Published in final edited form as:

Cancer. 2008 September 15; 113(6): 1480–1488. doi:10.1002/cncr.23698.

Development of a Fatigue and Functional Impact Scale (FFIS) in Anemic Cancer Patients Receiving Chemotherapy

David Cella, PhD¹, Hema N. Viswanathan, PhD², Ron D. Hays, PhD³, Tito R. Mendoza, PhD⁴, Kevin D. Stein, PhD⁵, David J. Pasta, MS⁶, Aimee J. Foreman, MA⁶, Saroj Vadhan-Raj, MD⁴, and Joel D. Kallich, PhD²

¹Evanston Northwestern Healthcare and Northwestern University, Evanston, Illinois, USA

²Amgen Inc., Thousand Oaks, California, USA

³University of California Los Angeles Department of Medicine/Division of General Internal Medicine & Health Services Research, Los Angeles, California, USA

⁴University of Texas MD Anderson Cancer Center, Houston, Texas, USA

⁵Behavioral Research Center, American Cancer Society, Atlanta, Georgia, USA

⁶ICON Clinical Research, San Francisco, California, USA

Abstract

Purpose—To develop a brief measure of fatigue and functional impact in cancer patients with anemia.

Patients and Methods—Data were obtained from a multi-site, phase 2 study of darbepoetin alfa ($n = 1,558$). Eligible patients were ≥ 18 years with nonmyeloid malignancies and anemia (hemoglobin ≤ 11 g/dL) receiving chemotherapy. Items from the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Brief Fatigue Inventory (BFI), Fatigue Symptom Inventory (FSI) and items adapted from the Medical Outcomes Study SF-36 physical functioning scale were evaluated for inclusion in the measure. Items were selected by identifying the best predictors of total FACT-F scores, hemoglobin, and adjusted VO_2 Max in regression models. Correlations were examined between scale scores and adjusted VO_2 Max, hemoglobin, performance, self-reported energy, and productivity.

Results—Data from 401 patients with complete data were used to identify eight items for the Fatigue and Functional Impact Scale (FFIS), which was then evaluated using 1,355 of the 1,558 patients. The FFIS had an estimated internal consistency reliability of 0.90. The FFIS had large correlations with the FACT-F ($r = 0.94$), FSI ($r = 0.80$) and BFI ($r = 0.86$) from which it was derived. The FFIS also correlated substantially with single item measures of energy ($r = 0.75$) and productivity ($r = 0.72$).

Conclusion—The FFIS is a reliable, brief, and practical tool potentially suitable for identifying fatigue and functional impact in cancer patients.

Keywords

fatigue; anemia; oncology; measurement; health-related quality of life

Introduction

Anemia resulting from chemotherapy or cancer itself is a significant clinical concern.¹⁻⁵ Research has shown associations between anemia and diminished health-related quality of life, including fatigue.⁶ Fatigue is the most commonly reported symptom in people with cancer, with prevalence in the range of 60-95%.⁷ It can be more debilitating than other symptoms or treatment-related complications.⁸ Increased fatigue levels have been found to correlate with impairment in structured motor performance tasks, including the six-minute walk.⁹ Early identification and treatment of fatigue is enabled by clinical tools drawn from research over the past decade¹⁰⁻¹³ and best practice guidelines drawn from available literature (<http://www.nccn.org/>). However, in spite of the evidence, fatigue often goes undetected or unreported in routine clinical practice.¹⁴⁻¹⁵ Patients sometimes fail to discuss their fatigue symptoms with physicians, and physicians may fail to adequately assess these symptoms.¹⁴⁻¹⁶

The first section of the International Statistical Classification of Diseases and Related Health Problems fatigue assessment tool (P-ICD10) in cancer has been proposed as a means of detecting clinically significant fatigue.¹⁷ This approach, however, has not correlated with measures of functional impairment. Several approaches have been used to measure self-reported fatigue, ranging from the use of a single item,¹⁸ to the development of multi-item instruments such as the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) score,¹⁹ the Piper Fatigue Scale,²⁰ and the Multidimensional Fatigue Inventory (MFI).²¹ These multi-item instruments are comprehensive, but their length may be a barrier to clinical use. A shortened tool that detects clinically meaningful fatigue may be more practical for use in clinical practice and beneficial to patient care. It is essential that patient-reported assessments used in clinical practice be easily administered as well as reliable and valid.²² The objective of this study was to develop a brief and valid measure of fatigue and functional impairment in cancer patients with anemia, receiving chemotherapy, using both self-reported and performance-based measures.

