test administrators, and are validated for comparison between groups of patients over short periods, rather than assessment of changes in individuals over time. Factors such as cost, feasibility, and clinical relevance, as well as a lack of defined thresholds for treatment intervention, also may limit the utility of standard HRQOL measures in the clinical setting.

Another inherent difficulty in longitudinal assessment of HRQOL is the phenomenon of “response shift,” in which changes occur in individuals’ internal standards, values, or conceptualization of HRQOL over time. Thus, in addition to changes in QOL over time, patients’ perceptions of what health and QOL mean to
### Table 1. Validated health-related quality-of-life instruments

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<tr>
<th>Measure</th>
<th>Generic instruments</th>
<th>Multiple sclerosis–specific instruments</th>
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<tr>
<td></td>
<td>EQ-SD(^7,8)</td>
<td>HRQOL-MS(^14)</td>
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<td>HUI(^9)</td>
<td>MSQOL-S(^16)</td>
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<td>SF-36(^10)</td>
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<td>NHP(^11)</td>
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<td>SIP(^12)</td>
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<td>DIP(^13)</td>
<td>Musi-QOL(^22)</td>
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<td>LMSQOL(^16)</td>
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<td>HRQOL-MS(^15)</td>
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<td>Bladder/bowel/sexual function</td>
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**Abbreviations:** DIP, Disability and Impact Profile; EQ-SD, EuroQOL; FAMS, Functional Assessment of Multiple Sclerosis; HRQOL-MS, Health-Related Quality of Life in Multiple Sclerosis; HUI, Health Utilities Index; LMSQOL, Leeds Multiple Sclerosis Quality of Life; MSIS-29, Multiple Sclerosis Impact Scale; MSQOL, Multiple Sclerosis Quality of Life Inventory; MSQOL-54, Multiple Sclerosis Quality of Life–54; MusiQOL, Multiple Sclerosis International Quality of Life; NHP, Nottingham Health Profile; PS, Performance Scales; QALY, quality-adjusted life-year; QOL, quality of life; RAYS, RAYS Scale; SF-36, Medical Outcomes Study 36-item Short Form Health Status Survey; SIP, Sickness Impact Profile; VAS, visual analogue scale.

\(^a\)Short, <10 minutes; moderate, 10–44 minutes; long, ≥45 minutes.
them may also change. In one study, MS patients treated with interferon beta-1b (IFNβ-1b) displayed considerable change in the importance of various HRQOL dimensions. For example, the relative value of the patients’ neurologic symptoms and psychosocial limitations increased over time, whereas the relative value of functional status decreased. Thus, response shift can affect the validity and reliability of an HRQOL measure over time. When not accounted for in HRQOL assessments, response shifts can mask differences between groups and cause underestimation of treatment effects, resulting in paradoxical or ambiguous findings.

These limitations in both research and clinical practice settings indicate the need for an HRQOL instrument that can accurately and completely assess HRQOL in the MS patient. Three MS-specific instruments that have been relatively widely used and validated in various clinical studies are the MSQOL-54, the MSQLI, and the MusiQOL. Their psychometric properties are well understood, and they all provide extensive pertinent information. Therefore, these three tools constitute a good starting point for the development of an ideal instrument.

**MSQOL-54**

The MSQOL-54 was developed by adding MS-specific questions to the SF-36, with the goal of developing a more comprehensive measure of HRQOL for MS patients. Despite the inability of the SF-36 to detect subtle disease-specific differences, it was selected as the core instrument for development of the MSQOL-54 because of its coverage of domains important to HRQOL and the relevance of these domains for MS patients. The incorporation of the SF-36 into the MSQOL thus resulted in the first MS-specific instrument for monitoring HRQOL.

The MSQOL-54 consists of 54 items divided into 12 multiple-item scales: four new scales, five unchanged SF-36 scales, and three SF-36 scales that were altered by the addition of one item each (Table 2). The new scales include measures of cognition, health distress, overall QOL, and sexual function. The MSQOL-54 has been translated into several languages and validated for use in different populations. Validation in a broad range of patients with clinically definite MS showed adequate internal and test-retest reliability and construct validity. Estimated time required for completion ranges from 11 to 18 minutes based on known rates of completion for the SF-36, although actual time for completion for MS patients has been reported to average 32 minutes.

In a nonrandomized study that used the MSQOL-54 to evaluate HRQOL in the MS population, IFNβ treatment was associated with poorer HRQOL such that after 2 years, IFNβ was associated with nonsignificant worsening in the physical composite score, despite significantly reduced relapse activity compared with placebo. Furthermore, significant negative effects on the mental composite score, emotional well-being, and health distress were observed over time. However, this longitudinal study did not account for response shift effects. Because patients can show a trend toward placing greater value on mental health and psychosocial limitations over time, response shift may have been a major contributor to the observed negative effects on the mental composite score. Another study showed that HRQOL, as assessed by the MSQOL-54, did not vary directly with disability status as measured by the EDSS, suggesting a strong influence of nonphysical factors on HRQOL. These examples highlight the importance of careful interpretation of results and the possible confounders produced by changes in patient perceptions.

