

# Patient Perspective: Fatigue as a Recommended Patient Centered Outcome Measure in Rheumatoid Arthritis

JOHN R. KIRWAN, PATRICIA MINNOCK, ADE ADEBAJO, BARRY BRESNIHAN, ERNEST CHOY, MAARTEN de WIT, MIEKE HAZES, PAM RICHARDS, KENNETH SAAG, MARIA SUAREZ-ALMAZOR, GEORGE WELLS, and SARAH HEWLETT

**ABSTRACT.** The Patient Perspective Workshop at OMERACT 8 considered evidence for the importance of fatigue to patients with rheumatoid arthritis (RA) and whether measurement of fatigue meets the requirements of the OMERACT filter. The workshop participants included 20 patients from 10 countries and 60 other OMERACT participants. Introductory papers and detailed notes for discussion group members set out the evidence from the literature and from recent analyses of clinical study data available to several participants. The workshop concluded that fatigue is a symptom that is important to patients, is commonly reported by patients, is often severe, can be measured by several current instruments that pass the OMERACT filter, is responsive to some interventions, and provides information additional to that commonly obtained from currently used outcomes. The final OMERACT plenary session endorsed by a very large majority (89%) the proposal that, in addition to the “core set” of outcome measures currently in widespread use, fatigue should be measured in future studies of RA whenever possible. (J Rheumatol 2007;34:1174–7)

*Key Indexing Terms:*

PATIENT CENTERED    VALIDITY    OUTCOMES    FATIGUE    RHEUMATOID ARTHRITIS

*From the University of Bristol Academic Rheumatology Unit, and United Bristol Healthcare NHS Trust, Bristol, UK; Department of Rheumatology, Our Lady's Hospice and St. Vincent's University Hospital, Dublin, Ireland; Academic Rheumatology Group, University of Sheffield Medical School, Sheffield, UK; Academic Department of Rheumatology, King's College, London, UK; Dutch Arthritis Patients' League; University Medical Center, Department of Rheumatology, Leiden, The Netherlands; University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, Alabama, USA; Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada; and Faculty of Health and Social Care, University of the West of England, and United Bristol Healthcare NHS Trust, Bristol, UK.*

*J.R. Kirwan, MD, Professor of Rheumatic Diseases, University of Bristol; P. Minnock, MSc, Department of Rheumatology, Our Lady's Hospice and St. Vincent's University Dublin; A. Adebajo, MD, Department Academic Rheumatology Group, University of Sheffield Medical School; B. Bresnihan, MD, Professor of Rheumatology, The Conway Institute of Biomolecular and Biomedical Research, University College Dublin and St. Vincent's University Hospital; E. Choy, MD, Academic Department of Rheumatology, GKT School of Medicine, London; M. de Wit, Dutch Arthritis Patients' League, Amsterdam; M. Hazes, MD, Leiden University Medical Center; P. Richards, Patient Research Partner, University of Bristol Academic Rheumatology Unit; K. Saag, MD, University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology; M. Suarez-Almazor, MD, Department of Medicine, Baylor College of Medicine; G. Wells, PhD, Department of Epidemiology and Community Medicine, University of Ottawa; S. Hewlett, PhD, Arthritis Research Campaign Professor of Rheumatology and Nursing, University of the West of England.*

*Workshop convenors: J. Kirwan, M. de Wit, S. Hewlett. Organizing group members: A. Adebajo, B. Bresnihan, E. Choy, M. de Wit, M. Hazes, P. Richards, K. Saag, M. Suarez-Almazor.*

*Address reprint requests to Prof. J.R. Kirwan, Rheumatology Unit, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW, UK. E-mail: John.Kirwan@Bristol.ac.uk*

The purpose of the Patient Perspective Workshop on Fatigue was to consider the evidence for the importance of fatigue to patients with rheumatoid arthritis (RA), to consider the evidence that measurement of fatigue meets the requirements of the OMERACT filter<sup>1</sup>, and to make recommendations to the OMERACT plenary discussions.

The workshop comprised 80 OMERACT participants, including 20 patients from 10 countries. It consisted of brief presentations followed by small group discussions and reports back to the workshop with further discussion. Reporters (see authorship list) then met with the session convenors to condense the discussions into a brief presentation to the final OMERACT plenary session and prepare the basis for this report.