Patients and Methods

Eligibility and Randomization

Data were obtained from a multi-site, open-label, non-comparative phase 2 study of darbepoetin alfa administered at a starting dosage of 3 mcg/kg every 2 weeks for up to 8 doses.²³ Eligible patients were ≥ 18 years of age, were receiving cyclic chemotherapy for nonmyeloid malignancies, and were anemic, determined by hemoglobin ≤ 11 g/dL during screening. Patients were scheduled to receive at least an additional 8 weeks of cyclic chemotherapy. Eligibility also required adequate renal and hepatic function, adequate iron stores (transferrin at $\geq 15\%$ and/or ferritin ≥ 10 ng/mL) and no evidence of nutritional anemia. Patients were enrolled between September 2001 and January 2003.

All patients received the FACT-F and to minimize redundancy and patient burden, were randomly assigned (1:1) to complete either the Brief Fatigue Inventory (BFI) plus a single item, "Unusually tired or fatigued in the last week," or to complete the Fatigue Symptom Inventory (FSI). All study procedures were approved by the institutional review board of each center and all subjects provided informed consent prior to data collection.

Study variables

Performance-Based Measures—The Modified Harvard Step Test (MHST) was administered at weeks 1 (baseline), 9, and 17 (end of study) to assess functional capacity based on a published nomogram for calculation of maximum oxygen uptake (VO_2Max).²⁴

Each of the three stages of the MHST required 3 minutes of continuous exercise at a pre-determined speed, followed by measurement of the exercise heart rate. Additional elements needed to estimate VO_2Max such as weight, age, and gender were collected. To assess anemia, hemoglobin was monitored every 2 weeks during the treatment phase.

Self-Reported Measures—Self-reported fatigue and physical functioning measures were administered at weeks 1 (baseline), 9, and 17 (end of study). All patients completed the 13-item FACT-F,¹⁹ and questions from either the BFI²⁵ or the FSI,¹¹ as randomized. All patients also responded to five questions from the Medical Outcomes Study (MOS) SF-36 physical functioning scale adapted to have values ranging from 0 (“Not limited at all”) to 10 (“Very limited”).²⁶ The five items were “Limited climbing several flights of stairs,” “Limited climbing one flight of stairs,” “Limited walking more than one mile,” “Limited walking several blocks,” and “Limited walking one block.” Higher scores indicated better health status for these measures.

All patients also answered one question each about energy and productivity. Energy was measured with a single item, “How much energy have you had during the past 4 weeks?” with possible values from 0 (“No energy at all”) to 10 (“A great deal of energy”). Patients were asked to rate their productivity using a single item, “Rate your productivity or effectiveness in your work or daily activities during the past 4 weeks.” Response options for the productivity measure ranged from 0 (“No productivity or no effectiveness”) to 10 (“Best possible productivity or effectiveness”).

At the MHST assessments, physical exertion was measured on the Borg Rating of Perceived Exertion (RPE), with response values ranging from 6, suggesting “No exertion,” to 20, suggesting “Extremely strenuous exercise.”²⁷ Clinicians recorded the patient's status using the Eastern Cooperative Oncology Group (ECOG) performance measure consisting of five levels ranging from 0 (“Fully active”) to 5 (“Dead”).²⁸

Statistical Analysis

Fatigue and physical functioning items from different scales were transformed to a possible range of 0 to 100, with higher scores indicating better health. To select items, data were analyzed using a scale development sample of 401 patients who had baseline hemoglobin, baseline FACT-F, at least one follow-up hemoglobin measurement, and who completed 3 minutes of one or more stages of the MHST. The scale development sample included 12 patients who did not have a follow-up FACT-F. Analyses were conducted separately for patients randomized to the FSI group and those randomized to the BFI group. To identify candidates for inclusion in the new measure, items from the FACT-F, MOS, BFI, and FSI were evaluated using linear regression and the RSQUARE selection method in the SAS REG procedure to determine the best combinations of predictors of the total FACT-F score, the adjusted VO_2Max , and hemoglobin, based on pooled data from all three assessments (baseline, week 9, and week 17). The best predictors were identified based on r-squared values.

Final item selection was guided by how well the change in candidate variables over time predicted change in the total FACT-F, change in measures of adjusted VO_2Max , and change in hemoglobin over time. The final measure was comprised of items identified from regression models using the entire scale development sample, and also identified separately in the groups randomized to either the FSI or BFI (because patients in the BFI group had missing values for FSI items and vice versa).

Evaluation of the new measure was conducted using an assessment sample consisting of the 1,355 patients from the source study who had a baseline and at least one follow-up FACT-F

assessment. The number of patients used in each analysis varies by the number of completed responses obtained for that particular item(s). Scale internal consistency was estimated using Cronbach's coefficient alpha. Pearson correlation coefficients were estimated between scores obtained from the new measure and the following variables: hemoglobin levels, exercise capacity (adjusted VO₂Max), FACT-F, BFI, FSI, perceived exertion, energy, productivity, and performance status (measured using the ECOG instrument). Change between baseline and week 9 was calculated for hemoglobin and exercise capacity as well as the self-reported measures, and correlations between change scores were examined. Correlations were calculated between scale scores and the full instruments from which the items were selected, and between scale scores and theoretically related constructs (adjusted VO₂Max, hemoglobin, ECOG performance status, self-reported energy, and productivity). In addition, bifactor analysis²⁶ was used to assess whether the final FFIS was sufficiently unidimensional.