**Value and Limitations of the MSQOL-54 in Clinical Research and Practice**

Notable floor and ceiling effects in several scales may limit the utility of the MSQOL-54 in MS. In particular, the floor effects in the physical functioning scales limit its use in the longitudinal assessment of HRQOL for wheelchair-bound MS patients. This is because functional limitation is assessed by “yes or no” questions, minimizing the scale’s sensitivity for severely disabled patients. This lack of sensitivity was observed in the unchanged SF-36 scales and was especially pronounced for patients with moderate or severe disability. Few advantages were observed for the altered SF-36 scales, and effect sizes for the newly added MSQOL scales were comparable to those obtained with the SF-36. Furthermore, the two new sexual scales were often not fully completed by patients and therefore may not have yielded valid results. Additionally, the time to complete the MSQOL-54 may represent a barrier to its use in clinical practice. Therefore, despite its acceptance as a relatively reliable HRQOL instrument and its widespread use, the MSQOL-54 has notable weaknesses.

**MSQLI**

The MSQLI was developed around the same time as the MSQOL-54. Like the MSQOL-54, it is based
on the SF-36, but unlike the MSQOL-54, the MSQLI added established disease-specific scales, such as the Modified Fatigue Impact Scale (MFIS), rather than individual questions (Table 2). Fischer et al. suggested that this modular, symptom-specific construction facilitates cross-disease comparisons, not only of the generic sections but also of disease symptoms that may affect HRQOL.

The MSQLI consists of 138 items divided into 10 multiple-item scales (Table 2). It can discriminate more disease-specific elements than the SF-36 and has a greater capacity than the MSFC to evaluate aspects of disability (eg, sexual, bowel, and bladder function). Although the MSQLI achieves more comprehensive measurements of HRQOL related to sexual, bladder, and visual dysfunction than the MSQOL-54, it takes longer for patients to complete (about 45 minutes).

The MSQLI has been used as a tool to assess HRQOL in several randomized, placebo-controlled studies of disease-modifying therapies for MS. A significant treatment benefit was observed on 8 of 11 subscales in 156 patients with secondary progressive MS treated for 2 years with intramuscular (IM) IFNβ-1a compared with 165 patients receiving placebo. After 24 months of therapy, patients receiving IM IFNβ-1a improved, compared with their baseline measures, in all subscales except the Bladder Control Scale.

The MSQLI was administered as part of both the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) and Safety and Efficacy of Natalizumab in Combination with Inter-
feron beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL). At baseline, lower HRQOL assessed by the Physical Component Summary (PCS) was associated with higher EDSS score, greater volume of T2-hyperintense and T1-hypointense lesions on MRI, the occurrence of relapse, and lower MSFC scores. In AFFIRM, significant improvements in the PCS and the Mental Component Summary (MCS) were observed at 2 years for natalizumab compared with placebo (\( P < .01 \) and \( P < .05 \), respectively). In SENTINEL, significant improvements in the PCS were observed at 2 years for natalizumab and IFN-\( \beta \)-1a versus IFN-\( \beta \)-1a alone (\( P < .001 \)). In both AFFIRM and SENTINEL, the use of natalizumab was associated with significant clinical benefits for disability progression, relapse, and MRI outcomes (\( P < .001 \)). Findings from AFFIRM and SENTINEL indicate that the SF-36 component of the MSQOL can successfully detect HRQOL differences between treatments at 2 years of therapy; however, the study may not have harnessed the full potential of the MSQOL by excluding assessment of individual, MS-specific dimensions.

**Value and Limitations of the MSQOL in Clinical Research and Practice**

The MSQOL is unique in its assessment of several MS-specific dimensions (eg, visual function, bowel and bladder control) and the flexibility of administration permitted by its modular structure. It therefore offers health-care providers a means to assess an array of problematic symptoms and thereby structure clinical discussion and provide symptomatic treatment in addition to disease-modifying therapy. The time needed to complete the MSQOL is the primary barrier to its use in clinical practice. Another potential obstacle to widespread use of the MSQOL in clinical studies is the lack of a convenient summary scale that incorporates the MS-specific individual scales to describe the patient’s overall HRQOL.

**MusiQOL**

The MusiQOL instrument is a multidimensional HRQOL instrument constructed by an international steering committee comprising neurologists, patients, and health economists. It consists of 31 questions divided into nine dimensions, including two dimensions not represented by the MSQOL-54 or MSQOL (symptoms and psychological well-being; Table 2). MusiQOL has been validated in 20 countries and 14 languages and in the following forms of MS: relapsing-remitting, secondary progressive, progressive relapsing, and clinically isolated syndrome. Unlike the MSQOL-54, concepts covered by the MusiQOL incorporate patient views and concerns and do not generally overlap with those of the SF-36. The MusiQOL showed high levels of internal consistency, reproducibility, and test-retest reliability. Notable ceiling effects were observed in MS patients on dimensions reported to have ceiling or floor effects in the SF-36 and MSQOL-54, and the MusiQOL is sensitive to change in both patient-reported and physician-diagnosed health status. The activity of daily living and psychological well-being dimensions were particularly sensitive to both improvement and worsening in health status. To date, however, no disease-modifying drug study has employed the MusiQOL.