## Introductory workshop presentations

An introductory report<sup>2</sup> and brief presentation (S. Hewlett) set out the evidence for the importance of fatigue. This was attested by discussions at previous OMERACT meetings<sup>3,4</sup> and several publications<sup>5–9</sup>. At OMERACT 7 there had been a clear acceptance that fatigue is a relevant and important symptom in RA<sup>4</sup>. A second brief presentation (J. Kirwan) outlined the results of a systematic review of fatigue measurement scales used in RA and evidence for their validity, reliability, and sensitivity to change. Twenty-three scales had been found, used in 71 clinical studies, and adequate evidence of passing the OMERACT filter was found for 6 scales. The full review is now in press<sup>10</sup>; the findings are summarized in Table 1. Full

**Table 1.** Approximate strength of evidence for scales currently used to measure fatigue in RA with adequate evidence of passing the OMERACT filter.

Scale	Face	Content	Validity		Reliability
			Criterion	Construct	
MAF global fatigue index	✓✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓
FACIT-F	✓✓	✓	✓✓	✓	✓✓
Ordinal scales (best scores)	✓✓✓	✓✓		✓✓	✓✓✓
POMS: fatigue/inertia	✓✓	✓✓	✓✓	✓	✓
SF-36: vitality (month)	✓✓	✓✓	✓✓	✓✓	✓✓
VAS (best scores)	✓✓	✓✓	✓	✓✓	✓

MAF: Multidimensional Assessment of Fatigue; FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue scale; POMS: Profile of Mood States Fatigue/inertia subscale; SF-36: Short-Form 36 Health Survey vitality subscale; VAS: visual analog scale. ✓: Some evidence; ✓✓: reasonable evidence; ✓✓✓: good evidence.

details were made available to each participant for reference during the discussion groups. In addition, 2 new studies of test-retest reliability were reported for the Multidimensional Assessment of Fatigue (MAF)<sup>11</sup>. In one (J. Kirwan, K. Mitchell), 15 patients with active RA completed the MAF on 2 occasions one week apart with no changes in therapy. In another (P. Minnock, B. Bresnihan), 12 patients about to start anti-tumor necrosis factor (TNF) therapy completed a numerical rating scale for fatigue on 2 occasions before treatment. The correlations between occasions were 0.854 and 0.653, respectively.

The question of whether fatigue measurements are sensitive to change after therapeutic intervention was also addressed. Eight published studies were identified showing changes. These included responses to anti-TNF therapy<sup>12-14</sup>, cognitive behavioral therapy<sup>15,16</sup>, erythropoietin and iron<sup>17</sup>, and exercise<sup>18,19</sup>. Further illustrative data (unpublished) were also presented as outlined in Table 2. The sensitivity of fatigue measurement to change was reported verbally for studies currently in press<sup>20</sup> or being prepared for publication (G. Wells).

It is reasonable to ask whether there is evidence of the independent contribution of fatigue measurement to the overall assessment of RA. To assess this, fatigue was taken as the dependent variable in a multiple regression analysis against all the other measures used in a study, to calculate the “explained variance” (square of the correlation coefficient). If

**Table 2.** Effect size (mean change/standard deviation of change) for 3 outcome measures in RA clinical studies.

Study	N	Outcome Measure		
		Fatigue	Pain	HAQ
CRx-102	15	1	0.68	0.59
Depomedrone	35	1.4	1.78	1.04
Anti-TNF	49	0.92	1.37	0.82

measuring fatigue provides some information that overlaps with other measures of RA, but also additional information that does not overlap, then we might expect an explained variance of (say) 25% to 50%. If fatigue is unrelated to any other measures of RA, with an explained variance close to 0, then this raises doubts whether fatigue really is part of the disease. If the explained variance is high (say > 90%), then all the information it contains must overlap with the other measures. (Even if this were the case, there might be reasons for measuring fatigue instead of one of the other items, but that is a separate argument.) Data from studies in Ireland (P. Minnock), the UK (J. Kirwan), and North America (data provided by G. Wells) were available for all or some of the WHO/ILAR core set of endpoints for RA clinical trials agreed at OMERACT 12<sup>1</sup>, and for a measurement of fatigue. Each study had data from baseline and at followup following various interventions (anti-TNF therapy, glucocorticoid therapy, disease modifying antirheumatic therapy). For each group of patients the changes in the values of the core set endpoints and fatigue were taken together. First, fatigue (as suggested above) and then each of the other outcomes measured was regressed in turn against all the other outcomes included in that study. This provided a measure of the variation in each outcome that could be accounted for (explained) by the variation in all the other outcomes, leaving a unique contribution (or “unexplained variance”) made by that outcome. The results in Table 3 show that the unique contribution of fatigue to the variance of the whole group of measures (13%–27%) is similar in size to that of each of the core set measures for RA. The details of these calculations were available to discussion group members.

