Rheumatoid arthritis (RA) is a chronic inflammatory disease that frequently leads to the deterioration and destruction of joints. The condition affects between 0.8% and 1% of the adult population, according to most authors, and is a leading cause of disability in the United States.  

The disability associated with RA has a significant impact on the patient, the family, the employer, and society. Many people with RA lose the ability to participate in leisure or volunteer activities or to perform routine tasks of self-care, such as bathing and cooking. In families in which the wife/mother has moderate/severe RA, family members report spending an average of an hour per day more on household work than do members of control families. In the worst cases, the patient's ability to lead an independent life is compromised. The limitations imposed by RA disability are associated with psychosocial problems, increased mortality, and loss of the patient's and/or caregiver's income. Employers are faced with costs associated with lost productivity and increased sick leave and healthcare, and with expenses required to change work routines, eg, move an employee with RA from a physically demanding to a less demanding occupation. The disability associated with RA is not necessarily inevitable; with the appropriate intervention, dysfunction can be delayed or perhaps even avoided. Because of the potential impact of medical and psychosocial interventions (ie, psychotherapy, relaxation training, or programs promoting perceived control over various aspects of RA) on RA-related disability, assessment of health-related quality of life (HRQOL) should be an integral part of ongoing treatment evaluations.

In recent years, emphasis has been placed on the use of HRQOL assessments in clinical trials. In fact, the American College of Rheumatology's (ACR) position that self-report questionnaires be a part of disease activity measurements has made these measurements an integral part of ongoing treatment evaluations.

Unlike most clinical assessments, measures
sures of HRQOL have the unique ability to provide insights into the net effect of treatment; that is, the balance between therapeutic benefits and adverse effects.12

Self-administered questionnaires have been found to be at least as effective as other clinical tools, including traditional joint counts and laboratory assessments, in documenting clinical status and predicting long-term functional declines, work disability, and mortality.13–19 Thus, these HRQOL self-reports can be useful tools to guide patient/physician decisions about RA therapies. The speed and ease with which several of these tests can be administered makes them particularly amenable to guiding patient therapy in the clinic. In addition, some of these measures offer a relatively simple way for clinicians to assess and quantify the psychosocial problems faced by patients.19 A recent study demonstrating that a lack of correlation between physicians’ ratings of patient health status and patients’ ratings of their own health emphasizes the need for greater communication between patients and physicians.20 Self-assessment questionnaires offer the opportunity for a standardized, quantifiable vehicle for patient–physician communication.

These self-reports can also help managed care administrators evaluate the efficacy of a new drug. Increasingly, HRQOL self-reported measures are a part of the materials reviewed by managed care providers in making formulary and reimbursement decisions. The abundance of studies and reports using such measures of RA necessitates that managed care administrators understand how to evaluate and interpret the results of HRQOL assessments. Several self-administered HRQOL measurements commonly used in RA are reviewed herein, along with brief summaries of how these measures have been used to test the efficacy of particular RA therapies.

Measuring Health-Related Quality of Life

Health-related quality of life is difficult to define because the concept has a different meaning to each person. Although it is related to functional ability, HRQOL also encompasses other parameters, such as psychological well-being. The various scales designed to measure aspects of HRQOL emphasize different domains, with some weighted more toward the physical domains of life, and others directed more toward the psychosocial aspects. For instance, the Health Assessment Questionnaire (HAQ) is designed to assess functional status but does not evaluate social activities or emotional well-being.21 The Arthritis Impact Measurement Scale (AIMS) is often used to assess emotional and social status.22

For an HRQOL instrument to be useful in clinical practice,23,24 it should:

- Be reliable and well validated
- Incorporate the patient’s perspective25
- Be responsive to change in the patient’s condition26
- Include domains reflecting all relevant areas of functioning
- Be easy to administer (ie, of an acceptable length to reduce respondent burden)
- Be easy and quick to score so results are available while the patient is at the clinic.

