Evaluating Severity and Status in Rheumatoid Arthritis

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ABSTRACT. There is general agreement regarding the most appropriate examinations and methods to use to evaluate change in status in randomized controlled trials (RCT). However, no guidelines exist to aid in determining and evaluating actual status rather than change in status, particularly when applied to individual patients with rheumatoid arthritis (RA). In addition, methods appropriate for clinical trials may not be useful in evaluating individual patients because of time constraints. This report reviews current methods of evaluation and develops modified methods, based on data bank research that will be useful in clinical practice and in the evaluation of RCT and observational studies. Using data from longitudinal observational data banks, further reduction in the number of joints examined is evaluated to reconcile the time constraints of clinical practice with the need to maintain reliability and validity. Percentile methods to determine severity status are applied to the variables used in RCT and extended further to observational studies and routine clinical practice. Shortened joint counts, based on modifications of the Ritchie method, are identified that allow for examination of groups of 18 (clinical-18) and 16 (clinical-16) joints, the clinical-16 omitting the metatarsophalangeal joints. Using percentile charts, actual severity valuations are given to the variables evaluated in the clinic as well as in RCT. Disease activity status of clinic patients can be determined quantitatively thus allowing clinicians further insight into the status and prognosis of their patients. By quantifying disease activity severity, clinicians and 3rd party payers can better evaluate the appropriateness of and response to disease modifying antirheumatic drugs and biologic therapies. Further, RCT can be evaluated as to severity status of patients participating, and the generalizability of RCT can be better evaluated. (J Rheumatol 2001;28:1453–62)

Key Indexing Terms:
DISEASE ACTIVITY HEALTH ASSESSMENT QUESTIONNAIRE JOINT COUNTS
DISEASE STATUS RHEUMATOID ARTHRITIS JOINT EXAMINATIONS

Rheumatoid arthritis (RA) is a complex disorder in which disease activity produces symptoms and damage, which in turn lead to personal and societal consequences[1-5], including work disability[1,6-13], high rates of service utilization[14-19], and premature mortality[1,20-26].

Depending on the purpose of the evaluation, one generally tries to separate the various components of illness into (1) disease activity, (2) patient symptoms and distress, (3) patient outcomes, (4) structural damage or disease outcome, and (5) societal consequences (Table 1, Figure 1). Each of these items reflects the *severity* or *status* of the patient in regard to that item. Therefore in characterizing a patient or a group of patients one may speak of radiographic severity, (severity of) disease activity, or symptom severity, for example. In addition to severity or status, a second measure of interest is the *change in severity* or *change in status*. In randomized controlled trials (RCT) the main outcome of interest is a change in status, but in observational studies (OS) actual status is most often the important outcome. In clinical care, the clinician initiates therapy on the basis of status and most often decides on the success of therapy and its continuance on the basis of status. That is, it is not the percentage of improvement that is important in the individual patient, but instead it is the actual severity level.

In RCT and OS, as well as in routine clinical care, the goal of therapy is to reduce or eliminate disease activity and symptoms. One of the difficulties in evaluating disease activity is that there are very few truly "objective" markers, of which acute phase reactants and joint swelling are the two in common use. Consequently surrogates for disease activity are utilized; the most common surrogates include pain, tender joint count, patient and physician global severity, and functional disability.

Psychosocial factors exert a strong influence on the intensity and reporting of symptoms, as well as in influencing patient outcomes. It is therefore possible to have a patient with limited disease activity who reports severe symptoms; and it is possible to have a patient with high levels of disease activity who tolerates the illness well and

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Table 1. The spectrum of disease activity, symptoms, and outcomes in RA.

Disease Activity	Current Symptoms	Patient Outcomes	Disease Outcomes
Acute phase reactants*			
ESR			AUC ESR
CRP			AUC CRP
Joint swelling*			
Joint tenderness*	Joint tenderness		
Pain*	Pain	AUC pain	
Patient global severity*	Patient global severity		
Physician severity*	Physician severity		
Functional ability*	Functional ability	Functional ability	
Grip strength	Grip strength	Grip strength	
Morning stiffness	Morning stiffness		
	Fatigue		
	Sleep disturbance		
	Anxiety		
	Depression		
		Work disability	
		Socioecomonic disadvantage	
		Psychosocial changes	
		Deformity	Deformity
		Arthritis surgery	Arthritis surgery
		Premature mortality	Premature mortality
			Radiographic abnormalities

*Surrogate marker.
AUC: area under the curve; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