**Table 3.** Relative unexplained variance\* (%) for outcome measures included in 3 clinical studies.

Outcome Measure	Study**		
	Anti-TNF (Dublin)	CRx-102 (Bristol)	Anti-TNF (Ottawa)
Fatigue VAS	22	27	13
Tender joints	20	13	11
Pain	19	10	5
Swollen joints	16	17	13
CRP/ESR	8	—	26
Patient global	8	13	5
HAQ	7	14	16
Clinician global	—	6	11

\* Each measure was regressed against all the others in a study. The proportion of variance not explained by the remaining variables was calculated. The relative unexplained variance was calculated as the unexplained variance of a measure multiplied by 100 divided by the sum of all the unexplained variances. \*\* Dublin (Minnock): 53 patients pre and post anti-TNF; Bristol (Kirwan): 12 treatment and 12 control patients in an RCT of glucocorticoids; Ottawa (Wells): 1043 treatment and control patients in 2 RCT of biologic agents.

Table 4. Topics in a fatigue research agenda.

Although measures of fatigue are usable now, there is room for improvement in design:
<ul style="list-style-type: none"><li>• Standardizing the VAS</li><li>• Multidimensional vs simple scales</li><li>• Find the ‘missing’ and inappropriate items in the current measures and update them</li><li>• Measures of fatigue should be tested “head-to-head”</li><li>• Is “fatigue” the best word to use?</li><li>• Consider severity and duration</li></ul>
Further clarification of the detailed relationship between fatigue and other outcomes
<ul style="list-style-type: none"><li>• Outcome measures in the core set</li><li>• Health status measures</li><li>• Quality of life measures</li><li>• Sleep</li><li>• Mood</li><li>• Physiological correlations</li></ul>
Consequences of fatigue
<ul style="list-style-type: none"><li>• Effect on other patient-centered outcomes (e.g., function, quality of life)</li><li>• Comparison to core measures as a determinant of functional outcomes</li></ul>
Fatigue variation
<ul style="list-style-type: none"><li>• Short-term variations</li><li>• Patterns of fatigue experienced over days and weeks</li></ul>
Interventions to reduce fatigue
<ul style="list-style-type: none"><li>• Drug treatments</li><li>• Supportive interventions (e.g., cognitive-behavioral therapy)</li></ul>

Discussion groups

Eight groups considered 3 questions, with each group concentrating first on an assigned question, but they were free to then discuss other issues. Each group was asked to spend the last 10 minutes considering the design of a visual analog scale for measuring fatigue. The purpose of this was to try and add a concrete element to the theoretical discussions, hence confronting the need to be specific when developing a measuring instrument. Discussions were energetic and took advantage of the presence of at least 2 patient participants in each group. In reporting back to the workshop, the following points were made about measuring fatigue.

- Fatigue was confirmed as an important outcome measure in RA, with strong face validity
- Fatigue provided additional information central to the understanding of the outcome of RA from a patient perspective
- Fatigue does not always vary in parallel with joint symp-

toms: it might relate to sleep disturbance, psychosocial dysfunction, or chronic pain

- Fatigue may relate to cytokine abnormalities that present therapeutic targets
- Fatigue measurement instruments in RA, while capturing some aspects of fatigue, require further refinement.

The workshop concluded that fatigue is a symptom that has high face validity, is commonly reported by patients, is often severe, can be measured by several current instruments that pass the OMERACT filter, is responsive to some interventions and provides information additional to that commonly obtained from currently used outcomes. In considering the usefulness of measuring fatigue in future clinical trials in RA, the workshop concluded that there is room for improvement in current scales and the potential for much further work on measuring and treating fatigue. However, measurement of fatigue in RA studies can be undertaken now, as some instruments are at least adequate. Such measurements will give a more complete picture of the benefits of interventions and provide material for further exploration of fatigue in RA. The research agenda that emerged from the workshop is summarized in Table 4.

