# Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale Relative to Other Instrumentation in Patients with Rheumatoid Arthritis

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*ABSTRACT.* ***Objective.*** This study validated a brief measure of fatigue in rheumatoid arthritis (RA), the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale.

***Methods.*** The FACIT Fatigue was tested along with measures previously validated in RA: the Multidimensional Assessment of Fatigue (MAF) and Medical Outcomes Study Short-Form 36 (SF-36) Vitality. The sample included 636 patients with RA enrolled in a 24 week double blind, randomized clinical trial (RCT) of adalimumab versus placebo.

***Results.*** The FACIT Fatigue showed good internal consistency (alpha = 0.86 to 0.87), strong association with SF-36 Vitality (r = 0.73 to 0.84) and MAF (r = –0.84 to –0.88), and the ability to differentiate patients according to clinical change using the American College of Rheumatology (ACR) response criteria (ACR 20/50/70). Psychometric performance of the FACIT Fatigue scale was comparable to that of the other 2 fatigue measures. A minimally important difference in FACIT Fatigue change score of 3–4 points was confirmed in a separate sample of 271 patients with RA enrolled in a second double blind RCT of adalimumab versus placebo.

***Conclusion.*** The FACIT Fatigue is a brief, valid measure for monitoring this important symptom and its effects on patients with RA. (J Rheumatol 2005;32:811–9)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS FATIGUE QUESTIONNAIRES

Fatigue, a subjective sensation of weakness, lack of energy, or tiredness[1], is experienced by virtually everyone at some time. Acute fatigue is usually self-limiting, occurs in healthy individuals, frequently results from overexertion or lack of sleep, and is typically relieved by rest[2]. In the general population, 20% of men and 30% of women complain of frequent tiredness[3]. On the other hand, chronic fatigue frequently accompanies medical illness, lasts longer than 6 months, is typically not related to overexertion, and is usually poorly relieved by rest[2]. Indeed, fatigue is often rated by patients with chronic disease as one of the key factors leading to decreased quality of life (QOL)[4]. Fatigue is the most common symptom reported by people with cancer[5] and is nearly ubiquitous among patients with many other chronic diseases.

Fatigue is multidimensional in expression, with influence on physical, emotional, cognitive, and even social aspects of life. This creates a challenge in its measurement. Fatigue frequently coexists and interacts with other factors, including mood disturbance, anemia, infection/fever, pain, sleep disturbance, and stress[6-8], making assessment of fatigue even more complex. The importance of fatigue and its impact on patients' QOL has been researched and documented for a number of diseases including cancer[9], multiple sclerosis[10], systemic lupus erythematosus[7], chronic viral and cholestatic liver disease[11], acquired immune deficiency syndrome[12], renal disease[13], and rheumatoid arthritis (RA)[8,14].

RA is a chronic inflammatory joint disease associated with deformities and joint destruction. Because the manifestations of RA include fatigue, chronic pain, and marked limitations in physical functioning and work disabilities, the disease has a profound effect on patients' QOL[15]. The disease affects roughly 1% of the population in the United States[16], is 2 to 3 times more common in women than in men, and has onset typically between 25 and 50 years of age[17]. An estimated 80% to 93% of individuals with RA experience fatigue[18], and 57% identify fatigue as the most problematic aspect of the disease[19]. Fatigue is such an integral feature of the disease that its absence is identified as a

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criterion for remission by the American College of Rheumatology (ACR)[20]. Fatigue associated with RA contributes to work disability, personal injury, inability to participate in rehabilitation programs, and strained relationships[19,21].

Our objective was to validate in patients with RA a brief (13 items), easy to administer fatigue scale that has previously been validated in patients with cancer[22] and the general population[9]. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire was originally developed to assess the fatigue associated with anemia[22]. This questionnaire is part of the FACIT measurement system, a comprehensive compilation of questions that measure health related QOL in patients with cancer and other chronic illnesses. The core of the FACIT system is the Functional Assessment of Cancer Therapy-General (FACT-G)[23], a 27 item general version of the questionnaire, which serves as a foundation onto which questions are added to address concerns or problems specific to a particular disease site, treatment, or symptom. Thirteen fatigue related questions are added to the FACT-G to make up the FACIT-F (available at www.facit.org). These 13 questions form the basis of this validation study.

## MATERIALS AND METHODS

*Source of data.* The validation sample consisted of 636 individuals with RA enrolled in a 2-arm (equal sample sizes), double blind, randomized 24 week clinical trial of adalimumab (Humira™, Abbott Laboratories, Abbott Park, IL, USA), a human tumor necrosis factor-α antagonist, plus current antirheumatic therapy versus placebo plus current antirheumatic therapy (referred to as STAR, the Safety Trial of Adalimumab in Rheumatoid Arthritis), in which 40 mg of adalimumab was administered by subcutaneous injection. Our study analyzed the pooled data of the entire sample, without unblinding the data as to treatment (adalimumab versus placebo). The demographic and clinical characteristics of this sample are summarized in Table 1. The study subjects had a median age of 56 years (range 21–86) and were largely non-Hispanic white (88%). The median level of serum C-reactive protein (CRP), an index of acute and chronic inflammation, was 9 mg/l (range 4–197). At baseline, the median number of tender joints was 25 out of a possible 68 (range 7–68). Of a maximum of 66 swollen joints, the STAR sample median was 19 (range 6–66).

