A Proposed 30–45 Minute 4 Page Standard Protocol To Evaluate Rheumatoid Arthritis (SPERA) That Includes Measures of Inflammatory Activity, Joint Damage, and Longterm Outcomes

THEODORE PINCUS, RAYE H. BROOKS, and LEIGH F. CALLAHAN

ABSTRACT. A proposed 4 page, 30–45 minute standard protocol to assess rheumatoid arthritis (SPERA) is described that includes all relevant measures of inflammatory activity such as joint swelling, measures of joint damage such as joint deformity, and outcomes such as joint replacement surgery, to monitor patients in longterm observational studies. Forms are included: (1) a patient self-report modified health assessment questionnaire (MHAQ) to assess function, pain, fatigue, psychological distress, symptoms, and drugs used; (2) assessor-completed forms: "RA clinical features" — criteria for RA, functional class, family history, extraarticular disease, comorbidities, joint surgery, radiographic score, and laboratory findings. (3) A 32 joint count with 5 variables: (a) a "shorthand" normal/abnormal so that normal joints require no further detailed assessment; (b) tenderness or pain on motion; (c) swelling; (d) limited motion or deformity; (e) previous surgeries; physical measures of function, i.e., grip strength, walk time, and button test. (4) Medication review of previous disease modifying antirheumatic drugs (DMARD), work history, and years of education. The forms allow cost effective acquisition of all relevant measures of activity, damage, and outcomes in routine clinical care, and allow recognition that measures of activity may show similar or improved values over 5–10 years, while measures of damage and outcomes indicate severe progression in the same patients. The SPERA is feasible to acquire most known relevant measures of activity, damage, and outcomes in RA in 30–45 min in usual clinical settings, to provide a complete database for analyses of longterm outcomes. (J Rheumatol 1999;26:473–80)

Key Indexing Terms:
CLINICAL TRIALS RHEUMATOID ARTHRITIS OUTCOME ASSESSMENT

Patients with rheumatoid arthritis (RA) experience inflammation that may persist throughout the disease course. Inflammation may lead to joint damage, which in turn may lead to severe longterm outcomes[1-3] (Table 1). Various types of measures have been developed to assess the 3 phases of RA, activity, damage, and outcomes[4,5]: Measures of inflammatory activity, such as joint tenderness and erythrocyte sedimentation rate (ESR) are reversible, and are appropriate primary endpoints in clinical trials and other short term clinical studies[6]. Measures of damage, such as radiographic erosion[3,7,8] and joint deformity[5,9], are generally irreversible, and not included in most clinical trials. Certain measures, such as functional disability and pain[4,10-12], are sensitive to both inflammatory activity and longterm damage. Longterm disease outcomes, such as work disability, joint replacement surgery, costs[13], extraarticular disease[14], and premature mortality[15], may not appear until after 5–15 years of disease (other than work disability[16-18]), and usually are not assessed in studies of patients with early disease.

Many studies have characterized each of these indicators of clinical status. Considerable data are available concerning effects of therapies on measures of inflammatory activity, and a few concerning effects on measures of damage[3]. However, relatively few studies have explored the continuum of these events over the course of disease. Therefore, relatively little information is available concerning possible effects of interventions, which are generally targeted toward disease activity, on longterm damage and outcomes.

The acquisition of such data might theoretically be possible through randomized controlled clinical trials. However, there has not been a clinical trial of greater than 3 years in RA, while at least 10 years of observation are needed to assess damage and outcomes[19,20]. Pragmatic and

From Vanderbilt University School of Medicine, Department of Medicine, Division of Rheumatology and Immunology, Nashville, TN; and the University of North Carolina at Chapel Hill, Thurston Arthritis Research Center, Chapel Hill, NC, USA.

Supported in part by grants from the Arthritis Foundation, the Jack C. Massey Foundation, and the Maury County Lupus Fund. The authors receive consulting fees and royalties for studies involving patient questionnaires.

T. Pincus, MD; R.H. Brooks, Department of Medicine, Division of Rheumatology and Immunology, Department of Medicine, Vanderbilt University School of Medicine; L.F. Callahan, PhD, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill.