A critical component of any functional or global status instrument is its ability to incorporate the patient’s perspective.25 Although there are multiple ways of attaining this goal, one of the simplest is through the use of a self-administered questionnaire. The importance of patient self-assessments of functional status has been recognized by the American College of Rheumatology (ACR), which includes them as 1 of 7 core disease activity measures recommended for assessments in RA clinical trials.27 Self-assessment reports can provide important insights into the balance between the efficacy and tolerability of new agents. Accordingly, the following discussion focuses on several self-reports that have been used in the evaluation of RA therapies.

WIDELY USED SCALES TO MEASURE FUNCTIONALITY AND HEALTH-RELATED QUALITY OF LIFE IN RHEUMATOID ARTHRITIS

The need for standardized scales has given rise to several popular self-assessment scales for determining the functionality and HRQOL of RA patients. The most commonly used self-assessment scales are discussed below and summarized in Table 1.21,22,26,30 These instruments have been used in large-scale studies and clinical trials to assess the efficacy of new therapies and to compare outcomes among patients.27 In addition, they have been used by clinicians to determine the effectiveness of treatments for individual patients. In addition, they have the potential to provide valuable cost-benefit information for healthcare administrators.
The Health Assessment Questionnaire

The HAQ, which is currently the most widely used assessment tool in RA, has been administered and validated throughout the world. It has been in use for nearly 2 decades and is an ACR-sanctioned instrument for assessing physical function. In 1992, Ramey and colleagues noted that the HAQ had been administered over 100,000 times since 1980 in a variety of national and international settings. To date, more than 363 published papers have described or utilized this instrument. Although originally developed for RA, this particular questionnaire has been applied to other diseases and disorders as well. Several versions of the HAQ exist, including a 20-page instrument sometimes referred to as the full HAQ, designed for use in longitudinal studies, which includes a disability index and 2 visual analog scales for measuring pain and global severity. A modified version of the HAQ is discussed below. The HAQ that is most often used in clinical studies is a 24-question instrument that rates disability in activities of daily living (ADL) and in instrumental ADL (IADL) of 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and activities (the only IADL component). Patients answer 2 to 3 questions per domain regarding their functionality according to a scale in which 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; and 3 = unable to do. A lower score is automatically raised to 2 if an aid, such as a walker or assistance from another person, was required. The highest score in each domain determines the category score. The category scores are then averaged to achieve the patient’s Disability Index.

The HAQ is self-administered and requires only a few minutes to complete and score. Results are readily available at the time of assessment, making the HAQ useful not only to researchers but also to clinicians. The speed with which the HAQ can be administered and scored offers the opportunity for the clinician to review the results with the patient in the clinic, thus allowing the patient's self-assessment to play a significant role in treatment plan.

The Health Assessment Questionnaire scores correlate well with clinical assessments of function. Perhaps of even more importance, HAQ Disability Index scores have been found to predict work disability. The HAQ does not address psychosocial domains of HRQOL, however, and some questions may not be relevant to all patients, eg, ability to cut meat. In addition, the instrument's 4-point response scales limit the amount of information provided.

The HAQ has been shown to be a good predictor of the indirect costs of RA and loss of income among RA patients. For example, the risk of incurring higher total indirect and nonmedical costs (including

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Table 1. Self-Assessment Measures Commonly Used to Assess Functional Status and Psychosocial Well Being in Patients With Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Aspects Assessed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Assessment Questionnaire (HAQ) Disability Index</td>
<td>Eight activities of daily living: dressing, arising, eating, walking, hygiene, reach, grip, and activities</td>
<td>Well-validated, short, easy to score; can be combined with domains from other instruments to provide comprehensive assessment of patient well-being</td>
</tr>
<tr>
<td>Modified Health Assessment Questionnaire (MHAQ)</td>
<td>Patient activity satisfaction, self-perception, stiffness, global function, helplessness, pain, fatigue, and gastrointestinal distress</td>
<td>Shorter disability domain and less sensitive than HAQ in assessing disability</td>
</tr>
<tr>
<td>Arthritis Impact Measurement Scale (AIMS)</td>
<td>Physical activity, activities of daily living, dexterity, mobility, social role and activity, pain, depression, and anxiety</td>
<td>Comprehensive, but takes a long time to administer and is complicated to score</td>
</tr>
<tr>
<td>SF-36 Arthritis-Specific Health Index (ASHI)</td>
<td>Physical and social limitations due to health concerns, limitations in usual roles due to health concerns, social limitations due to physical or emotional concerns, pain, general mental outlook, energy and fatigue, and general health perceptions</td>
<td>Good overview of general status but not as easy to complete as HAQ; arthritis-specific scoring algorithm</td>
</tr>
</tbody>
</table>