One set of confirmatory analyses included data from a second sample of 271 patients with RA enrolled in a separate 4-arm (equal sample sizes) 24 week, randomized, double blind, placebo controlled clinical trial comparing adalimumab (20, 40, or 80 mg administered by subcutaneous injection) plus continued methotrexate versus placebo plus continued methotrexate [referred to as ARMADA, the Anti-TNF Research Program of the Monoclonal Antibody D2E7 (adalimumab) in Rheumatoid Arthritis]. This sample was also pooled across treatment conditions and doses for the purpose of analysis. Demographic and clinical descriptions of this second sample are also presented in Table 1. This ARMADA sample was comparable to the STAR sample, with the exception of the baseline median CRP value, which was higher than that in the STAR trial (22 mg/l vs 9 mg/l, respectively; $p < 0.0001$).

*Clinical outcome measures.* The primary clinical endpoint for this validation study was the definition of improvement developed by the ACR[24]. This criterion is a composite measure used to categorize patients with RA as "improved" or "not improved," expressed as a percentage. For example, a patient is said to achieve ACR20 if he or she demonstrates at least a 20% improvement in both tender and swollen joint counts and at least a 20% improvement in 3 of the 5 remaining ACR core measures: patient and physician global assessments of disease activity, pain, patient-assessed disability, and an acute phase reactant (i.e., Westergren erythrocyte sedimentation rate or CRP level). Comparable improvements of at least 50% are referred to as ACR50, and improvements of at least 70% are referred to as ACR70. Intended as a single primary endpoint for analysis, the ACR20 is a standardized definition of improvement to allow comparison across trials. Since its development, this measure has been incorporated into a number of clinical trials for RA[25-27] and has been accepted by the US Food and Drug Administration as evidence of clinical efficacy of investigational antirheumatic drugs[28].

*Patient-reported fatigue instruments.* The FACIT measurement system is a comprehensive compilation of questions that measure health related QOL in patients with chronic illnesses. The FACIT-F[22] includes the 27 items from the FACT-G (described above) plus 13 additional fatigue related items (FACIT Fatigue scale). High FACIT-F scores represent better QOL and less fatigue (range 0 to 52). In patients with cancer, the 13 item FACIT Fatigue scale showed excellent internal consistency and stability (test-retest reliability) and predicted group differences in hemoglobin level and performance status[22]. Thus, the 13 item FACIT Fatigue scale has strong psychometric properties and utility independent of the core FACT-G in patients with cancer.

The Medical Outcomes Study Short-Form 36 (SF-36) is a generic instrument that assesses well being and has been validated in normal and medical populations[29]. Designed to assess functional status, well being, and general perceptions of health, the SF-36 includes 8 subscales: physical

*Table 1.* Demographic and baseline clinical characteristics of study samples.

| | STAR, n = 636 | ARMADA, n = 271 |
|---|---|---|
| Sex, n (%) | | |
| Male | 130 (21) | 63 (23) |
| Female | 501 (79) | 208 (77) |
| Race/ethnicity, n (%) | | |
| White, non-Hispanic | 553 (88) | 220 (81) |
| Black, non-Hispanic | 31 (5) | 23 (9) |
| Other | 47 (7) | 28 (10) |
| Age, median (range), yrs | 56 (21–86) | 56 (28–84) |
| C-reactive protein, median (range), mg/l | 9 (4–197) | 22 (0.5–226) |
| Tender joint count (of 68 joints), median (range), n | 25 (7–68) | 26 (9–68) |
| Swollen joint count (of 66 joints), median (range), n | 19 (6–66) | 15 (2–43) |

STAR: Safety Trial of Adalimumab in Rheumatoid Arthritis; ARMADA: Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis.

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functioning (10 items), bodily pain (2 items), vitality (4 items), social functioning (2 items), mental health (5 items), general health perceptions (5 items), role limitations due to physical problems (4 items), and role limitations due to emotional problems (3 items). A high SF-36 score indicates better health (range 0 to 100). The SF-36[30,31] and the vitality scale specifically[31,32] have been found to be valid in studies of patients with RA. For purposes of this validation study, data from the 4 item SF-36 vitality scale (SF-36 Vitality) will be analyzed and compared with data from the 13 item FACIT Fatigue scale.

The Multidimensional Assessment of Fatigue (MAF) contains 16 items that measure 4 dimensions of fatigue: severity (2 items), distress (1 item), timing (2 items), and degree of interference in activities of daily living (11 items)[33]. A Global Fatigue Index (GFI), ranging from 1 to 50, can also be calculated, a high score indicating high levels of fatigue. The GFI is the sum of (1) the total of MAF items 1, 2, and 3; (2) the average of items 4 through 14; and (3) item 15 after it has been converted to a 0 to 10 scale. This measure has been shown to be reliable and valid in patients with human immunodeficiency virus infection[34], multiple sclerosis[35], cancer[36], and RA[21].

*Analysis plan.* The focus of analyses for this study was data from the STAR. However, we have included descriptive statistics on the ARMADA trial sample and measures for comparison. Patient and clinical data used for the validation analyses included the pretreatment (baseline), mid-study (Week 12), and end of study (Week 24) timepoints of the 24 week trials. Descriptive statistics for demographic and clinical variables and patient-completed questionnaires (e.g., FACIT Fatigue scale, MAF, SF-36 Vitality) at baseline were calculated for the STAR and ARMADA trials. The MAF was not used in the ARMADA trial.