Final plenary session

A summary of the findings of the workshop was presented to the OMERACT plenary session, including Tables 1–4. The plenary session then considered and voted on the questions in Table 5. There was a large majority (89%) in favor of the proposal that, in addition to the core set outcome measures<sup>22</sup>, fatigue should be measured in future studies of RA whenever possible. There was also substantial endorsement of further research into measuring and understanding fatigue in RA.

REFERENCES

1. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198-9.
2. Kirwan JR, Hewlett S. Patient perspective: reasons and methods for measuring fatigue in rheumatoid arthritis. *J Rheumatol* 2007;34:1171-3.
3. Kirwan J, Heiberg T, Hewlett S, et al. Outcomes from the patient perspective workshop at OMERACT 6. *J Rheumatol* 2003;30:868-72.
4. Kirwan JR, Hewlett S, Heiberg T, et al. Incorporating the patient perspective into outcome assessment in rheumatoid arthritis — progress at OMERACT 7. *J Rheumatol*

Table 5. Results (%) of plenary session voting.

Question	Disagree/Strongly Disagree	Neutral	Agree/Strongly Agree
1. When fatigue is measured in RA an instrument that has been validated in RA should be used	4	6	90
2. Fatigue should be measured in clinical trials and clinical studies of RA whenever possible	2	9	89
3. Additional studies should be undertaken to define an optimal fatigue instrument in RA	6	4	90
4. We support a research agenda aimed at understanding fatigue in RA and the development of therapeutic interventions	2	5	93

- 2005;32:2250-6.
5. Minnock P, Bresnihan B. Pain outcome and fatigue levels reported by women with established rheumatoid arthritis [abstract]. *Arthritis Rheum* 2004;50 Suppl:S471.
6. Carr A, Hewlett S, Hughes R, et al. Rheumatology outcomes: the patient's perspective. *J Rheumatol* 2003;30:880-3.
7. Ahlmen M, Nordenskiöld U, Archenholtz B, et al. Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. *Rheumatology Oxford* 2005;44:105-10.
8. Hewlett S, Cockshot Z, Byron M, et al. Patients' perceptions of fatigue in rheumatoid arthritis: Overwhelming, uncontrollable, ignored. *Arthritis Care Res* 2005;53:697-702.
9. Hewlett S, Carr M, Ryan S, et al. Outcomes generated by patients with rheumatoid arthritis: how important are they? *Musculoskeletal Care* 2005;3:131-42.
10. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use. *Arthritis Care Res* 2007; (in press).
11. Tack BB. Dimensions and correlates of fatigue in older adults with rheumatoid arthritis [PhD dissertation]. San Francisco: University Of California, San Francisco; 1991.
12. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:811-9.
13. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor- $\alpha$  monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. *Arthritis Rheum* 2003;48:35-45.
14. Russell AS, Conner-Spady B, Mintz A, Mallon C, Maksymowych WP. The responsiveness of generic health status measures assessed in patients with rheumatoid arthritis receiving infliximab. *J Rheumatol* 2003;30:941-7.
15. Sinclair VG, Wallston KA, Dwyer KA, Balckburn DS, Fuchs H. Effects of a cognitive-behavioral intervention for women with rheumatoid arthritis. *Res Nursing Health* 1998;21:315-26.
16. Evers A, Kraaijaat F, van Riel P, de Jong A. Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 2002;100:141-53.
17. Kaltwasser JP, Kessler U, Gottschalk R, Stucki G, Möller B. Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis. *J Rheumatol* 2001;28:2430-6.
18. Daltroy LH, Robb-Nicholson C, Iversen MD, Wright EA, Liang MH. Effectiveness of minimally supervised home aerobic training in patients with systemic rheumatic disease. *Br J Rheumatol* 1995;34:1064-9.
19. Neuberger GB, Press AN, Lindsley HB, et al. Effects of exercise on fatigue, aerobic fitness, and disease activity measures in persons with rheumatoid arthritis. *Res Nursing Health* 1997;20:195-204.
20. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology Oxford* 2006;45:885-9.
21. Boers M, Tugwell P, Felson DT, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *J Rheumatol* 1994;21 Suppl 41:86-9.
22. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.