In addition to the correlations, the newly created measure was compared to other measures of fatigue and functional capacity by gauging how well each scale or group of items predicted pre-defined outcomes that were recoded to a binary (Yes/No) response. Outcomes of interest included VO₂Max, exercise heart rate, and Borg scale (RPE), all measured at the time of the MHST if the MHST was within 3 days of the patient self-report. Energy, productivity, and ECOG performance status were measured at the time of the patient self-report. Hemoglobin was as measured up to 3 days before the patient self-report. In addition, two variables ("Completed MHST" and "Attempted MHST") were defined to capture MHST performance. The MHST was considered completed if it had a duration of 180 seconds and was completed within 3 days of the patient self-report (it was considered attempted if carried out within 3 days of the patient self-report and the duration was <180 seconds).

The cutpoints were based on the percentile distribution of values of each outcome for cross-sectional variables. For example, if a cutpoint of 40 was selected based on the distribution of the variable, we created a binary value of 1 if ≥ 40 , and 0 if < 40 . In the case of longitudinal variables measuring change over time, the cutpoints were based on the distribution of each change score. Zero was always one of the cutpoints for change scores because it is always of interest. Additional cutpoints were selected to be round numbers that still included a reasonable fraction of the cases both above and below the cutpoint. Comparison among measures was based on calculating the area under the Receiver-Operator Curve (ROC), the C-index, of each scale for each outcome. Higher values are better, with a value of 1.0 representing perfection (the instrument is able to perfectly predict the outcome) and a value of 0.5 indicating the instrument is performing only about as well as one would expect by chance.

To approximate the scores expected if both the BFI and FSI had been collected, sensitivity analyses were conducted whereby missing values for the single BFI and FSI items selected for inclusion in the tool were imputed based on regression models using the global FACT-F, energy, productivity, ECOG performance, perceived exertion, adjusted VO₂Max, and hemoglobin as independent variables.

Results

Patient characteristics

A total of 1588 patients from 219 participating community oncology practices who met eligibility criteria were enrolled in the trial. The scale development sample of 401 patients was used for the item selection process and the assessment sample of 1355 patients was used for the assessment of the newly developed measure. Sociodemographic characteristics of

these samples are summarized in Table 1. The patients averaged 60 years of age, and most patients were white (81%) and female (68%).

Item Selection

Based on examination of the predictors of the global FACT-F scores, VO₂Max, and hemoglobin, 6 items from the FACT-F, 4 items from the MOS, 4 items from the BFI, and 3 from the FSI were identified as the best predictors. These 17 items were included in final item selection, which was based on changes over time.

Predictors of change in FACT-F scores over time—In subgroup analyses based on the entire scale development sample and on the BFI and FSI subsamples, three items that consistently predicted the change in FACT-F scores over time were, “I have trouble starting things because I am tired,” “I must limit social activity because I am tired,” and “I feel weak all over” from the FACT-F which explained 83% to 85% variance in change in FACT-F scores over time. The R² obtained from the model increased from 86% to 88% with the addition of a fourth item, “I feel tired,” from the FACT-F (Multiple R = 0.933). The addition of a fifth item increased the variance explained to 89%.

Predictors of change in VO₂Max over time—Items that consistently predicted change in VO₂Max over time were “I feel fatigued” and “I feel listless (washed out)” from the FACT-F, “Limited climbing several flights of stairs” and “Limited walking one block” from the MOS (Multiple R = 0.229). Addition of a single item, “What is your level of fatigue on average?” from the FSI increased the variance explained from 15% to 21%. The best additional predictor from the BFI, “How much has fatigue interfered with your relationship with other people?” increased the variance explained from 21% to 24%. Dropping the single item predictors from the BFI and FSI substantially reduced the amount of variance explained.

Predictors of change in hemoglobin over time—In the combined group of patients, best predictors of change in hemoglobin were “Limited climbing several flights of stairs,” “Limited climbing one flight of stairs,” from the MOS and “I feel weak all over” from the FACT-F (Multiple R = 0.268). In the FSI subgroup, the addition of a fourth item, “Rate how much, in the past week, fatigue interfered with your mood” from the FSI improved the variance explained in change in hemoglobin from 13% to 14%. Prediction of change in hemoglobin over time was markedly poorer in the BFI group.