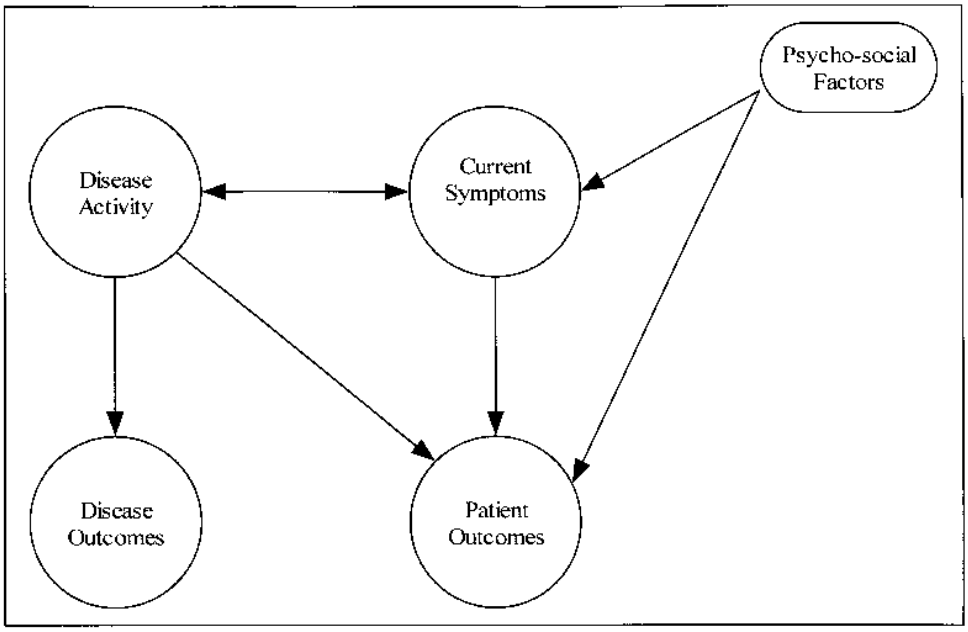

Figure 1. The interrelationship between disease activity, symptoms, outcomes, and psychosocial factors.

has few complaints. Patients such as these occur frequently in clinical practice, where they make evaluation of disease activity difficult. In RCT, on the other hand, the randomization process distributes such patients to the different study arms on a random basis.

Psychosocial factors and patient distress are not just nuisance factors. In the clinic they frequently underlie the main reason for the clinic visits. In addition, they influence the intensity and extent of the treatment. Patients with high levels of anxiety and/or pain, for example, will receive more treatments than those with lower levels who have the same level of disease activity[27]. The "squeaky wheel" does receive the grease.

MATERIALS AND METHODS

Data in this paper are from a number of sources. In Tables 2–6 data are from the outpatient clinic of the Arthritis Center in Wichita, KS, USA. Data in this series represent a 100% sample of all patients with RA seen from 1974 through February 1999. These patients were seen as part of their ordinary clinical care. The details of this data set have been described[8,28]. All patients satisfied American College of Rheumatology (ACR) criteria for RA[29].

The CLINHAQ was administered at each clinic visit[28,30-32]. This instrument contains self-reports for the Health Assessment Questionnaire (HAQ) disability index[33,34], Arthritis Impact Measurement Scales (AIMS) anxiety and depression index[35,36], visual analog scale (VAS) pain, VAS global severity, VAS gastrointestinal symptoms, VAS sleep problems, VAS fatigue, satisfaction with health, patient estimate of health status, and work ability. The Westergren erythrocyte sedimentation rate (ESR) was measured by standard methodology[37,38].

Data were analyzed using Stata version 6.0[39]. Tables 3–5 report population averaged analyses determined by a generalized estimating equation (GEE) procedure. Coefficients are interpretable in the same way as in ordinary linear regression. Stata's implementation of the GEE procedure is an extension of generalized linear models (GLM) that properly handles panel data[39]. In the analyses used in this report we specified the robust Huber/White/sandwich estimator of variance. This estimator produces consistent standard errors even if the within-group correlations are not as hypothesized by the specified correlation structure[39]. Correlation coefficients were Pearson. Statistical significance was set at the 0.05 level.

Tables 8–10 make use of data from a large national rheumatology sample of RA patients (N = 6025). Patients completed the CLINHAQ questionnaire as they enrolled into the National Data Bank for Rheumatic Diseases, a longitudinal computerized data bank. Enrollment occurred in 2 groups. The first group was patients with RA enrolled in 1998, during a 30 day period, from the practices of 300 US rheumatologists. The second group consisted of all RA patients from the practices of 12 rheumatology groups during 1999. For the purpose of this study these 2 groups were combined into a single group of "general" RA patients, and are characteristic of RA patients generally in the practice of US rheumatologists during 1998 and 1999.

Tables 8–10 display the percentiles associated with specific study variable values. From these tables it is possible to understand the percentile position associated with a specific value, thereby determining the relative severity of a value (or patient with that value) in comparison with US rheumatology patients in general.

RESULTS

Specific disease activity measures. There is now general agreement that the best activity measures are those listed with an asterisk in column 1 of Table 1. They form the basis of the American College of Rheumatology (ACR) "core set" of variables for use in RCT[40] as well as being part of the ACR improvement criteria[41]. They are, similarly, recommended for inclusion in observational studies[42]. The Disease Activity Scale of van der Heijde and colleagues, widely used in Europe, includes a number of these variables as well[43,44]. Grip strength and morning stiffness, shown in Table 1, are also measures of disease activity, although not widely used as much as they once were.

At the current time the variables in column 1 are included in most RCT and OS. Clinicians, however, do not ordinarily perform these measures or record them[30], although it is clear that they pay attention to them, but in less formal ways. Clinicians do not perform the tests because of reasons of time and because the same information can be obtained by other nonformal means.

The joint count. The joint count has long held the central place in RA evaluation[45-70]. Swollen joint counts are known to better reflect disease activity than tender joint counts, where the patient's perception of pain and distress influences the reporting of joint tenderness[66,71]. Uncommonly, swollen joints may sometimes be seen in apparently inactive disease. In the past, essentially all accessible joints were examined for swelling and tenderness, the so-called "ARA" 68 joint count[45,72]. In addition, joints were rated on a 0–3 scale as to the extent of swelling and tenderness. There were several problems with this approach. In practice, it took a long time to complete the examination, making it practical only for well funded RCT. Egger, *et al* in 1985 showed that the joint counts could be reduced to 36 without loss of ability in RCT[67], and 4 years later Fuchs, *et al* eliminated the hips, ankles, and feet in a 28 joint count examination[63]. Studies by the ACR committee led by Felson confirmed that counts (0–1) provided as much information as scores (0–3) owing to the variability among examiners[40]. Through the decade of the 1990s the 28 count of swollen and tender joints became established as the norm[57,59,73]. Interestingly, in RCT the tender joint count performed almost as well as the swollen joint count, but the combination of both joint measures led to somewhat increased accuracy. Thompson, *et al* pointed out that tender joint counts are more sensitive to change and more reproducible than swollen joint counts, but that swollen joint counts are a more accurate measure of joint inflammation and predict future damage better than do tender joint count[66]. The reasons behind these changes for clinical trials were the desire to make the examination shorter and easier, to eliminate joints that did not reflect RA activity, and to strengthen the reliability of the examinations.