Address reprint requests to Dr. T. Pincus, Vanderbilt University School of Medicine, Division of Rheumatology and Immunology, 203 Oxford House, Box 5, 1313 21st Avenue South, Nashville, TN 37232-4500; E-mail: theodore.pincus@vanderbilt.edu

Table 1. Some measures of inflammatory activity, damage, and outcomes in RA.

Type of Prognostic Marker or Outcome	Activity Markers, Prognostic of Short Term Outcomes	Activity and/or Damage Markers, Prognostic of Intermediate Term and Longterm Outcomes	Damage Markers, Prognostic of Longterm Outcomes	Longterm Outcomes
Global	Physician assessment of global status (C), patient assessment of global status (C), ARA functional class	Extraarticular disease, comorbid diseases		Work disability, extraarticular disease, comorbid diseases, premature mortality, costs, drug toxicities
Joint Count	Tenderness (C), swelling (C), pain on motion	Limited motion	Deformity	Joint destruction, joint replacement surgery
Laboratory	Acute phase reactant — ESR or CRP (C)			
Radiographic		Joint space narrowing (C)*, erosion (C)*	Malalignment	Radiographic destruction, joint replacement surgery
Questionnaire	Pain (C)	Functional disability (C), psychological distress		Functional disability, psychological distress
Physical functional		Grip strength, walk time, button time		Functional disability

(C): included in WHO/ILAR Core Set[6] recommended for use in clinical trials.
*Included in WHO/ILAR core set for studies longer than one year.

intrinsic limitations as well as costs of clinical trials constrain application of this method in longterm studies of chronic diseases such as RA[19,20].

These considerations have led to development of longitudinal databases in RA over the last 2 decades. Such databases have been analyzed in studies of RA over more than 30 years[21], and have provided information concerning severe longterm outcomes of RA that is not available through randomized controlled clinical trials[1,2]. However, few reports are available to guide researchers who attempt to develop longitudinal databases[22], in contrast to an extensive literature to guide randomized controlled clinical trials[23]. Therefore, clinicians and researchers who wish to collect data from patients seen in routine clinical care to characterize the longterm course of RA are generally required to "reinvent" data collection procedures and content, not infrequently resulting in limited conclusions despite extensive efforts. The effort to establish comprehensive databases may appear overwhelming, and most rheumatologists have limited baseline data to assess the longterm course of RA.

We describe a proposed standard protocol to evaluate rheumatoid arthritis (SPERA) that may be completed in 30–45 minutes (other than radiographic scoring and laboratory testing, done off-site). While description of this protocol remains a "progress report," as further improvements under development are always desirable, the SPERA incorporates experience in longterm studies over the last 15 years of 3 different cohorts of 75[17], 210[5], and 1416[24] patients with RA, in which more than 95% of patients studied at

baseline were accounted for over 5 or more years. We suggest that this type of protocol be incorporated into care of all patients with RA as a baseline for longterm observations.

RATIONALE FOR INCLUSION OF MEASURES OF DAMAGE AND OUTCOMES IN RA DATABASES

Measures of damage and outcomes are required to recognize the severe longterm consequences of RA. Studies that suggest that the course of RA is milder at this time compared to earlier studies may present valid conclusions. However, at least 4 reports document that measures of activity may remain unchanged or even show improvement over 5–10 years, while measures of damage may show progression in the same patients[5,25-27].

Hawley and Wolfe reported that grip strength, global severity, joint tenderness, morning stiffness, ESR, and hemoglobin (Hb) were unchanged or improved over 5 or 10 years, while functional disability on the Health Assessment Questionnaire (HAQ) progressed in the same patients[25]. Mulherin, *et al* reported that grip strength, Ritchie Index for joint tenderness, Hb, and ESR were improved over 6 years, while radiographic erosions progressed[26]. Fex, *et al* reported that morning stiffness, Ritchie index, and Hb improved and scores for function, pain, and global activity remained unchanged while radiographs progressed over 5 years[27]. Callahan, *et al* reported that certain measures of activity were improved, including joint swelling, joint tenderness, pain scores, and rheumatoid factor (RF) titer; some measures were unchanged, including joint pain on motion, ESR, Hb, and modified HAQ scores; while most measures of damage indicated disease progression, including joint count deformity, walk time, and radiographic scores, over the 5 year period (Figure 1)[5]. Therefore, longitudinal studies that include only measures of activity may be interpreted as indicating a favorable course, and underestimate damage and poor outcomes.