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HRQOL in Rheumatoid Arthritis
loss of wages) has been found to double with every unit increase in HAQ score. Given the correlation between functional status scores and work disability, interventions that improve functional ability are likely to reduce work disability and have a positive financial impact on patients and their employers.

Over the past 20 years, the validity of the HAQ has been demonstrated in clinical trials of the effects of disease-modifying antirheumatic drugs (DMARDs). For example, in the 1980s, the HAQ was used in a double-blind, placebo-controlled, prospective study of oral gold (auranofin) in 330 patients who had had unremitting RA for 6 months or more. Patients in the auranofin group showed significant improvements in HAQ scores relative to baseline and relative to placebo after 6 months (P = .01). Results were similar using 2 other validated function measures: the Keitel Assessment (which focuses on range of motion tasks) and the Quality of Well-Being Scale (which focuses on health-related limitations in mobility, physical activity, and social activity in a single index score).

The value of the HAQ in studies of early DMARDs was confirmed in a prospective study conducted in the 1990s that included 440 patients with RA. A total of 160 patients completed 5 years of treatment with intramuscular gold (sodium aurothiomalate). No significant change in HAQ scores was found between study outset and year 5 in gold-treated patients who had disease duration of more than 2 years at the outset of the study (Figure 1). Patients who started gold treatment within 2 years of initial symptoms, however, were 30% less disabled after 5 years than at study onset.

Recent studies using the newer disease-modifying agents termed biologic response modifiers (BRMs) have used the HAQ. Two of these BRMs, etanercept and infliximab, target tumor necrosis factor (TNF), a cytokine thought to play a pivotal role in the pathogenesis of RA. These studies have demonstrated the correlation between clinical improvement and improved function and psychosocial well-being.

Etanercept monotherapy was tested in a phase 3 clinical trial of 234 patients with refractory RA. Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to 2 TNF molecules. Patients in the study had long-standing RA and had displayed an inadequate response to previous DMARD therapy. In this study, as in many studies of RA therapy, response to therapy was measured using the ACR criteria. An ACR 20% or 50% response was defined as a 20% or 50% reduction in tender joint count and swollen joint count, and a 20% or 50% improvement in at least 3 of the following: patient’s assessment of pain, patient’s global assessment of disability, and acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein level).

Etanercept monotherapy was shown to be effective in reducing disease activity in these patients. At 6 months, 59% of patients receiving etanercept 25 mg subcutaneously twice weekly achieved 20% ACR response compared with 11% of patients receiving placebo (P < .001) (Figure 2). Also, 40% of patients in the 25-mg group achieved 50% ACR response at 6 months compared with only 5% in the placebo group (P < .001).

The efficacy of etanercept in reducing disease activity was also seen in this study’s HAQ results. The HAQ administered included the disability index, a general health assessment question, and an arthritis-specific question; the HAQ scores for patients receiving etanercept improved significantly over 6 months compared with those of patients receiving placebo. Patients receiving etanercept 25 mg reported mean improvements of 39% for disability index (vs 2% in the placebo group, P < .05), 33% for general health status (vs −12% placebo,
P < .05), and 44% for arthritis-specific health status (vs −22% placebo, P < .05).³⁹