The establishment of the 28 tender and swollen joint count poses problems for the clinician. All clinicians know that ankle, hip, and metatarsophalangeal (MTP) joint involvement can be associated with severe pain. Therefore it might be possible to have significant and clinically important joint involvement and yet have low joint counts since

the hips, ankles, and MTP joints are excluded in the ACR 28 tenderness and swelling counts: that is, the joint count might not reflect the activity or severity of the patient.

The consequence of excluding hips, ankles, and feet among clinic patients has not been examined. For this report we evaluated 26,032 examinations in 1762 patients with RA seen during routine clinical care. Table 2 presents these data as well as data from the Smollen, *et al* analysis of 735 RCT patients[73]. There are more painful joints in the RCT, reflecting the selection of patients with active disease. Although the hip joint was less frequently involved than other joints (clinic: 7.5% of examinations, RCT: ~20% of examinations), in GEE analyses (Tables 3–5) all joints were independent predictors of pain, and all joints except MTP were independent predictors of HAQ disability and ESR scores. The associations between tender joint counts and other clinical measures are shown in Table 6. These data suggest that evaluation of all of the joints provides additional information about the status of RA clinic patients.

Table 2. Percentage with painful joints in the clinic (n = 26,302) and in randomized controlled trials (RCT) (n = 735). Clinical data are from the Wichita Data Bank of the National Data Bank for Rheumatic Diseases; RCT data from Smolen, *et al*[59,73].

Joint Group	Clinical Data	RCT Data
Wrist	69.6	77
MCP	58.8	~65
PIP	36.8	~60
Shoulder	36.0	60
Knee	30.6	58
MTP	28.9	~55
Elbow	25.7	57
Ankle	22.3	47
Hip	7.5	20

MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; MTP: metatarsophalangeal joint.

Table 3. Painful joint predictors of VAS pain scores among 1464 RA patients and 16,748 observations from routine clinical practice. Analyses performed using generalized estimating equations with robust standard errors[39]. Data are from the Wichita Data Bank of the National Data Bank for Rheumatic Disease.

Joint Group	Coefficient	SE	Z	p	95% LCI	95% UCI
Shoulder	0.80	0.05	17.52	0.000	0.71	0.89
Knee	0.68	0.05	12.98	0.000	0.58	0.71
Wrist	0.40	0.05	8.50	0.000	0.30	0.49
PIP	0.39	0.05	8.32	0.000	0.29	0.48
Elbow	0.41	0.05	7.88	0.000	0.30	0.51
Ankle	0.41	0.05	7.55	0.000	0.30	0.51
MCP	0.37	0.05	7.29	0.000	0.27	0.47
Hip	0.56	0.09	6.53	0.000	0.39	0.73
MTP	0.30	0.05	6.08	0.000	0.20	0.39
Constant	3.38	0.07	51.78	0.000	3.25	3.51

LCI: lower confidence interval; UCI: upper confidence interval; PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint; MTP: metatarsophalangeal joint.

In addition to the ACR and European 28 joint count, a number of other attempts have been made to use a more manageable joint count. The Ritchie index simplified the process by examining some joints (e.g., metacarpophalangeal, proximal interphalangeal, and MTP joints) in groups rather than examining each joint separately[46]. The Hart-modified Ritchie index dropped the scoring of the joints for swelling and tenderness in favor of a simple count[62]. This method was found to be the most reliable method by Thompson, *et al* compared to the full 68 joint count of the ARA[45].

The choice of a joint count for evaluation in the clinic. The swollen and/or tender joint counts that are in common use in RCT are designed for the purpose of most parsimoniously distinguishing active drug from its comparator; they are not

Table 4. Painful joint predictors of HAQ scores among 1753 patients with RA and 22,744 observations from routine clinical practice. Analyses performed using generalized estimating equations (GEE) with robust standard errors[39]. Data are from the Wichita Data Bank of the National Data Bank for Rheumatic Disease.

Joint Group	Coefficient	SE	Z	p	95% LCI	95% UCI
Shoulder	0.19	0.01	15.36	0.000	0.16	0.21
Knee	0.13	0.01	9.14	0.000	0.10	0.16
Hip	0.17	0.02	7.42	0.000	0.13	0.22
Wrist	0.09	0.01	7.03	0.000	0.06	0.11
MCP	0.07	0.01	5.62	0.000	0.05	0.10
PIP	0.06	0.01	5.03	0.000	0.04	0.09
Elbow	0.06	0.01	4.35	0.000	0.03	0.08
Ankle	0.06	0.01	3.93	0.000	0.03	0.08
MTP	0.01	0.01	1.08	0.282	–0.01	0.04
Constant	0.98	0.02	46.05	0.000	0.94	1.02

SE: standard error; LCI: lower confidence interval; UCI; upper confidence interval; PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint; MTP: metatarsophalangeal joint.

Table 5. Painful joint predictors of ESR among 1865 patients with RA and 20,267 observations from routine clinical practice. Analyses performed using generalized estimating equations (GEE) with robust standard errors[39]. Data are from the Wichita Data Bank of the National Data Bank for Rheumatic Disease.