Based on the above regression results, a set of six core items consisting of four items from the FACT-F and two from the MOS were identified for inclusion in the FFIS. In addition, a single item from the BFI, “How much has fatigue interfered with your relationship with other people?” was also identified for inclusion in the FFIS in the subset of patients taking the BFI. Similarly, an additional item from the FSI, “What is your level of fatigue on average?” was identified in the subset of patients taking the FSI. The items, means, and range for each item in the FFIS are shown in Table 2.

Psychometric Properties

Using the assessment sample, we examined the internal consistency reliability of the FFIS separately in the BFI and FSI subsamples, pooled across assessments. Cronbach's coefficient alpha was .91 in the BFI subsample and .90 in the FSI subsample, and corrected item-to-scale correlations for the items ranged from .66 to .79 except that the FSI item correlated .62 with the rest of the scale. We were concerned that the two stair-climbing items from the MOS physical functioning scale might represent a different domain than the other six items, so we performed a bifactor analysis to address this question. We found that the two stair-

climbing items had high loadings on the general factor, but those items also shared noteworthy bivariate association beyond their relationship to the other items in the FFIS (i.e., item dependency). Forming subscales from the four FACT items, the two stair-climbing items, and the BFI or FSI item resulted in pairwise correlations among the subscales of .60 to .69. We also checked for item dependency between the two items on social functioning, but it was not different than among other pairs of items. We elected not to adjust the scoring algorithm to accommodate the identified item dependency, in order to preserve the simplicity of the FFIS.

Correlations between FFIS scores and other self-reported measures and functional capacity are shown in Table 3. Correlations between FFIS scores and related concepts, such as self-reported energy and productivity, are high—providing evidence of construct validity. The correlations between change scores for the FFIS and change scores for other self-report measures were nearly as high. However, the correlations between FFIS scores and objective measures (including hemoglobin) were more modest (magnitude 0.24 to 0.38 for data at a single point in time and 0.16 to 0.20 for change scores). Adjusted VO₂Max was not correlated with FFIS scores.

ROC Analysis

Tables 4a–b show the ROC analysis for the longitudinal change scores from baseline to week 9. In each table, the columns detail the alternative instruments; the last column details the one item from the BFI that is in the FFIS (Table 4a) or the one item from the FSI that is in the FFIS (Table 4b). The rows in each table represent the alternative criteria (outcomes), namely the various measures that the new measure should predict. Multiple alternative cutpoints are given, as no universally-accepted cutpoint is available for these outcomes. For the FFIS column, the entries are the area under the ROC curve for that instrument and that outcome, otherwise known as the C-index. For the other columns, the entry in the table is the deviation in the C-index for that measure relative to the FFIS. A positive value means that the measure performs better than the FFIS for that outcome and a negative value means that the measure performs worse than the FFIS for that outcome. An instrument with better sensitivity for given specificity, or better specificity for given sensitivity, would have a higher C-index. The FFIS performs well in the change score analysis. This is especially important for evaluating improvement in functional capacity from the change in the self-reported scale.

Analysis of Imputed Values

No patient has data for all eight items of the FFIS because no patient completed both the BFI and FSI. We imputed the missing score using regression and compared that to the score obtained by averaging the available items. The correlation between the imputed score and the score obtained by averaging the available items was 0.998. The imputed score gave very similar results in ROC analyses.

Discussion

The FFIS, an eight-item instrument, was derived from existing self-reported measures, 11-19-25-26 and has potential for use as a short measure to identify fatigue and functional impairment in anemic patients receiving chemotherapy. Items were selected for potential inclusion based on their ability to predict hemoglobin, functional capacity measured by adjusted VO₂Max, and global FACT-F scores; final item selection considered change in hemoglobin, adjusted VO₂Max, and global FACT-F scores over time.

The FFIS performed almost as well as, or better than, the full versions of the fatigue measures from which it was derived. The validity of the FFIS was confirmed by high correlations between FFIS scores and self-reported energy and productivity scores, as well as by correlations found with other measures of patient-reported fatigue. It is not surprising that the FFIS correlates well with the FACT-F given that the global FACT-F score was used as an outcome variable in item selection, but that does not diminish the utility of this shortened instrument. Correlations with hemoglobin and change in hemoglobin were modest but not unexpectedly so. We also found that FFIS scores were not significantly correlated with change in adjusted VO₂Max over time. It is possible that decreased adjusted VO₂Max may indicate difficulty performing daily activities without actually experiencing fatigue.

The FFIS involves less respondent burden because it is shorter than existing multi-item fatigue measures.^{19-21,25-29} The instrument is easy to score and expected to require 2–3 minutes to complete. Inclusion of two items adapted from the physical functioning subscale of the MOS added an easy-to-understand activity component that assessed functional impairment (limitations in climbing stairs) beyond the general symptoms of fatigue alone. The brevity and ease of use of the FFIS suggests that the instrument may be suitable for the assessment of anemia-related functional capacity deficits in clinical practice. Furthermore, because the FFIS was developed based on patients with various tumor types, the results can be considered generalizable to a range of cancer patients.