Improvement in the HAQ Disability Index also mirrored clinical improvement in a 6-month randomized, placebo-controlled trial of etanercept plus methotrexate (MTX).⁴⁰ Many patients with persistently active RA despite MTX therapy (mean duration 13 years) demonstrated rapid and sustained clinical improvement with the addition of etanercept (Table 2).⁴⁰ Significantly more patients who received etanercept plus MTX than MTX plus placebo achieved a 50% ACR response at 1 month and thereafter, and significantly more patients experienced a 70% ACR response at 3 months and thereafter.⁴⁰ Patients in the etanercept group experienced an improvement in the HAQ median Disability Index of 47%, a significant change compared with that seen in placebo-treated patients (27%; P < .001).⁴⁰

The HAQ has also been used to study the effect of infliximab on HRQOL in patients with RA. Infliximab is a chimeric monoclonal antibody that binds to TNF, thereby inhibiting TNF from binding to its receptors and neutralizing its activity. Anti-Tumor Necrosis Factor in RA with Concomitant Therapy (ATTRACT) trial, involving 428 patients with active RA despite MTX therapy, compared outcomes for patients randomized to MTX plus infliximab or placebo. Results showed a significant improvement in HAQ scores after 54 weeks of treatment in patients who received combination therapy versus MTX alone (23% vs 3% median improvement; P < .001).⁴¹ The improvement in HAQ in patients in the infliximab plus MTX arm relative to the MTX plus placebo arm is not surprising, as all patients enrolled in this trial had shown an inadequate response to MTX. Infliximab is indicated for use only in combination with MTX.⁴³

The HAQ and the modified HAQ (MHAQ), a shortened version of the HAQ, have been used in studies of another new RA therapy, leflunomide. Two double-blind, placebo-controlled, randomized trials compared the benefits of leflunomide, a DMARD that inhibits pyrimidine synthesis, with those of sulfasalazine (European trial) or MTX (North American trial). Patients treated with leflunomide in the 6-month European trial had significantly greater reductions in HAQ scores than did those who received sulfasalazine or placebo (−.50 vs −.29, P = .0086; and −.50 vs −.04, P = .0001, respectively). In the 12-month North American trial, similar benefits were observed in MHAQ scores with leflunomide compared with placebo (−.29 vs .07; P = .0001) or MTX (−.29 vs −.15; P ≤ .05). The HAQ also was used in a 24-week multicenter, randomized, placebo-controlled trial comparing combination therapy with MTX and leflunomide versus MTX and placebo. The HAQ Disability Index improved by 29% in patients treated with leflunomide and MTX.
compared with 5% in those who received placebo and MTX (P < .0001). It should be noted that use of leflunomide with MTX is not an approved indication.

Given the effects of these 3 new DMARDs on HRQOL, as assessed by HAQ scores, it is of interest that all 3 drugs have been shown to slow the progressive bone destruction of RA in radiographic analyses. Etanercept has been found to retard radiographic progression more effectively than MTX in MTX-naïve patients with early RA (disease duration of less than 3 years), whereas infliximab slowed progression relative to MTX in a trial of MTX-refractory patients with long-standing disease. The effects of leflunomide on bone destruction are significantly better than placebo and similar to or slightly less than those of MTX.

**Modified Health Assessment Questionnaire**

Like the HAQ, the MHAQ is self-administered and easy to score. It is appropriate for use by both the researcher and clinician. The MHAQ has been shown to correlate with the ACR response criteria and to be sensitive to changes in disease status. However, the MHAQ is not as sensitive as the HAQ in measuring treatment changes. Furthermore, the MHAQ addresses only 8 activities of daily living, making it less sensitive than the HAQ in assessing disability. Thus, the MHAQ may underestimate the magnitude of disability in those patients who are most severely affected.

The MHAQ contains additional items not found in the HAQ, however, including sections on patient activity satisfaction, global function, and helplessness. It also contains visual analog scales to assess pain, fatigue, and gastrointestinal distress. In a 12-month study of 438 patients with RA (average disease duration, approximately 6.5 years) randomly assigned to receive either leflunomide, MTX, or placebo, leflunomide and MTX both resulted in significant improvements in MHAQ and HAQ scores compared with placebo (P < .05 and P < .0001, respectively). Because the HAQ and the MHAQ have different scaling and measurement properties, they must be considered as 2 separate instruments.