Joint Group	Coefficient	SE	Z	p	95% LCI	95% UCI
Knee	7.57	0.45	16.80	0.000	6.69	8.45
Elbow	5.90	0.46	12.93	0.000	5.01	6.80
Shoulder	5.13	0.42	12.24	0.000	4.31	5.96
Wrist	3.50	0.40	8.82	0.000	2.72	4.28
Ankle	3.28	0.44	7.38	0.000	2.41	4.15
PIP	2.63	0.39	6.77	0.000	1.87	3.39
Hip	3.91	0.70	5.62	0.000	2.55	5.28
MCP	1.91	0.38	5.01	0.000	1.16	2.66
MTP	0.58	0.42	1.38	0.168	–0.25	1.41
Constant	23.33	0.55	42.23	0.000	22.24	24.41

SE: standard error; LCI: lower confidence interval; UCI; upper confidence interval; PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint; MTP: metatarsophalangeal joint.

Table 6. Correlations between tender joint count and clinical variables in clinical practice (Wichita Data Bank).

Variable	Observations	Correlation 18 Joint Count	Correlation 16 Joint Count
Pain	17091	0.425	0.423
Global	25414	0.386	0.399
HAQ	23486	0.383	0.394
Grip strength	25795	–0.375	–0.384
ESR	21449	0.312	0.328
CRP	5899	0.320	0.333
AM stiffness	25788	0.261	0.264
Fatigue	6587	0.349	0.343

HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

designed for optimum use in the clinic. The omission of the hips, ankles, and feet from the examination does not result in a satisfactory examination for clinical purposes. In addition, data on which joints perform best were derived from clinical trials in which patients were selected on the basis of their having disease activity of a sufficient level for entry into the trial.

For use in the clinic, the issues are somewhat different. A joint count should capture clinically relevant joints and be simple enough so that it can be performed rapidly. Based on research of the last two decades, it seems clear now that a large number of joints are infrequently involved and can be excluded from analyses. From the data of Smollen, *et al* joints that were painful in RCT in 45% or more cases included proximal interphalangeal, metacarpophalangeal, wrists, elbows, shoulders, knees, ankles, and MTP[59,73]. The hips were painful in only 20% of patients. The authors indicated that ankles might have been more important than previously thought. They also indicated that feet should be made part of the clinical examination.

Although joint counts may be reduced, there is no statistical penalty for the addition of the hips, ankles, and knees to the 28 joint count. Based on the data from RCT and the data presented here today, it seems possible to construct a joint count short enough and simple enough to be used in the clinic as a measure of disease activity. We propose an 18 tender and/or swollen joint count that uses Ritchie grouping of the MCP, PIP, and MTP joints. Such a joint count actually examines 42 joints, but with Ritchie compression that number reduces to 18. It is also possible to eliminate the MTP joint, further reducing the joint count to 16. This type of joint count has been shown to be as sensitive to clinical change as those used in RCT[74]. The clinical and ACR/EULAR joint count details are shown in Table 7. Although rheumatologists examine joints frequently, recording of counts in clinical practice is rare. We believe that further reducing the burden of joint examination by using a 16 or 18 joint count might encourage formal joint evaluation.

Pain. Pain is usually assessed with a VAS or a categorical scale, the most common measure being the VAS scales[75-83]. The VAS scale is based on a 10 cm line (although longer lengths can be used)[84]. VAS that provide at least 10 points of discrimination are adequate[76]. The exact metric is not important, although 0–10 or 0–3 is most commonly used. A 0–5 or 0–7 categorical scale may be easier to understand when each rank is labeled (e.g., very severe pain, severe pain, mild pain, etc.). But in actual use there seems to be little difference in the results regardless of which scale is used. VAS can be produced that can be scored almost instantaneously without the use of a ruler (http://www.arthritis-research.org/questionaire.html).

The time period of the assessment is usually "the last week," "today," or "the last 3 days." Longer time periods depend on memory for pain, and are known to be more inac-

Table 7. ACR and EULAR 28 joint counts and clinical 16 and 18 joint counts.

Joint Count	Swelling and/or Tenderness	"Ritchie" Grouped Joints	Number of Joints	Joints Added to 28 Joint Count
ACR – 28	Swelling and tenderness	None	28	
Clinical – 18	Swelling and tenderness	MCP, PIP, MTP	18	Hips, ankles, MTP
Clinical – 16	Swelling and tenderness	MCP, PIP	16	Hips, ankles

MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; MTP: metatarsophalangeal joint.

curate. Probably the most common time frame is the "last week." Pain assessment in RA usually asks, "how much pain have you had...."

Global severity. Patient global severity is measured in a manner similar to VAS and categorical scales for pain. Physician global became part of the ACR criteria in deference to regulatory authorities, but does not appear to add additional information. In the clinic, moreover, a physician rater may change his opinion in time as to what is severity, and physician raters differ strikingly in their definitions of severity.

Acute phase reactants. ESR and C-reactive protein (CRP) yield about equivalent information regarding disease activity[37], although CRP is a more direct measure of inflammation. Quantitative information on normative and percentile values is also available[37,38].

Functional status measures. The 3 most used scales are the Health Assessment Questionnaire (HAQ)[34,85], the modified Health Assessment Questionnaire (MHAQ)[86,87], and the Arthritis Measurement Impact Scales (AIMS)[35,88]. All provide valid and reliable information about patient functional status. The HAQ and MHAQ are more suitable for clinic use because of their shorter length[30]. These questionnaires can be administered within the usual routine of clinical practice with ease[30]. They are also the most frequent functional status questionnaires used in RCT.