The reliability and internal consistency of the FACIT Fatigue scale, MAF, and SF-36 Vitality at baseline and at 12 and 24 weeks were evaluated using Cronbach's alpha. Convergent validity of the measures was assessed using Spearman correlation coefficients calculated at baseline and at 12 and 24 weeks.

We calculated the change in fatigue scores from baseline to 24 weeks for the FACIT Fatigue scale, SF-36 Vitality, and MAF based on ACR20, ACR50, and ACR70 clinical groups (i.e., those who failed to achieve ACR20, those who achieved ACR20 but failed to achieve ACR50, those who achieved ACR50 but not ACR70, and those who achieved ACR70). A linear test for trend was computed using general linear model contrast coefficients for mean fatigue scores by ACR clinical group to evaluate whether fatigue scores showed a consistent linear increase across these clinically distinct groups. Pairwise comparison tests using Tukey's Honestly Significant Difference were conducted to test whether mean change scores were different between ACR groups. To evaluate sensitivity to change of the FACIT Fatigue scale, we computed the effect sizes and standardized response means of the mean change from baseline for the ACR clinical groups. The effect size was calculated as the mean change score for each clinical group divided by the pooled baseline standard deviation (SD); the standardized response mean was calculated as the mean change score for each clinical group divided by the pooled SD of the change[37]. For comparison, we calculated the standardized response means of the MAF and SF-36 Vitality measures.

Potential minimally important difference (MID) thresholds in scores between baseline and Week 24, or the change score associated with clinical meaning ($\Delta_F$), were calculated using (1) effect sizes of 0.2 and 0.5 SD units, calculated as the difference between baseline and Week 24 fatigue scores divided by the baseline SD; and (2) groups with 1 standard error of measurement (SEM) change, calculated as the SD multiplied by the square root of 1 minus the reliability coefficient (alpha)[38,39]. Five MID groups were created using 0.2 and 0.5 SD cutoffs for each of the 3 fatigue measures: major worsening ($\Delta_F \leq -0.5$ SD), minor worsening ($-0.5$ SD $< \Delta_F \leq -0.2$ SD), unchanged ($-0.2$ SD $< \Delta_F \leq 0.2$ SD), minor improvement (0.2 SD $< \Delta_F \leq 0.5$ SD), and major improvement ($\Delta_F > 0.5$ SD). Each instrument served as a reference for the other 2 measures. Thus, the change from baseline to 24 weeks in the FACIT Fatigue scale and MAF was evaluated by the SF-36 Vitality MID group, the change in FACIT Fatigue scale and SF-36 Vitality by the MAF MID group, and the change in SF-36 Vitality and MAF by the FACIT Fatigue scale MID group. Analyses using 2-tailed t tests were conducted to determine the difference of the mean change from zero within each of the 5 MID groups for each measure, and analysis of variance was used to evaluate the equivalence of change score means across the 5 MID groups.

Finally, a confirmatory analysis was performed to determine the degree to which classification of FACIT Fatigue scale scores using the MID values (0.2 and 0.5 SD units) calculated with STAR data agreed with classification of scores with ARMADA data. Cohen's kappa[40] was calculated to determine the degree to which this classification scheme agreed across datasets.

## RESULTS

Descriptive statistics for baseline, Week 12, and Week 24 scores for the FACIT Fatigue scale, SF-36 Vitality, and MAF for STAR and ARMADA are reported in Table 2. In STAR, the FACIT Fatigue scale (alpha = 0.86 to 0.87), SF-36 Vitality (alpha = 0.84 to 0.88) and MAF (alpha = 0.93 to 0.96) all had good internal consistencies at baseline, Week 12, and Week 24. Correlation coefficients showed a very high degree of association among all 3 measures of fatigue at baseline, Week 12, and Week 24, ranging from –0.68 to –0.88 ($p < 0.001$). (Coefficients of association with MAF are negative because high scores on that scale reflect worse fatigue.)

To evaluate the sensitivity of the FACIT Fatigue scale, SF-36 Vitality, and MAF to change in clinical status, analyses of fatigue measure change scores by ACR clinical group were conducted. Four unique ACR clinical groups were established: those who failed to achieve ACR20 status, those who achieved ACR20 status as their best response, those who achieved ACR50 as their best response, and those who achieved ACR70 status. Because the Week 12 results were very similar to the Week 24 results, only the Week 24 (end of study) results are presented. Table 3 displays the mean and SD of the raw baseline scores and Week 24 change scores for each fatigue measure as well as the effect size, standardized response mean, and statistical significance associated with the differences in change scores among the 4 ACR groups. There was a significant linear trend toward an increase in fatigue scores across the ACR groups ($p = 0.0001$). Average change scores were significantly different between those who failed to achieve ACR20 and those who achieved ACR20 as their best response ($p < 0.0001$), and between those who achieved ACR20 as their best response and those who achieved ACR50 as their best response ($p < 0.0001$). However, the mean change for those who achieved ACR50 as their best response versus those who achieved ACR70 was not significantly different ($p = 0.5477$).