The study from which the data to develop the FFIS was obtained had some limitations. Administration of the MHST was not consistent across study sites and the completion rate among patients of even the first stage of the MHST was poor. The scale development sample, which required at least one stage of the MHST to be completed, included only about 25% of the patients (401/1588) and was biased towards patients with better functional capacity. The analysis was limited to patients who had completed the MHST test and may have excluded patients with more impaired physical functioning. The small size of the scale development sample meant that we had diminished ability to examine relationships between patient self-report questions and adjusted VO₂Max. Another limitation of the study was that patients were randomized to receive either the BFI or the FSI, so no patient received all eight FFIS items, though this was not found to impact FFIS scores. Also, the timing of the MHST and the PRO measures was not standardized and the assessments could have been up to three days apart.

Despite consisting of only eight items, the FFIS addresses issues related to limitations in social activities and interference in relationships with others, although there are some aspects of fatigue that it does not capture. Also, the physical components of functioning are limited to climbing stairs, which focuses on the lower extremities. However, Lai et al. found that fatigue was sufficiently unidimensional to render it suitable for applications such as item response theory that require unidimensionality.³⁰⁻³¹ This finding was based on a bifactor analysis conducted using data from a study of 555 cancer patients who were administered a 72-item fatigue bank covering a range of fatigue-related concerns including intensity, frequency and interference with physical, mental, and social activities.³¹ The FFIS may not be as responsive to change in fatigue as more comprehensive measures of fatigue.¹⁹⁻²⁰ However, longer multidimensional instruments are associated with more respondent burden which can be an issue in repeated administrations with patients already fatigued as a result of disease progression or chemotherapy. The respondent burden associated with completing the eight-item FFIS is expected to be minimal due to the brevity and ease of completion of the scale.

The FFIS may be valuable as a tool to identify patients with fatigue and functional impairment who can be further evaluated to identify the underlying causes of fatigue and

potential interventions. Screening tools in office-based practice have been found to result in improved detection of problems and earlier treatment.^{32,33} It is possible that implementation of the FFIS may result in improved identification of fatigue and functional impairment in cancer patients with anemia and lead to better management of such symptoms. Screening tools that are brief can be easier to use in routine clinical practice. The Patient-Reported Outcomes Measurement Information System (PROMIS) Network, part of the National Institutes of Health Roadmap Initiative, has initiated the formation of item banks including development of a short-form measure of fatigue impact and experience.³⁴ Future research is required to evaluate the performance of the FFIS as a standalone instrument in longitudinal studies and in comparison with the PROMIS fatigue measure in patients with chemotherapy-induced anemia. Examining the relationship between hemoglobin change and improvement in FFIS scores in the context of response to anemia treatment will be of value. Although some research has been conducted on the correlation between patient self-reports and observed performance measures,⁹ this remains an important topic for additional research using the FFIS. It would be especially valuable to describe the relationship between the FFIS and performance indicators of fatigue and physical functioning that do not focus primarily on the lower extremities. Further research using in-depth qualitative patient interviews may be helpful to evaluate content validity and better understand the concept of fatigue in this patient population and the impact of fatigue on patients' daily lives.

The initial findings suggest that the FFIS has good psychometric properties and it is expected to be quick and easy to use. Future studies are needed to further evaluate the FFIS in different populations of patients with cancer. Development of a simpler format with standardized response categories and further evaluation in longitudinal clinical studies with more established scales may be useful. Examination of the sensitivity and specificity of the FFIS and the feasibility of incorporating the instrument in clinical practice is needed. It will be essential to examine the effectiveness of using the FFIS in future research and study the associated impact on patient outcomes.

Acknowledgments

We wish to thank Gardiner-Caldwell London for assistance in editing and formatting the manuscript. We acknowledge Lori Potter and Eric Elkin of ICON Clinical Research for their contributions toward the statistical analyses.

Sources of support/funding and conflicts of interest: This research was supported by Amgen, Inc. Ron Hays was supported in part by the UCLA Center for Health Improvement in Minority Elderly/Resource Centers for Minority Aging Research, NIH/NIA/NCMHD, under Grant 2P30-AG-021684.