Assessing the status of the individual patient. There are no defined gold standards of severity for the variables used in the assessment of RA. More joints are worse, as are greater pain and higher levels of acute phase reactants. For this reason results of RCT have been described in the past in terms of mean differences between active drug and comparator, and more recently in differences in the percentage of patients who meet 20%, 50%, and 70% improvement criteria. Although these methods are appropriate in measuring a *change in status* in RCT, they are not usually helpful in assessing *actual status* in clinic patients, which is the metric most useful to the clinician. Tables 8-10

Table 8. Centile scores for disease status/activity measures: National Data Bank — all patients with RA (N = 6025).

Variable	5	10	20	25	30	40	50	60	70	75	80	90	95
HAQ	0.000	0.000	0.375	0.500	0.625	0.875	1.000	1.250	1.500	1.625	1.750	2.125	2.375
MHAQ	0.000	0.000	0.000	0.125	0.125	0.250	0.375	0.500	0.750	0.875	0.875	1.125	1.500
Pain	0.500	0.500	1.500	2.000	2.000	3.000	4.000	4.500	5.500	6.500	6.500	8.000	8.500
Global severity	0.500	0.500	1.500	2.000	2.000	3.000	3.500	4.500	5.500	5.500	6.000	7.500	8.000
Fatigue	0.000	0.500	2.000	2.000	2.500	3.500	4.500	5.500	6.500	7.000	7.500	8.500	9.000
Sleep	0.000	0.000	0.500	0.500	1.000	2.000	3.000	4.000	5.500	6.500	6.500	8.000	9.000
GI scale	0.000	0.000	0.000	0.000	0.500	0.500	1.500	2.000	2.500	3.500	4.500	6.000	7.500
Anxiety	0.660	1.320	1.980	2.310	2.640	3.300	3.630	4.290	4.950	5.280	5.610	6.600	7.260
Depression	0.330	0.660	1.320	1.320	1.650	1.980	2.310	2.640	3.300	3.630	3.960	4.950	5.940

HAQ: Health Assessment Questionnaire; M: modified; GI: gastrointestinal.

Table 9. Centile scores for disease status/activity measures: National Data Bank — women with RA (N = 4912).

Variable	5	10	20	25	30	40	50	60	70	75	80	90	95
HAQ	0.000	0.125	0.500	0.625	0.750	0.875	1.125	1.375	1.625	1.750	1.875	2.125	2.375
MHAQ	0.000	0.000	0.000	0.125	0.125	0.250	0.375	0.625	0.750	0.875	1.000	1.250	1.500
Pain	0.500	1.000	1.500	2.000	2.500	3.000	4.000	5.000	6.000	6.500	7.000	8.000	9.000
Global severity	0.500	0.500	1.500	2.000	2.000	3.000	4.000	4.500	5.500	5.500	6.000	7.500	8.000
Fatigue	0.500	1.000	2.000	2.500	3.000	4.000	4.500	5.500	6.500	7.500	7.500	8.500	9.000
Sleep	0.000	0.000	0.500	1.000	1.000	2.000	3.000	4.500	5.500	6.500	7.000	8.000	9.000
GI scale	0.000	0.000	0.000	0.500	0.500	0.500	1.500	2.000	3.500	4.000	4.500	6.500	7.500
Anxiety	0.990	1.320	1.980	2.310	2.640	3.300	3.960	4.620	5.280	5.280	5.610	6.600	7.260
Depression	0.330	0.660	1.320	1.320	1.650	1.980	2.310	2.970	3.300	3.630	3.960	5.280	6.270

Table 10. Centile scores for disease status/activity measures: National Data Bank — men with RA (N = 1108).

Variable	5	10	20	25	30	40	50	60	70	75	80	90	95
HAQ	0.000	0.000	0.125	0.125	0.250	0.500	0.750	1.000	0.188	1.250	1.500	1.875	2.125
MHAQ	0.000	0.000	0.000	0.000	0.125	0.125	0.250	0.500	0.625	0.750	0.875	1.000	1.375
Pain	0.000	0.500	1.500	1.500	2.000	2.500	3.500	4.500	5.000	5.500	6.500	7.500	8.500
Global severity	0.000	0.500	1.000	1.500	2.000	2.500	3.500	4.500	5.000	5.500	6.000	7.000	8.000
Fatigue	0.000	0.500	1.000	1.500	2.000	2.500	3.500	4.500	5.500	6.500	6.500	8.000	8.500
Sleep	0.000	0.000	0.000	0.000	0.500	1.500	2.000	3.500	4.750	5.500	6.500	7.500	8.500
GI scale	0.000	0.000	0.000	0.000	0.000	0.500	0.500	1.500	2.000	2.500	3.500	5.500	6.500
Anxiety	0.000	0.990	1.650	1.980	1.980	2.640	3.300	3.960	4.620	4.950	5.280	6.270	6.930
Depression	0.000	0.330	0.990	1.320	1.320	1.650	1.980	2.640	2.970	3.300	3.630	4.620	5.429

describe percentile ranks for some of the assessments described above, and include other assessments such as fatigue and sleep disturbance. These tables are derived from a large sample of RA patients followed by US rheumatologists, and can be considered representative of patients with RA seen in rheumatology practice. From such data is it possible to place into perspective the relative severity of RA patients (or RA patients in RCT and OS) by comparing their results with the percentile severity rankings of RA patients generally.

As an example of this ability, Table 11 examines the scores of participants in clinical trials and observational studies. As can be seen, scores of study participants were, as expected, more severe than those of average, approximating the 65–70% percentile of severity.