In addition, for all 3 measures there was a gradient of effect size and standardized response means by ACR group, with effect size and standardized response means increasing as ACR status improved (i.e., from ACR20 to ACR50 to ACR70). Following the convention established by Cohen[41] that suggests an effect size around 0.2 is small, around 0.5 is

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*Table 2.* Descriptive statistics for fatigue measures by assessment period.

| Scale | STAR n | STAR Mean | STAR SD | STAR Alpha* | STAR SEM | STAR Range | ARMADA** n | ARMADA** Mean | ARMADA** SD | ARMADA** Alpha* | ARMADA** SEM | ARMADA** Range |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | | | | | | |
| FACIT Fatigue scale | 631 | 29.17 | 11.06 | 0.86 | 4.14 | 2–52 | 270 | 27.87 | 11.00 | 0.86 | 4.12 | 1–49 |
| SF-36 Vitality | 631 | 35.13 | 20.83 | 0.84 | 8.33 | 0–95 | 271 | 33.20 | 20.02 | 0.81 | 8.73 | 0–90 |
| MAF | 621 | 26.79 | 11.94 | 0.93† | 3.16 | 1–50 | — | — | — | — | — | — |
| Week 12 | | | | | | | | | | | | |
| FACIT Fatigue scale | 596 | 34.38 | 11.36 | 0.87 | 4.10 | 2–52 | 255 | 35.39 | 11.29 | 0.87 | 4.06 | 5–52 |
| SF-36 Vitality | 597 | 46.67 | 23.54 | 0.88 | 8.15 | 0–100 | 254 | 50.46 | 24.02 | 0.90 | 7.99 | 0–100 |
| MAF | 583 | 20.99 | 12.88 | 0.95† | 2.88 | 1–50 | — | — | — | — | — | — |
| Week 24 | | | | | | | | | | | | |
| FACIT Fatigue scale | 578 | 34.69 | 11.21 | 0.86 | 4.19 | 2–52 | 161 | 38.71 | 9.73 | 0.81 | 4.24 | 11–52 |
| SF-36 Vitality | 578 | 48.06 | 23.94 | 0.88 | 8.29 | 0–100 | 161 | 57.92 | 22.31 | 0.90 | 7.63 | 0–100 |
| MAF | 567 | 20.69 | 13.32 | 0.96† | 2.66 | 1–50 | — | — | — | — | — | — |
| Early termination (all visits) | | | | | | | | | | | | |
| FACIT Fatigue scale | — | — | — | — | — | — | 98 | 29.18 | 11.86 | 0.87 | 4.28 | 6–51 |
| SF-36 Vitality | — | — | — | — | — | — | 98 | 39.96 | 24.12 | 0.90 | 7.63 | 0–85 |
| MAF | — | — | — | — | — | — | — | — | — | — | — | — |

† Cronbach's alpha for MAF computed for 5 items, based on scoring algorithm described in text. * Cronbach's alpha. ** ARMADA did not include Multidimensional Assessment of Fatigue. SEM: standard error of measurement, computed as SD (sqrt [l–r]), where r = test reliability (Cronbach's alpha).

*Table 3.* Change in fatigue measures by change in ACR20, ACR50, ACR70 status (baseline to Week 24).

| Scale | ACR Group | n | Baseline Mean | Baseline SD | Pooled SD at Baseline | Change Score Mean | Pooled Change Score SD | Effect Size* | Standardized Response Mean† |
|---|---|---|---|---|---|---|---|---|---|
| FACIT Fatigue | Did not achieve ACR20 | 295 | 28.6 | 10.8 | 11.0 | 2.1 | 8.6 | 0.19 | 0.25 |
| scale | Best response ACR20 | 150 | 29.3 | 11.5 | | 6.6 | | 0.60 | 0.77 |
| | Best response ACR50 | 69 | 30.6 | 10.9 | | 10.4 | | 0.95 | 1.21 |
| | Best response ACR70 | 57 | 30.9 | 11.0 | | 12.4 | | 1.13 | 1.45 |
| p = 0.001 for linear test for trend in change scores across categories | | | | | | | | | |
| SF-36 Vitality | Did not achieve ACR20 | 296 | 34.0 | 19.9 | 20.6 | 5.2 | 20.0 | 0.25 | 0.27 |
| | Best response ACR20 | 150 | 36.2 | 21.1 | | 14.5 | | 0.71 | 0.76 |
| | Best response ACR50 | 69 | 37.3 | 21.6 | | 23.5 | | 1.14 | 1.24 |
| | Best response ACR70 | 57 | 37.2 | 21.8 | | 31.4 | | 1.52 | 1.65 |
| p = 0.001 for linear test for trend in change scores across categories | | | | | | | | | |
| MAF | Did not achieve ACR20 | 286 | 27.5 | 11.6 | 11.9 | –2.1 | 10.8 | –0.18 | –0.20 |
| | Best response ACR20 | 143 | 26.5 | 12.5 | | –7.2 | | –0.61 | –0.67 |
| | Best response ACR50 | 68 | 25.1 | 11.4 | | –11.0 | | –0.93 | –1.02 |
| | Best response ACR70 | 57 | 25.3 | 12.0 | | –14.9 | | –1.25 | –1.38 |
| p = 0.001 for linear test for trend in change scores across categories | | | | | | | | | |

* Change score mean divided by the pooled baseline SD. † Change score mean divided by the pooled change score SD.

moderate, and around 0.8 is large, the effect sizes for those who achieved ACR20 were found to be moderate in size, and the effect sizes for those who achieved ACR50 and ACR70 were large for all 3 measures (Table 3). The difference in FACIT Fatigue scale change scores between adjacent ACR groups (i.e., did not achieve ACR20 versus best response = ACR20; best response = ACR20 versus best response = ACR50; best response = ACR50 versus best response = ACR70) at Week 24 offers guidance regarding clinical significance of change scores. The differences in the change score from worst to best responders are 4.5, 3.8, and 2.0, with a mean change between clinical groups of 3.5, which is equivalent to an effect size of 0.32 (Table 3). This suggests a reasonable starting point for a minimal clinically important difference.