References

1. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst.* 1999; 91:1616–1634. [PubMed: 10511589]
2. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol.* 1997; 15:1218–1234. [PubMed: 9060566]
3. Littlewood TJ, Bajetta E, Nortier J, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind placebo-controlled trial. *J Clin Oncol.* 2001; 19:2865–2874. [PubMed: 11387359]
4. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol.* 1998; 16:3412–3425. [PubMed: 9779721]

5. Gabrilove JL, Cleeland C, Livingston RB, Sarokhan B, Winer E, Einhorn L. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol*. 2001; 19:2875–2882. [PubMed: 11387360]
6. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol*. 1998; 25:43–46. [PubMed: 9671330]
7. Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Huntingt)*. 1998; 12:369–377. [PubMed: 10028520]
8. Harper P, Littlewood T. Anaemia of cancer: impact on patient fatigue and long-term outcome. *Oncology*. 2005; 69 2:2–7. [PubMed: 16244504]
9. Mallinson T, Cella D, Cashy J, Holzner B. Giving meaning to measure: linking self-reported fatigue and function to performance of everyday activities. *J Pain Symptom Manage*. 2006; 31:229–241. [PubMed: 16563317]
10. Hwang SS, Chang VT, Cogswell J, Kasimis BS. Clinical relevance of fatigue levels in cancer patients at a Veterans Administration Medical Center. *Cancer*. 2002; 94:2481–2489. [PubMed: 12015774]
11. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res*. 1998; 7:301–310. [PubMed: 9610214]
12. Tchekmedyian NS. Anemia in cancer patients: significance, epidemiology, and current therapy. *Oncology (Huntingt)*. 2002; 16:17–24. [PubMed: 12380951]
13. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. *Br J Cancer*. 2004; 91:822–828. [PubMed: 15238987]
14. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. *Semin Hematol*. 1997; 34:4–12. [PubMed: 9253778]
15. Curt G, Johnston PG. Cancer fatigue: the way forward. *Oncologist*. 2003; 8 1:27–30. [PubMed: 12626786]
16. Dillon E, Kelly J. The status of cancer fatigue on the Island of Ireland: AIFC professional and interim patient surveys. *Oncologist*. 2003; 8 1:22–26. [PubMed: 12626785]
17. Van Belle S, Paridaens R, Evers G, et al. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. *Support Care Cancer*. 2005; 13:246–254. [PubMed: 15549424]
18. Kirsh KL, Passik S, Holtsclaw E, Donaghy K, Theobald D. I get tired for no reason: a single item screening for cancer-related fatigue. *J Pain Symptom Manage*. 2001; 22:931–937. [PubMed: 11728796]
19. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*. 1997; 13:63–74. [PubMed: 9095563]
20. Piper B, Lindsey A, Dodd M. The development of an instrument to measure the subjective dimension of fatigue. *Key Aspects of Comfort: Management of Pain, Fatigue and Nausea*. 1989:199–208.
21. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995; 39:315–325. [PubMed: 7636775]
22. Francis KT. Fitness assessment using step tests. *Compr Ther*. 1987; 13:36–41. [PubMed: 3568602]
23. Vadhan-Raj S, Mirtsching B, Charu V, et al. Assessment of hematologic effects and fatigue in cancer patients with chemotherapy-induced anemia given darbepoetin alfa every two weeks. *J Support Oncol*. 2003; 1:131–138. [PubMed: 15352656]
24. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol*. 1954; 7:218–221. [PubMed: 13211501]
25. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999; 85:1186–1196. [PubMed: 10091805]

26. Reise SP, Morizot J, Hays RD. The role of the bifactor model in resolving dimensionality issues in health outcomes measures. *Qual Life Res.* 2007; 16 1:19–31. [PubMed: 17479357]
27. Borg G. Borg's Perceived Exertion and Pain Scales. *Human Kinetics.* 1998
28. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5:649–655. [PubMed: 7165009]
29. Schwartz AL. The Schwartz Cancer Fatigue Scale: testing reliability and validity. *Oncol Nurs Forum.* 1998; 25:711–717. [PubMed: 9599354]
30. Lai JS, Cella D, Chang CH, Bode RK, Heinemann AW. Item banking to improve, shorten and computerize self-reported fatigue: an illustration of steps to create a core item bank from the FACIT-Fatigue Scale. *Qual Life Res.* 2003; 12:485–501. [PubMed: 13677494]
31. Lai JS, Crane PK, Cella D. Factor analysis techniques for assessing sufficient unidimensionality of cancer related fatigue. *Qual Life Res.* 2006; 15:1179–1190. [PubMed: 17001438]
32. Haughey MT, Calderon Y, Torres S, Nazario S, Bijur P. Identification of depression in an inner-city population using a simple screen. *Acad Emerg Med.* 2005; 12:1221–1226. [PubMed: 16293899]
33. Carroll JC, Reid AJ, Biringer A, et al. Effectiveness of the Antenatal Psychosocial Health Assessment (ALPHA) form in detecting psychosocial concerns: a randomized controlled trial. *Cmaj.* 2005; 173:253–259. [PubMed: 16076821]
34. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. *J Clin Oncol.* 2007; 25:5106–5112. [PubMed: 17991929]