DISCUSSION

We have provided a number of tools by which RA may be evaluated in the clinic and in research studies. The data derived from our data bank regarding the importance of joints omitted by the ACR 28 joint count underscore a "town versus gown" or clinic versus RCT problem. The suggestion that joint counts can be further shortened by the modified Ritchie method might be of great use to the overburdened clinician. It should be very easy to test how much information is lost (if any) by the modifications we have suggested here. All that is necessary is to examine the results of recent RCT with different joint examinations. The statistical tests (and clinical thinking) should inform us whether there are any differences between the examinations and whether these differences are both clinically and statistically important.

Table 11. Clinical activity measures in randomized controlled trials and observational studies.

Trial	Pain	CRP	ESR	Global	HAQ	MHAQ	Swollen Joint Count	Tender Joint Count
RCT DMARD/Biologics								
LEF US 301[89]	5.9	2.08	39.0	5.6	1.30	0.8	13.7	15.5
LEF MN 301[90]		4.45	55.7		1.89		16.2	18.8
LEF MN 302		4.22	51.0		1.50		15.8	17.2
Etanercept[91]	6.7	4.7	35	7.0	1.6		25	33
Infliximab[92]	7.0	3.1		6.6	1.8		19	32
Combination therapy[93]			37	4.8	0.9		13	18
MTX/AZA[94]	6.2		37	6.1				
Average percentile ranking, %	75		73	80	70	35		
RCT NSAID								
Celecoxib[95]	4.7	1.51				1.2		
Average percentile ranking, %	64					60		
Observational studies								
Multinational[96]			26.1		1.0			
Saskatoon/Montreal[97]	4.1			4.1	1.4			
Early RA (Sweden)[98]			25.4		1.0			
Wichita clinic patients	4.8	1.78	35.0	4.6	1.2			
Population (Norway)[99]	4.6					0.7		
Average percentile ranking, %	53		47	57	54	66		

LEF: leflunomide; AZA: azathioprine; MTX: methotrexate; HAQ: Health Assessment Questionnaire; M: modified; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

We have also provided simple nomograms by which clinicians can evaluate the disease activity severity of their patients. In the event that not all the examinations are performed, it is still possible to use a subset of assessments, average them, and obtain an overall severity score. As can be seen from Table 11, severity levels tend to be consistent across the clinical measures. Data such as these will allow clinicians to document the severity status of their patients, and may be useful in justifying therapeutic changes. The percentile charts can be used to evaluate the severity of patients entering RCT and also to evaluate the final status of patients as they complete trials. Such data may be more useful than percentage change in evaluating the clinically useful results of therapy.

This paper is about disease activity. Clearly there is more to RA than disease activity, and social and psychological factors play a major role in RA management. In addition, although the study variables are useful in identifying disease activity, they are not all useful in predicting outcome. Variables such as the HAQ remain among the most important predictors of longterm outcome. It is important that prediction of outcome also be integrated into the management of RA.

In summary, shortened joint counts and questionnaire data can be used within the time constraints imposed by the clinic. They can provide accurate, detailed information about disease activity that is suitable for clinical use and for documentation that may be required by 3rd party payers. With the use of the percentile tables the status of patients in the clinic as well as in clinical trials can be determined.

REFERENCES

1. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum 1984;27:864-72.
2. Magnusson S. Treatment of rheumatoid arthritis — does it affect society's cost for the disease? Br J Rheumatol 1996;35:791-5.
3. Reisine S, Fifield J, Winkelman DK. Employment patterns and their effect on health outcomes among women with rheumatoid arthritis followed for 7 years. J Rheumatol 1998;25:1908-16.
4. Fifield J, Reisine S. Going beyond demographic characteristics in arthritis research: reflections on process in the experience of arthritis [editorial]. Arthritis Care Res 1996;9:421-3.
5. Wolfe F. Psychological distress and rheumatic disease. Scand J Rheumatol 1999;28:131-6.
6. Jantti J, Aho K, Kaarela K, Kautiainen H. Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20 year study. Rheumatology 1999;38:1138-41.
7. Sokka T, Kautiainen H, Mottonen T, Hannonen P. Work disability in rheumatoid arthritis 10 years after the diagnosis. J Rheumatol 1999;26:1681-5.
8. Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Work disability: A prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-17.
9. Mau W, Bornmann M, Weber H. The occurrence of sick-leave in the first year of rheumatoid arthritis. A comparison with the members of the compulsory health insurance. Z Rheumatol 1997;56:1-7.
10. Fifield J, Reisine S, Sheehan TJ, Mcquillan J. Gender, paid work, and symptoms of emotional distress in rheumatoid arthritis patients. Arthritis Rheum 1996;39:427-35.
11. Doeglas D, Suurmeijer T, Krol B, Sanderman R, van Leeuwen M, van Rijswijk M. Work disability in early rheumatoid arthritis. Ann Rheum Dis 1995;54:455-60.
12. Reisine S, Fifield J. Family work demands, employment demands and depressive symptoms in women with rheumatoid arthritis. Women Health 1995;22:25-45.
13. Yelin EH, Henke CJ, Epstein WV. Work disability among persons with musculoskeletal conditions. Arthritis Rheum 1986;29:1322-33.
14. Gabriel SE, Crowson CS, Luthra HS, Wagner JL, O'Fallon WM. Modeling the lifetime costs of rheumatoid arthritis [see comments]. J Rheumatol 1999;26:1269-74.
15. van Jaarsveld CH, Jacobs JW, Schrijvers AJ, Heurkens AH, Haanen HC, Bijlsma JW. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. Br J Rheumatol 1998;37:837-47.
16. Clarke AE, Zowall H, Levinton C, et al. Direct and indirect medical costs incurred by Canadian patients with rheumatoid arthritis: a 12 year study. J Rheumatol 1997;24:1051-60.
17. Lanes SF, Lanza LL, Radensky PW, et al. Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting: the importance of drug and surgery costs. Arthritis Rheum 1997;40:1475-81.
18. Prashker MJ, Meenan RF. The total costs of drug therapy for rheumatoid arthritis. A model based on costs of drug, monitoring, and toxicity [see comments]. Arthritis Rheum 1995;38:318-25.
19. Yelin E, Callahan LF, Arnett F, et al. The economic cost and social and psychological impact of musculoskeletal conditions. Arthritis Rheum 1995;38:1351-62.
20. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: Have we made an impact in 4 decades? J Rheumatol 1999;26:2529-33.
21. Isomaki HA. Mortality in patients with rheumatoid arthritis. In: Wolfe F, Pincus T, editors. Rheumatoid arthritis: pathogenesis, assessment, outcome, and treatment. New York: Marcel Dekker; 1994:235-46.
22. Lindqvist E, Eberhardt K. Mortality in rheumatoid arthritis patients with disease onset in the 1980s. Ann Rheum Dis 1999;58:11-4.
23. Myllykangas-Luosujarvi RA, Aho K, Isomaki HA. Mortality in rheumatoid arthritis. Semin Arthritis Rheum 1995;25:193-202.
24. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously - predictive markers, socioeconomic status and comorbility [editorial]. J Rheumatol 1986;13:841-5.
25. Symmons DPM, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: Early presenters continue to do well. J Rheumatol 1998;25:1072-7.
26. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
27. Wolfe F, Cathey MA. Analysis of methotrexate treatment effect in a longitudinal observational study: utility of cluster analysis. J Rheumatol 1991;18:672-7.
28. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis: A 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. Arthritis Rheum 1998;41:1072-82.
29. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
30. Wolfe F, Pincus T. Current comment — Listening to the patient — A practical guide to self-report questionnaires in clinical care. Arthritis Rheum 1999;42:1797-808.
31. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: A 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571-82.