Further analyses were conducted to determine the change score for each measure that might be associated with the minimum change required to be considered important. Using conventions in the literature[38,39], an MID in scores was estimated by effect size (based on a proportion of SD units) and by the score change equivalent to one SEM. The Cohen convention[41], although limited by the absence of

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clinical anchors, does offer a common unit (effect size) by which various instruments can be compared. A small effect can be compared to a moderate effect within one instrument and across others. It is likely in most applications that the MID of a given instrument lies somewhere between Cohen's small (0.2 SD) and moderate (0.5 SD) effect sizes[41]. These distribution-based estimates of MID can be confirmed or adjusted using available relevant clinical anchors by comparison. Wyrwich and Wolinsky[42] suggest that the SEM, computed as the SD multiplied by the square root of 1 minus the reliability coefficient (alpha), offers an advantage over the use of the SD alone because it factors in the reliability of a test and renders the estimate of MID to be less sample-dependent. Thus, the distribution-based MID in change scores for the FACIT Fatigue scale ranged from 2.2 (d = 0.2) to 5.5 (d = 0.5), with the SEM suggesting an intermediate MID value of 4.10. The range of potential distribution-based MID values for the SF-36 Vitality was 4.1 to 10.3, and for MAF was 2.4 to 5.9.

As described (see Analysis Plan, above), to compare fatigue change scores among groups defined by the range of MID criteria, 5 distinct groups were created: those who reported major worsening, those who reported minor worsening, an unchanged group, those who reported minor improvement, and those who reported major improvement. Using each of the 3 fatigue measures alternately as the reference measure for purposes of defining these groups, the mean change from baseline to Week 24 for each group was computed for the remaining 2 measures. Thus, changes from baseline to Week 24 in FACIT Fatigue scale and MAF were evaluated across 5 groups of patients defined by SF-36 Vitality change scores (Table 4), changes in FACIT Fatigue scale and SF-36 Vitality were evaluated across 5 groups of patients defined by MAF change scores (Table 5), and changes in SF-36 Vitality and MAF were evaluated across 5 groups of patients defined by FACIT Fatigue scale change scores (Table 6). For all 3 sets of analyses, all change scores were consistent with the direction (i.e., worse vs improved) and magnitude (e.g., 0.2 SD vs 0.5 SD) of the defined groups. Change scores across these 5 distinct groups were significantly different from one another ($p < 0.0001$) for all comparisons. In addition, the order of means across adjacent categories for the 6 comparisons in Tables 4 through 6 was consistent with the classification according to the criterion instrument that determined group assignment. For example, FACIT Fatigue scale mean change scores in those SF-36 Vitality–defined MID groups representing the largest effect sizes ($\leq$ –0.5 SD and > 0.5 SD) were larger than the change scores for MID groups defined by lesser effect sizes. The average difference between means of adjacent categories (last column of Tables 4 through 6) offers an estimate of an MID that, because they are based on the 0.2 to 0.5 SD ranges for classifying patients, one would expect to be comparable to the distribution-based estimates. Thus, for example, the average distance between adjacent categories of the MAF-defined groups for the FACIT Fatigue is 3.74 (Table 5, last column), which compares to the distribution-based FACIT Fatigue MID range of 2.2 to 5.5.

Agreement of the computation of MID in FACIT Fatigue scale and SF-36 Vitality change scores was further compared between data from STAR and ARMADA (MAF was not assessed in this latter trial). MID values using both 0.2 SD and 0.5 SD were compared between both trials. The FACIT Fatigue scale scores associated with the defined effect sizes were nearly identical between the 2 trials, with the weighted kappa being 1.00 for the FACIT Fatigue scale and 0.97 for the SF-36 Vitality scale.

Because the 3 fatigue measures performed similarly when comparing groups on average scores, additional analyses were conducted to determine whether the 3 fatigue measures were equivalent in their coverage of the full spectrum of fatigue in this patient population. Item response theory (IRT) was used to examine how fully the questions on the 3 fatigue scales measured patients' self-reported fatigue

*Table 4.* FACIT Fatigue scale and MAF change scores (baseline to Week 24) by SF-36 Vitality minimally important difference (MID)* groups.

| | $\leq$ –0.5 SD | > –0.5 to $\leq$ –0.2 SD | > –0.2 to $\leq$ 0.2 SD | > 0.2 to $\leq$ 0.5 SD | > 0.5 SD | Average Difference† |
|---|---|---|---|---|---|---|
| FACIT Fatigue scale change scores | | | | | | |
| MID groups | $\Delta_{VT} \leq -10.3$ (n = 50) | $-10.3 < \Delta_{VT} \leq -4.1$ (n = 73) | $-4.1 < \Delta_{VT} \leq 4.1$ (n = 53) | $4.1 < \Delta_{VT} \leq 10.3$ (n = 136) | $\Delta_{VT} > 10.3$ (n = 262) | |
| Mean | –4.25 | –0.1 | 2.22 | 3.9 | 10 | 3.56 |
| SD | 7.65 | 6.19 | 5.99 | 6.93 | 9.37 | |
| p value†† | < 0.001 | 0.919 | 0.045 | < 0.001 | 0.001 | |
| MAF change scores | | | | | | |
| MID groups | $\Delta_{VT} \leq -10.3$ (n = 49) | $-10.3 < \Delta_{VT} \leq -4.1$ (n = 72) | $-4.1 < \Delta_{VT} \leq 4.1$ (n = 49) | $4.1 < \Delta_{VT} \leq 10.3$ (n = 128) | $\Delta_{VT} > 10.3$ (n = 258) | |
| Mean | 5.27 | –0.46 | –0.72 | –4.5 | –11.14 | 4.10 |
| SD | 9.08 | 9.2 | 8.36 | 9.68 | 11.42 | |
| p value†† | < 0.001 | 0.708 | 0.626 | < 0.001 | < 0.001 | |