Table 1
Characteristics of the Study Population

Characteristic	Scale Development Sample <i>N</i> = 401 [*]	Assessment Sample <i>n</i> = 1,355 [†]
Age (years), mean ($\pm$ SD, Range)	56.44 ($\pm$ 13.28; 20–85)	60.00 ($\pm$ 12.95; 20–90)
Sex		
Male	156 (39%)	439 (32%)
Female	245 (61%)	916 (68%)
Race		
White	301 (75%)	1095 (81%)
Black	58 (14%)	168 (12%)
Asian	16 (4%)	33 (2%)
Other	26 (7%)	59 (4%)
Education	(<i>n</i> = 385)	(<i>n</i> = 1,266)
Less than high school	50 (13%)	236 (19%)
High school graduate	110 (29%)	425 (34%)
College or higher	225 (58%)	605 (48%)
Tumor Type	(<i>n</i> = 401)	(<i>n</i> = 1,297)
Breast	126 (31%)	377 (29%)
Lung	40 (10%)	235 (18%)
Gynecological	36 (9%)	134 (10%)
Gastrointestinal	91 (23%)	226 (17%)
Lymphoid	45 (11%)	129 (10%)
Genitourinary	16 (4%)	62 (5%)
Other Malignancy	47 (12%)	134 (10%)
Marital Status	(<i>n</i> = 397)	(<i>n</i> = 1,291)
Married	271 (68%)	827 (64%)
Not Married	126 (32%)	464 (36%)

^{*} Patients used to develop the FFIS;

[†] All patients; Note: range = minimum to maximum.

Table 2
Items Included in the Fatigue and Functional Impact Scale (FFIS)

Item	N*	Mean (SD)	Theoretical range
I feel weak all over (FACT-F)	3785	61.33 (32.00)	0–100
I feel tired (FACT-F)	3766	49.04 (30.27)	0–100
I have trouble starting things because I'm tired (FACT-F)	3788	59.81 (31.83)	0–100
I must limit social activities because I'm tired (FACT-F)	3799	56.81 (33.84)	0–100
Limited: climbing one flight of stairs (MOS)	3762	62.21 (34.42)	0–100
Limited: climbing several flights of stairs (MOS)	3750	45.72 (35.29)	0–100
Average level of fatigue (FSI)	1712	52.65 (24.12)	0–100
Level of interference, relationship with others (BFI)	2062	69.17 (29.89)	0–100

N*: Number of complete item responses for the assessment sample

FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MOS, Medical Outcomes Study; FSI, Fatigue Symptom Inventory; BF, Brief Fatigue Inventory.

Table 3
Correlations with Fatigue and Functional Impact Scale (FFIS) Scores Using Pooled Data from All Assessments and Using Change Scores from Baseline to Week 9 (Assessment Sample, N = 1355)

	<i>Correlations based on aggregated data using all assessments</i>		<i>Correlations based on longitudinal data using change scores</i>	
	Pearson's R	N*	Pearson's R	N*
Global FACT-F	.93	3801	.90	1283
Global BFI	.87	2073	.73	692
Global FSI	.80	1714	.69	580
Energy	.75	3785	.57	1274
Productivity (from the MOS)	.72	3772	.52	1264
Adjusted VO ₂ Max	−.02	3157	−.00	1004
Borg Rating of Perceived Exertion (RPE)	−.38	3123	−.20	999
ECOG (measured at MHST)	−.31	3270	−.18	1069
Hb (measured at MHST)	.26	3198	.16	1039
Hb (measured at patient self-report)	.24	3491	.16	1115

N*: Number of complete item responses for the assessment sample

FACT-F, Functional Assessment of Cancer Therapy-Fatigue; BFI, Brief Fatigue Inventory; FSI, Fatigue Symptom Inventory; MOS, Medical Outcomes Study; RPE, Rating of Perceived Exertion; ECOG, Eastern Cooperative Oncology Group; MHST, Modified Harvard Step Test; Hb, hemoglobin.

Table 4a
C-Index (Area Under the ROC Curve), Stage 1 Change Scores from Baseline to Week 9 (In Variable-Specific Units): BFI Group Only