32. Wolfe F. Health status questionnaires. Rheum Dis Clin N Am 1995;21:445-64.
33. Wolfe F, Hawley DJ, Cathey MA. The assessment and prediction of functional disability in RA. J Rheumatol 1991;18:1298-306.
34. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
35. Meenan RF, Gertman PM, Mason JH, Dunaif R. The Arthritis Impact Measurement Scales. Arthritis Rheum 1982;25:1048-53.
36. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis: the Arthritis Impact Measurment Scales. Arthritis Rheum 1980;23:146-52.
37. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol 1997;24:1477-85.
38. Wolfe F, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. J Rheumatol 1994;21:1227-37.
39. Stata Corporation. Stata Statistical Software: Release 6.0. College Station, TX: Stata Corporation; 1999.
40. 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. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-40.
41. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
42. Wolfe F, Lassere M, van der Heijde D, et al. Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. J Rheumatol 1999;26:484-9.
43. van der Heijde DMFM, van 't Hof M, van Riel PL, van de Putte LBA. Validity of single variables and indices to measure disease activity in rheumatoid arthritis. J Rheumatol 1993;20:538-41.
44. van der Heijde DMFM, van 't Hof M, van Riel PLCM, van de Putte LBA. Development of a Disease Activity Score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.
45. Cooperating Clinics of the American Rheumatism Association. A seven-day variability study of 499 patients with peripheral rheumatoid arthritis. Arthritis Rheum 1965;8:302-35.
46. Lansbury J, Haut DD. Quantification of the manifestations of rheumatoid arthritis. 4. Area of joint surfaces as an index to total joint inflammation and deformity. Am J Med Sci 1956;232:150-5.
47. Steinbrocker O, Blazer A. A therapuetic score card for rheumatoid arthritis: A standardized method of appraising results of treatment. N Eng J Med 1946;235:501-6.
48. Alarcon GS, Tilley BC, Li SH, Fowler SE, Pillemer SR. Self-administered joint counts and standard joint counts in the assessment of rheumatoid arthritis. J Rheumatol 1999;26:1065-7.
49. Calvo FA, Calvo A, Berrocal A, et al. Self-administered joint counts in rheumatoid arthritis: Comparison with standard joint counts. J Rheumatol 1999;26:536-9.
50. Wong AL, Wong WK, Harker J, et al. Patient self-report tender and swollen joint counts in early rheumatoid arthritis. J Rheumatol 1999;26:2551-61.
51. Escalante A. What do self-administered joint counts tell us about patients with rheumatoid arthritis? Arthritis Care Res 1998; 11:280-90.
52. Taal E, Abdel-Nasser AM, Rasker JJ, Wiegman O. A self-report Thompson articular index: What does it measure? Clin Rheumatol 1998;17:125-9.
53. Scott DL, Choy EHS, Greeves A, et al. Standardising joint assessment in rheumatoid arthritis. Clin Rheumatol 1996; 15:579-82.
54. Prevoo MLL, Kuper IH, Van 't Hof MA, van Leeuwen MA, van de Putte LBA, van Riel PLCM. Validity and reproducibility of self-administered joint counts. A prospective longitudinal followup study in patients with rheumatoid arthritis. J Rheumatol 1996;23:841-5.
55. Scott DL, Houssien DA. Joint assessment in rheumatoid arthritis. Br J Rheumatol 1996;35:14-8.
56. Fuchs HA. Joint counts and physical measures. Rheum Dis Clin N Am 1995;21:429-44.
57. Felson D, Anderson J, Boers M, et al. Reduced joint counts in rheumatoid arthritis clinical trials. Arthritis Rheum 1994;37:463-4.
58. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum 1994;37:470-5.
59. Prevoo MLL, van Riel PLCM, Van 't Hof MA, et al. Validity and reliability of joint indices — a longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol 1993;32:589-94.
60. Stewart MW, Palmer DG, Knight RG, Highton J. A self-report articular index — relationship to variations in mood and disease activity measures. Br J Rheumatol 1993;32:631-2.
61. Atkins CJ, Zielinski A, Klinkhoff AV, et al. An electronic method for measuring joint tenderness in rheumatoid arthritis. Arthritis Rheum 1992;35:407-10.
62. Thompson PW, Hart LE, Goldsmith CH, Spector TD, Bell MJ, Ramsden MF. Comparison of four articular indices for use in clinical trials in rheumatoid arthritis — patient, order and observer variation. J Rheumatol 1991;18:661-5.
63. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified 28 joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531-7.
64. Klinkhoff AV, Bellamy N, Bombardier C, et al. An experiment in reducing interobserver variability of the examination for joint tenderness. J Rheumatol 1988;15:492-4.
65. Lewis PA, O'Sullivan MM, Rumfeld WR, Coles EC, Jessop JD. Significant changes in Ritchie scores. Br J Rheumatol 1988; 27:32-6.
66. Thompson PW, Silman AJ, Kirwan JR, Currey HL. Articular indices of joint inflammation in rheumatoid arthritis. Correlation with the acute-phase response. Arthritis Rheum 1987;30:618-23.
67. Egger MJ, Huth DA, Ward JR, Reading JC, Williams HJ. Reduced joint count indices in the evaluation of rheumatoid arthritis. Arthritis Rheum 1985;28:613-9.
68. Langley GB, Fowles M, Sheppeard H, Wigley RD. A simple pressure dolorimeter for the quantification of joint tenderness in inflammatory arthritis. Rheumatol Int 1983;3:109-12.
69. Buchanan WW. Assessment of joint tenderness, grip strength, digital joint circumference and morning stiffness in rheumatoid arthritis. J Rheumatol 1982;9:763-6.
70. Ritchie DM, Boyle JA, McGinnis JM. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393-406.
71. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. J Rheumatol 1997;24:20-7.
72. Cooperating Clinics Committee of the ARA. A controlled trial of gold salt therapy in rheumatoid arthritis. Arthritis Rheum 1973;16:353-8.
73. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the 28 joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38-43.
74. Wolfe F, Hawley DJ, Cathey MA. Measurement of gold treatment effect in clinical practice: evidence for effectiveness of intramuscular gold therapy. J Rheumatol 1993;20:797-802.
75. Collins SL, Moore RA, Mcquay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997;72:95-7.