$\Delta_{VT}$: SF-36 Vitality mean change score. * Defined as 0.5 and 0.2 SD of the change score. † Average difference between adjacent categories in row. †† p value for 2-tailed t test of Ho: mean change = 0. F-test of Ho: means are equivalent across categories and significant for both rows, p value < 0.001.

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*Table 5.* FACIT Fatigue scale and SF-36 Vitality change scores (baseline to Week 24) by MAF minimally important difference (MID)* groups.

| | ≤ –0.5 SD | > –0.5 to ≤ –0.2 SD | > –0.2 to ≤ 0.2 SD | > 0.2 to ≤ 0.5 SD | > 0.5 SD | Average Difference† |
|---|---|---|---|---|---|---|
| FACIT Fatigue scale change scores | | | | | | |
| MID groups | $\Delta_{MAF} \leq -5.9$ (n = 331) | $-5.9 < \Delta_{MAF} \leq -2.4$ (n = 73) | $-2.4 < \Delta_{MAF} \leq 2.4$ (n = 110) | $2.4 < \Delta_{MAF} \leq 5.9$ (n = 55) | $\Delta_{MAF} > 5.9$ (n = 62) | |
| Mean | 10.73 | 4.12 | 1.45 | –1.06 | –4.22 | 3.74 |
| SD | 9.15 | 5.03 | 5.19 | 6.43 | 7.09 | |
| p value†† | < 0.001 | < 0.001 | 0.045 | 0.301 | < 0.001 | |
| SF-36 Vitality change scores | | | | | | |
| MID groups | $\Delta_{MAF} \leq -5.9$ (n = 270) | $-5.9 < \Delta_{MAF} \leq -2.4$ (n = 78) | $-2.4 < \Delta_{MAF} \leq 2.4$ (n = 109) | $2.4 < \Delta_{MAF} \leq 5.9$ (n = 55) | $\Delta_{MAF} > 5.9$ (n = 62) | |
| Mean | 22.4 | 10.83 | 4.28 | 1.64 | –5.0 | 6.85 |
| SD | 20.89 | 16.36 | 13.31 | 16.16 | 19.12 | |
| p value†† | < 0.001 | < 0.001 | 0.016 | 0.511 | 0.033 | |

$\Delta_{MAF}$: MAF mean change score. * Defined as 0.5 and 0.2 SD of the change score. † Average difference between adjacent categories in row. †† p value for 2-tailed t test of Ho: mean change = 0. F-test of Ho: means are equivalent across categories and significant for both rows, p value < 0.001.

*Table 6.* SF-36 Vitality and MAF change scores (baseline to Week 24) by FACIT Fatigue scale minimally important difference (MID)* groups.

| | ≤ –0.5 SD | > –0.5 to ≤ –0.2 SD | > –0.2 to ≤ 0.2 SD | > 0.2 to ≤ 0.5 SD | > 0.5 SD | Average Difference† |
|---|---|---|---|---|---|---|
| SF-36 Vitality change scores | | | | | | |
| MID groups | $\Delta_{Fatigue} \leq -5.5$ (n = 54) | $-5.5 < \Delta_{Fatigue} \leq -2.2$ (n = 39) | $-2.2 < \Delta_{Fatigue} \leq 2.2$ (n = 145) | $2.2 < \Delta_{Fatigue} \leq 5.5$ (n = 92) | $\Delta_{Fatigue} > 5.5$ (n = 244) | |
| Mean | –8.15 | –2.69 | 7.34 | 8.37 | 23.98 | 8.03 |
| SD | 19.38 | 15.43 | 15.28 | 17.26 | 19.65 | |
| p value†† | < 0.001 | 0.350 | < 0.001 | < 0.001 | < 0.001 | |
| MAF change scores | | | | | | |
| MID groups | $\Delta_{Fatigue} \leq -5.5$ (n = 52) | $-5.5 < \Delta_{Fatigue} \leq -2.2$ (n = 38) | $-2.2 < \Delta_{Fatigue} \leq 2.2$ (n = 139) | $2.2 < \Delta_{Fatigue} \leq 5.5$ (n = 89) | $\Delta_{Fatigue} > 5.5$ (n = 238) | |
| Mean | 8.19 | 0.09 | –0.76 | –4.86 | –13.24 | 5.36 |
| SD | 9.82 | 8.88 | 7.49 | 6.05 | 10.97 | |
| p value†† | < 0.001 | 0.953 | 0.332 | < 0.001 | < 0.001 | |

$\Delta_{Fatigue}$: FACIT Fatigue Scale mean change score. * Defined as 0.5 and 0.2 SD of the change score. † Average difference between adjacent categories in row. †† p value for 2-tailed t test of Ho: mean change = 0. F-test of Ho: means are equivalent across categories and significant for both rows, p value < 0.001.