### Table 2. American College of Rheumatology Responses With Etanercept Plus MTX or Placebo Plus MTX*

<table>
<thead>
<tr>
<th>Amount of Improvement and Duration of Treatment</th>
<th>Etanercept Plus MTX (% of Patients)</th>
<th>Placebo Plus MTX (% of Patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% (ACR 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>66</td>
<td>33</td>
<td>.003†</td>
</tr>
<tr>
<td>24 weeks</td>
<td>71</td>
<td>27</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>50% (ACR 50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>42</td>
<td>0</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>24 weeks</td>
<td>39</td>
<td>3</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>70% (ACR 70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>15</td>
<td>0</td>
<td>.03‡</td>
</tr>
<tr>
<td>24 weeks</td>
<td>15</td>
<td>0</td>
<td>.03‡</td>
</tr>
</tbody>
</table>

*Patients who withdrew from the study were considered not to have had a response at all points after withdrawal, irrespective of the actual clinical response.
†The P value was calculated by the χ² test.
‡The P value was calculated by Fisher’s exact test.

ACR indicates American College of Rheumatology; MTX, methotrexate. Data from Weinblatt et al.

The AIMS is a comprehensive, self-administered instrument for assessing the effects of rheumatic disease. The AIMS evaluates physical activity as well as other parameters such as social role and activity, pain, depression, and anxiety. The incorporation of psychosocial factors into the AIMS might be one of its most important characteristics. For example, a study of young women with early RA demonstrated that over time, levels of disability were determined as much by psychosocial factors as by disease severity and pain.

Although the AIMS is valid and reliable, the questionnaire requires approximately 20 to 30 minutes to complete and is complicated to score. Accordingly, the AIMS is not readily useful to the
clinician. A revised version of this instrument, the AIMS2, corrects some of these shortcomings, but still takes substantial time to administer. A 2-page derivative of the AIMS2, termed the AIMS2—Short Form (AIMS2-SF) has been developed recently and may prove useful in clinical investigations. One study has shown that the AIMS2-SF generates data that are in agreement with the limited comparative information is available. A caveat of the study, however, was that the AIMS2-SF scores were derived from patient responses to the original AIMS2 and therefore the similarity between the 2 tests may have been over-simplified. Because the AIMS and its revised versions have been used less extensively than the HAQ, limited comparative information is available.

**Short-Form Health Survey and Arthritis-Specific Health Index**

The 36-item Short-Form Health Survey (SF-36) is a self-administered general health questionnaire that can be useful in monitoring the overall physical and psychosocial status of patients. The SF-36 consists of 36 items that are grouped to form 8 different scales. Four of the SF-36 scales—Physical Functioning, Role-Physical, Bodily Pain, and General Health—are clustered to form the Physical Component Summary (PCS) measure. The other 4 scales—Vitality, Social Functioning, Role-Emotional, and Mental Health—are clustered to form the Mental Component Summary (MCS) measure. The SF-36 can be completed in 10 minutes, although completion may take longer for patients with disabilities. At least 2 studies have reported patients experiencing confusion with SF-36 questions.

Although the SF-36 is not specific for RA, test results from patients with RA can be readily compared with results obtained from patients with other diseases or the general population. Thus, SF-36 data can be used to compare the burden of different diseases. Such comparison may be important to managed care administrators when making resource allocation decisions. Recently developed norm-based scoring for the SF-36 standardizes each of the 8 scales, which improves interpretation and facilitates comparison of results across scales.

The SF-36 is a broader-probing questionnaire than the HAQ; the instrument includes questions about emotional role functioning, social functioning, vitality, and mental health. The advantages of the SF-36, however, do not indicate that disease-specific measures, such as the HAQ, should be abandoned. Scores from the SF-36 correlate well with HAQ scores and ACR core disease activity measures. The 2 types of tests can be thought of as complementary; general tests offer the advantage of easy comparison with other diseases and the general population, and disease-specific assessments better capture all of the aspects of physical health in RA patients.