76. Jensen MP, Turner JA, Romano JM. What is the maximum number of levels needed in pain intensity measurement? Pain 1994; 58:387-92.
77. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217-26.
78. Ferraz MB, Quaresma MR, Aquino LRL, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990;17:1022-4.
79. Seymour RA, Simpson JM, Charlton JE, Phillips ME. An evaluation of length and end-phrase of visual analogue scales in dental pain. Pain 1985;21:177-85.
80. Carlsson AM. Assessment of chronic pain. I. aspects of the reliability and validity of the visual analogue scale. Pain 1983;16:87-101.
81. Dixon JS, Bird HA. Reproducibility along a 10 cm vertical visual analogue scale. Ann Rheum Dis 1981;40:87-9.
82. Scott J, Huskisson EC. Vertical or horizontal visual analogue scales. Ann Rheum Dis 1979;38:560.
83. Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. Pain 1978;5:5-18.
84. Huskisson EC. Measurement of pain. Lancet 1974;2:1127-31.
85. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. J Rheumatol 1988;15:1480-8.
86. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346-53.
87. Pincus T, Callahan LF, Brooks RH, Fuchs HA, Olsen NJ, Kaye JJ. Self-report questionnaire scores in rheumatoid arthritis compared with traditional physical, radiographic, and laboratory measures. Ann Intern Med 1989;110:259-66.
88. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum 1992;35:1-10.
89. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
90. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group [see comments]. Lancet 1999;353:259-66.
91. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
92. Maini R, St. Clair EW, Breedveld F, et al. Infliximab chimeric anti-tumour necrosis factor alpha monoclonal antibody versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
93. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353:1568-73.
94. Willkens RF, Stablein D. Combination treatment of rheumatoid arthritis using azathioprine and methotrexate: A 48 week controlled clinical trial. J Rheumatol 1996;23:64-8.
95. Simon LS, Weaver AL, Graham DY, et al. Antiinflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis — A randomized controlled trial. JAMA 1999;282:1921-8.
96. Viller F, Guillemin F, Briancon S, Moum T, Suurmeijer T, Vandenheuvel W. Compliance to drug treatment of patients with rheumatoid arthritis: A 3 year longitudinal study. J Rheumatol 1999;26:2114-22.
97. Clarke AE, Levinton C, Joseph L, et al. Predicting the short term direct medical costs incurred by patients with rheumatoid arthritis. J Rheumatol 1999;26:1068-75.
98. Eberhardt KB, Rydgren LC, Pettersson H, Wollheim FA. Early rheumatoid arthritis — onset, course, and outcome over 2 years. Rheumatol Int 1990;10:135-42.
99. Kvien TK, Kaasa S, Smedstad LM. Performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. II. A comparison of the SF-36 with disease-specific measures. J Clin Epidemiol 1998;51:1077-86.