along the fatigue severity continuum. Specific interest was in the question of which instrument, if any, was better "targeted" to this RA population. IRT allows determination of which questions differentiate people at low, middle, and high ranges of what is being measured — in this case, fatigue. The results in Figure 1 show that the 4 items from the SF-36 Vitality scale tend to locate on the high end of the fatigue continuum (i.e., they differentiate people with relatively low fatigue very well, but they do not differentiate people with moderate to severe fatigue as well). In contrast, the MAF was targeted in the middle range of fatigue (compare in Figure 1 the range of MAF item plots to the distribution of patients). Finally, the FACIT Fatigue scale covered essentially the entire range of the distribution of patients, with the exception of those with very little fatigue. Both FACIT Fatigue and MAF covered a wider range of self-reported fatigue than SF-36 Vitality, and FACIT Fatigue covered a wider range than MAF.

## DISCUSSION

The goal of our study was to validate a brief measure of fatigue, originally developed to assess anemia related fatigue in patients with cancer, in a sample of patients with RA. The FACIT Fatigue scale, a 13 item measure of fatigue, showed good internal consistency in patients with RA, which was comparable to that of 2 other fatigue scales previously validated in this population, the SF-36 Vitality scale and the MAF. The baseline FACIT Fatigue scale scores were strongly associated with scores on the SF-36 Vitality and MAF, providing evidence of convergent validity. Changes in FACIT Fatigue scale scores over 24 weeks successfully discriminated between groups defined by levels of the clinical endpoint, the ACR20, ACR50, and ACR70. Thus, patients in ACR groups reflecting greater clinical improvement in RA also showed larger increases in their FACIT Fatigue scale scores, indicating decreased levels of fatigue. Further, these changes in FACIT Fatigue scale scores were associated with

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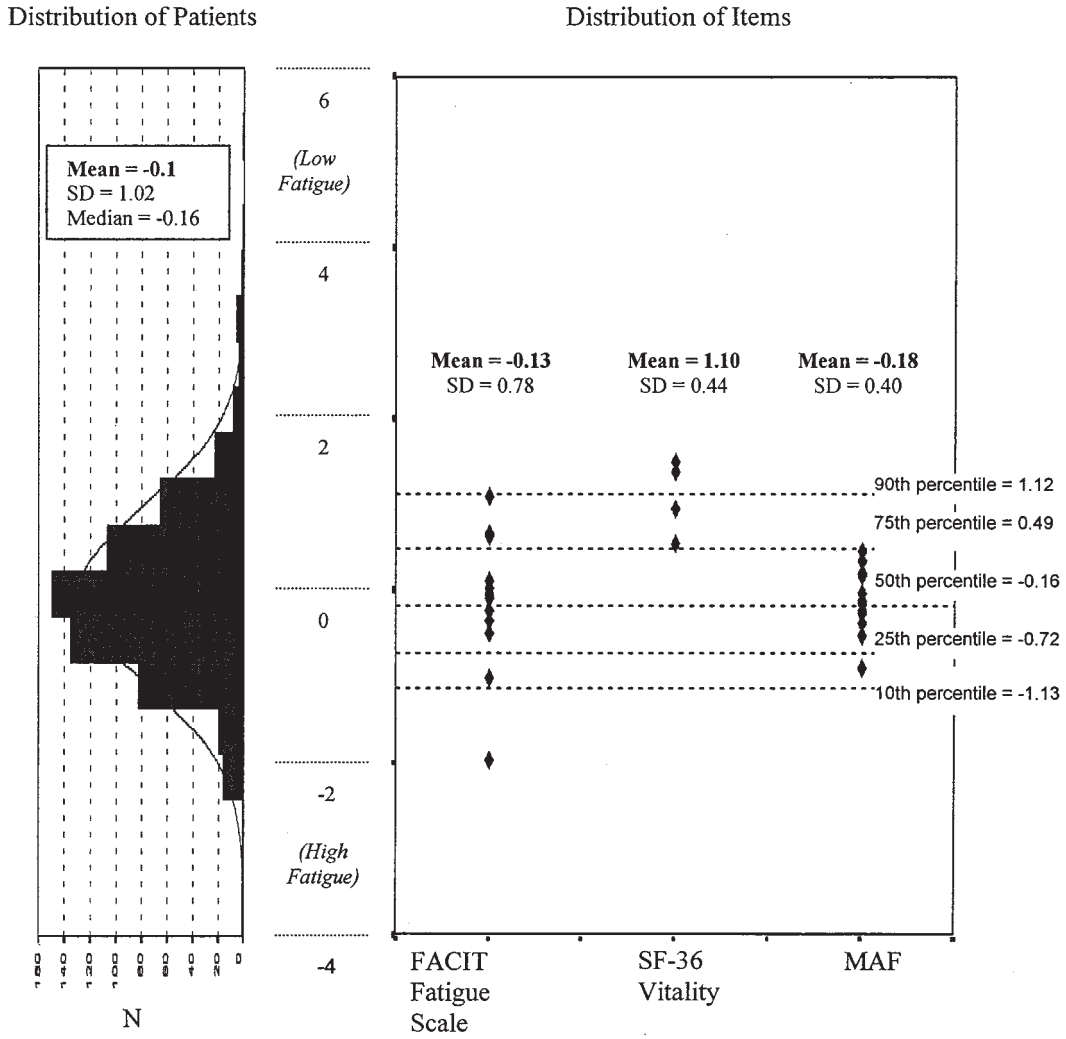


*Figure 1.* Item coverage of the fatigue continuum at baseline of STAR (n = 625). The fatigue measure for each person on each questionnaire was transformed to a common interval scale (y-axis) using item response theory. The location of each item reflects the relative probability that a problem will be endorsed. Because items perform best when targeted to people at the same location on the continuum, one can directly compare the distribution of items on the right with people on the left. ◆: individual item location on the fatigue continuum (average item response category is plotted); STAR: Safety Trial of Adalimumab in Rheumatoid Arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; SF-36: Short-Form 36; MAF: Multidimensional Assessment of Fatigue.

moderate to large effect sizes. Similar results were observed for the SF-36 Vitality and MAF measures.