A disadvantage of the SF-36 is that the scale measuring role limitations is not well suited to patients with severe RA. Furthermore, generic measures such as the SF-36 are not likely to be as sensitive to treatment differences and changes in function.

In the 12-month North American trial comparing leflunomide, MTX, and placebo in RA, significant improvements for leflunomide versus placebo were seen in 5 of 8 SF-36 scales, and for leflunomide versus MTX, in 2 of 8 scales ($P < .05$). In the ATTRACT trial, the physical component summary of the SF-36 improved significantly in patients who received infliximab plus MTX versus MTX alone (34% vs 9%; $P < .001$). Treatment-related changes in the mental component summary of the SF-36 were not significant.

The Arthritis-Specific Health Index (ASHI) was constructed to improve the responsiveness of the SF-36 to changes in the severity of arthritis by including an arthritis-specific scoring algorithm that combines the 8 scales in the original SF-36 into a single index. Among RA patients, the ASHI has been demonstrated to be more valid than the SF-36 and PCS or MCS for distinguishing between treated versus untreated patients and clinical responders versus non-responders. Initial findings suggest that the ASHI may be a valid and useful tool to measure RA patient health status, as it measures a combination of generic and RA-specific parameters. Further research, however, needs to be conducted to test the validity of the ASHI.

**Future Challenges**

Many challenges lie ahead to assure that the maximal benefits of self-assessment measures are realized both in the clinic and in managed care administrations. Standardized tests such as the HAQ need to be administered on a regular basis in the clinic to allow more data to be collected, thus boosting the power of the individual HAQ score. In addition, the threshold for minimally important clinical changes need to be better defined in both disease-specific and generic measures. Defining clinically relevant changes would allow the meaning of changes in scores to be more readily interpreted.

The power of HRQOL self-assessment scales to measure and predict functional outcome suggests...
that they have the potential to be linked to present and future medical costs. Future studies measuring the relationship between changes in HRQOL scores and cost of medical care will be important in allowing managed care to assess the true financial impact of new RA therapies. For example, it is possible that HRQOL improvements may mirror a decrease in costly medical services, thus indicating that new RA therapies, such as the BRMs etanercept and infliximab, may be cost effective.

Conclusions

An important goal of RA therapy is to improve each patient’s long-term functional status and HRQOL at a reasonable cost. Several validated self-report measures are available to help clinicians and managed care providers attain this goal. Questionnaires such as the IHAQ can predict important long-term outcomes, including work disability and mortality, and have been used to demonstrate the importance of early aggressive therapies and the effectiveness of new therapies for RA.

When choosing a self-assessment measure, a variety of factors must be balanced: time needed to take and score the instrument, clinical relevance of the instrument, previous validation of the instrument, and ease with which results can be interpreted and compared as necessary. The brevity, clinical relevance, and extensive validity of the IHAQ makes it a highly useful instrument.22,69 The more often a disease-specific standardized test such as the HAQ is administered, the more readily HAQ results will have the potential to benefit the patient and the healthcare industry.

Self-assessment reports of physical function and HRQOL are valuable for patients, their clinicians, and managed care administrators. The importance of instruments, such as the IHAQ, lies in their ability to provide key data on disability and HRQOL from the unique perspective of the patient. The demonstrated relationships between functionality, HRQOL, and prognosis further support the use of such instruments. Information so gained then enables the clinician to select the most appropriate therapies and ensure that the patient remains comfortable, functioning, and productive. In managed care settings, IHAQ results can be used to aid the development of cost-effective therapeutic guidelines and interventions that prevent disease progression and subsequent debilitation.

Further studies examining the relationship between HRQOL scores and medical costs are needed to allow managed care administrators to efficiently use HRQOL data in cost-benefit analyses. An emphasis on the routine use of self-reports, coupled with new therapies capable of improving HRQOL, maintaining functional status, and favorably altering the disease course, may help bring about a significant decline in the severity, progression, and costs—both human and financial—of RA-related disability.

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