**Value and Limitations of the MusiQOL in Clinical Research and Practice**

The MusiQOL is currently limited by the lack of data regarding responsiveness of the instrument compared with other clinical end points. Nevertheless, it offers an advantage over other QOL instruments in that the information it provides is based on the views and perceptions of the patient. It is shorter than the other MS-specific QOL instruments and is well accepted. The average time required for completion of the MusiQOL is about 10 minutes, and with the exception of symptoms and psychological well-being; Table 2). MusiQOL has been validated in 20 countries and 14 languages and in the following forms of MS: relapsing-remitting, secondary progressive, progressive relapsing, and clinically isolated syndrome. Unlike the MSQOL-54, concepts covered by the MusiQOL incorporate patient views and concerns and do not generally overlap with those of the SF-36. The MusiQOL showed high levels of internal consistency, reproducibility, and test-retest reliability. Notable ceiling effects were observed in MS patients on dimensions reported to have ceiling or floor effects in the SF-36 and MSQOL-54, and the MusiQOL is sensitive to change in both patient-reported and physician-diagnosed health status. The activity of daily living and psychological well-being dimensions were particularly sensitive to both improvement and worsening in health status. To date, however, no disease-modifying drug study has employed the MusiQOL.

**Discussion**

Most patients with MS live an almost normal life span while experiencing increasing disease-related challenges. A patient diagnosed with MS 20 years ago would have had no options initially for disease-modifying therapy, while just a few years later having four drugs from which to choose: three different IFN-\( \beta \) products and glatiramer acetate. Within the last 3 years, the first monoclonal antibody, natalizumab, has become available for MS patients, and several emerging therapies may be approved within the next several years. Although these
emerging therapies have the potential for greater efficacy compared with established therapies, they may also bring more serious adverse effects. Thus, this new treatment landscape brings a greater need to correlate therapies to changes in HRQOL. This may allow us to determine whether patients’ lives are really being improved by these therapies and which ones have the best effects.

Multiple studies have suggested that disease-specific instruments give a better indication of the disease’s impact on HRQOL than generic instruments because generic instruments often lack sensitivity in MS patients. The MS-specific instruments, such as the MSQOL-54, MSQLI, and MusiQOL, can discern true changes in MS patients’ HRQOL. Given these benefits, MS-specific instruments should be routinely included in MS patients’ health-care programs. However, these instruments have limitations that must be overcome. Instruments are needed that address the cognitive deficits and psychiatric comorbidities often experienced by MS patients. Moreover, further research should evaluate the appropriateness of using the available instruments in clinical trials by verifying their sensitivity and specificity for MS symptoms. The emergence of new MS therapies has brought a golden opportunity to address these issues in ongoing clinical studies.

Inconsistent use of MS-specific instruments and the time required to administer them have limited our understanding of the true effects of MS therapies on HRQOL, making it impossible to accurately assess subjective improvement in MS patients’ lives. For example, if only select subscales of an instrument are used for assessment (as in the case of the MSQOL), the reliability and validity of the other psychometric properties of the scale remain unclear. Effective assessment of HRQOL requires serious consideration of the tools themselves and the way they are applied in research and clinical practice settings. This may be accomplished through the following steps: first, continued refinement of the best existing instruments; second, more systematic collection of HRQOL data in both research and clinical practice settings (eg, standardized frequencies and conditions for administration); and, finally, despite possible limitations, the development of simplified formats (similar to the SF-12 as compared to the SF-36), especially for daily clinical practice, and alternative strategies for administration, such as via the Internet.

**Conclusion**

MS-specific HRQOL instruments are valuable tools for assessing patient-perceived and clinician-evaluated severity of MS and effects of treatment. The use of MS-specific HRQOL instruments in clinical research and practice settings holds promise for determining the relationship between MS therapies and HRQOL in MS patients. The routine, consistent use of such tools in these settings could facilitate the optimal use of current and future therapies for MS patients.

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**References**


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**Practice Points**

- Assessment of patients’ health-related quality of life (HRQOL) is an important aspect of research and clinical practice in MS.
- HRQOL instruments specific for MS are potentially valuable tools that should be routinely employed in health-care programs. However, the shortcomings of currently available HRQOL instruments hinder their routine use.
- Continued refinement of the best existing instruments, more systematic collection of HRQOL data in clinical practice and research settings, and development of simplified formats may result in improved HRQOL assessment and treatment of MS patients.