The comparability of the FACIT Fatigue scale with the SF-36 Vitality and MAF was further examined setting each of the 3 fatigue measures as a reference to create 5 distinct groups of patients based on the guidelines of 0.2 and 0.5 SD units following Cohen[41]. These 5 groups were then compared to one another using the other 2 fatigue measures. Regardless of the instrument used to classify patients (Tables 4 through 6), the results consistently converged on the conclusion that each instrument supports the validity of the other and produces comparable estimates of an MID or change score. One notes, however, that SF-36 Vitality scores and, to a lesser extent, FACIT Fatigue scale scores increased among the patients classified as unchanged by other measures. This requires further study to determine the extent to which one instrument's change relates to that of another. Nevertheless, each instrument shows excellent reliability, concurrent validity, and responsiveness to ACR clinical classification.

The MID values for the FACIT Fatigue scale were confirmed in a second sample of patients with RA that produced nearly identical values. A 3 to 4 point change in the FACIT Fatigue scale can be considered clinically significant. The FACIT Fatigue scale was comparable to the SF-36 Vitality and MAF in its psychometric performance, offering clinicians and investigators another choice in the measurement of this important concern of patients with RA.

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When might someone wish to use the FACIT Fatigue scale in RA over other available instruments? The evaluative performance of the 3 instruments across these 2 trials was very comparable; effect sizes for treatment differences were similar, regardless of instrument choice. Thus, as evaluative instruments measuring group change, all performed well. However, the 13 item FACIT Fatigue showed a broader coverage of the fatigue continuum in RA patients than the longer (16 item) MAF. The shorter (4 item) SF-36 Vitality scale, while it has the advantage of brevity, was targeted toward the healthy end of the fatigue spectrum, suggesting it would not be ideal when planning studies with patients in the moderate to severe fatigue range (Figure 1). Two instruments (FACIT and SF-36) offer normative data from the general population[9,29]. The FACIT Fatigue adds to this the availability of normative data on patients with cancer[9].

Fatigue is a highly prevalent symptom of RA[18] and affects patients with all levels of RA severity. Patients have identified fatigue as the most problematic aspect of their disease[19], and it may represent an even greater burden for some patients than pain. Fatigue may be especially salient for patients with recent-onset RA and lower disease activity, because as disease activity increases, other features of the disease, such as pain, depression, and functional losses, become more prominent[8]. Despite this, fatigue in RA has been relatively neglected in the arthritis literature. Fatigue is not included among the outcome measures proposed by the ACR[24] and the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Committee[43].

In contrast, fatigue has now achieved recognition as a prominent and distressing symptom among patients with cancer and is one of the prime targets of symptom management therapies[44,45]. These data on fatigue in patients with RA allow the degree of fatigue suffered by these patients at baseline (pretreatment) assessment in the STAR to be put into perspective. For example, the mean score of 29.2 on the FACIT Fatigue scale indicates patients with RA are roughly 0.5 SD less fatigued than are cancer patients with moderate to severe anemia who are about to begin erythropoietin therapy[9]. However, this score of 29.2 is more than 1.0 SD worse than the scores of nonanemic patients with cancer receiving outpatient therapy for their disease and 1.5 SD worse than the general population of the US[9]. This places the average patient with RA beginning this trial below the 10th percentile of fatigue scores (i.e., worse fatigue) in the US population and below the 15th percentile of fatigue scores in nonanemic patients with cancer[9], suggesting that greater attention to this debilitating symptom is warranted in the RA population.

The significance of fatigue for patients with RA has apparently failed to capture the attention of many clinicians. Nearly 90% of rheumatologists do not assess fatigue during their clinical encounters with patients, and only 4% assess fatigue at least 75% of the time[46]. Wolfe and Pincus[47] have argued for the collection of patient-reported fatigue data to better identify patients with RA who require or would benefit from intensive symptom palliation. Formal, quantitative information would also allow clinicians to track fatigue levels and response to therapy over time. In addition to meeting formal measurement requirements, self-report instruments must also possess clinical relevance and feasibility[47]. The FACIT Fatigue scale is an example of such an assessment tool that is psychometrically sound and places minimal burden on patients to answer and clinic staff to score and interpret. Available computer-administered assessment and scoring programs make its routine use in clinical practice highly feasible.

This study has provided evidence of the validity of the FACIT Fatigue scale in patients with RA. The validation of the scale in RA expands the range of chronic illnesses in which the FACIT Fatigue scale may have utility. It also expands fatigue assessment options in rheumatology. Although the importance of assessment of multidimensional quality of life has begun to achieve recognition in RA, the 13 item Fatigue scale provides a brief alternative when the clinical or research interest is symptom-focused.

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