Outcomes	N	FFIS	Full FACT-F	4 FACT-F items in FFIS	Full MOS	2 MOS items in FFIS	Full BFI	1 BFI item in FFIS
Energy (n = 665)								
≤0	326	.755	-.004	-.002	-.074	-.088	-.065	-.110
≤-1	177	.738	+.013	+.005	-.070	-.077	-.053	-.126
≤-2	93	.762	+.020	+.005	-.063	-.068	-.055	-.153
Productivity (n = 659)								
≤0	324	.744	-.001	-.004	-.049	-.073	-.044	-.102
≤-10	156	.755	-.003	-.008	-.057	-.069	-.056	-.133
≤-20	87	.741	+.006	-.003	-.044	-.059	-.047	-.136
VO ₂ Max (n = 521)								
≤0	249	.514	+.007	+.005	+.011	+.020	+.003	-.021
≤-0.01	238	.513	+.006	+.007	+.003	+.012	+.007	-.020
≤-0.10	156	.498	+.001	+.010	+.020	-.001	+.012	+.014
RPE (completers) (n = 159)								
≥0	101	.692	-.081	-.046	-.023	-.004	-.096	-.126
≥1	48	.618	-.070	-.036	-.006	-.007	-.024	+.001
≥2	37	.638	-.068	-.045	+.012	-.008	-.004	-.003
HR (completers) (n = 164)								
≤0	101	.596	-.009	-.005	+.011	-.018	-.057	-.041
≤-5	71	.621	+.001	+.004	-.029	-.059	-.048	-.020
≤-10	47	.629	+.018	+.024	-.072	-.062	-.084	-.039
Hb (n = 587)								
≤0	123	.541	-.000	-.010	+.008	-.000	-.023	-.043
≤-1	40	.616	+.006	+.002	-.034	-.029	-.019	-.084
≤-2	13	.678	-.020	-.031	-.040	-.091	+.044	-.034
ECOG (n = 556)								
≥1	76	.620	-.025	-.013	-.020	-.019	-.015	-.035
≥0	511	.610	+.012	+.004	-.041	-.060	-.040	-.020

ROC, Receiver-Operator Curve; BFI, Brief Fatigue Inventory; FFIS, Fatigue and Functional Impact Scale; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MOS, Medical Outcomes Study; RPE, Rating of Perceived Exertion; HR, heart rate; Hb, hemoglobin; ECOG, Eastern Cooperative Oncology Group.

The FFIS column gives the C-index (area under the ROC curve) for that instrument and that outcome and the subsequent columns give the deviation in the C-index for that measure relative to the FFIS.

Table 4b
C-Index (Area Under the ROC Curve), Change Scores from Baseline to Week 9 (In Variable-Specific Units): FSI Group Only

Outcomes	N	FFIS	Full FACT-F	4 FACT-F items in FFIS	Full MOS	2 MOS items in FFIS	Full FSI	1 FSI item in FFIS
Energy (n = 553)								
≤0	278	.779	+0.44	+0.21	-.064	-.120	-.016	-.150
≤-1	175	.776	+0.33	+0.06	-.064	-.108	-.045	-.131
≤-2	84	.789	+0.13	-.004	-.043	-.085	-.049	-.123
Productivity (n = 552)								
≤0	279	.736	+0.31	+0.05	-.052	-.073	-.013	-.128
≤-10	171	.725	+0.31	+0.06	-.066	-.078	-.028	-.113
≤-20	89	.741	+0.13	+0.02	-.075	-.064	-.016	-.099
VO₂Max (n = 442)								
≤0	201	.509	+0.11	+0.08	+0.027	-.004	+0.026	+0.014
≤-0.01	188	.510	+0.03	+0.02	+0.028	-.017	+0.027	+0.025
≤-0.10	123	.529	+0.02	+0.11	+0.005	-.015	+0.017	-.002
RPE (completers) (n = 129)								
≥0	65	.623	-.019	-.001	-.017	-.037	-.061	-.129
≥1	32	.660	-.009	-.023	+0.045	-.026	-.019	-.071
≥2	22	.655	-.021	-.026	+0.041	-.004	-.029	-.127
HR (completers) (n = 129)								
≤0	81	.517	-.021	-.015	-.016	+0.014	+0.018	+0.064
≤-5	61	.505	+0.30	-.002	+0.015	-.011	+0.063	+0.072
≤-10	43	.516	-.025	-.016	+0.007	N/A	+0.032	+0.067
Hb (n = 483)								
≤0	115	.595	-.025	-.019	-.017	-.029	-.051	+0.008
≤-1	38	.564	-.049	-.029	+0.027	+0.028	-.005	+0.048
≤-2	10	.555	+0.15	N/A	-.000	+0.062	-.003	+0.059
ECOG (n = 467)								
≥1	68	.568	+0.14	-.001	+0.033	-.023	-.015	-.036
≥0	427	.715	-.032	-.040	-.004	-.007	-.072	-.123

ROC, Receiver-Operator Curve; FSI, Fatigue Symptom Inventory; FFIS, Fatigue and Functional Impact Scale; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MOS, Medical Outcomes Study; RPE, Rating of Perceived Exertion; HR, heart rate; Hb, hemoglobin; ECOG, Eastern Cooperative Oncology Group.

The FFIS column gives the C-index (area under the ROC curve) for that instrument and that outcome and the subsequent columns give the deviation in the C-index for that measure relative to the FFIS.