It may be suggested that measures of damage and outcomes need not be included in short term clinical studies such as clinical trials of less than one year. However, data from clinical trials often provide the best available baseline data for longterm observational studies[28]. Only about 30 extra minutes beyond that expended in routine care are needed to incorporate the additional measures of the SPERA into any database of patients with RA.

SPERA

Measures beyond indicators of activity to be included in any baseline database of patients with RA are listed in Table 2. A standard protocol to collect all this information within 30–45 minutes involves collection of 4 pages. Page 1 is a patient self-report questionnaire (not shown). Page 2 (Figure

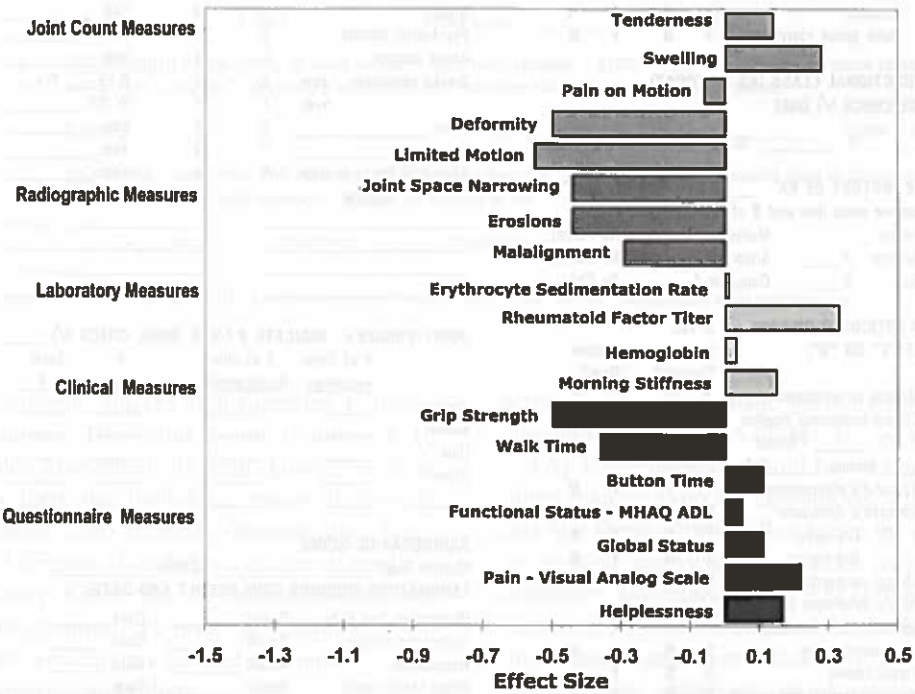

Figure 1. Changes in measures in 100 patients with rheumatoid arthritis over 5 years determined according to effect size. Note that certain measures of activity are improved, including joint swelling, joint tenderness, pain scores, and rheumatoid factor titer; some measures are unchanged, including joint pain on motion, ESR, hemoglobin, and modified HAQ scores; while most measures of damage indicated disease progression, including joint count deformity, walk time, and radiographic scores, over the five year period. Longitudinal studies that include only measures of activity may be interpreted as indicating a favorable course, and underestimate damage and poor outcomes. MHAQ:modified health assessment questionnaire; ADL: activities of daily living. Reprinted with permission[5].

Table 2. Measures in addition to those of inflammatory activity that should be included in longterm databases of RA.

1. Joint count deformity and/or limited motion
2. Radiograph of hands and/or feet
3. Extraarticular features of disease
4. Comorbidities or coexistence of other diseases
5. Record of major therapies — start and stop dates of all DMARD
6. Record of all joint surgeries, including joint replacement
7. Work status at onset of RA and through course of disease
8. Measures of costs: work losses, treatments and surgeries, intangible costs to families
9. Death

2) is a background information investigator review that includes American College of Rheumatology (ACR) Criteria for RA[29], ACR Functional Class[30], comorbidities, extraarticular disease, surgeries, radiographic score, family history of RA, laboratory data including HLA haplotype, ESR, C-reactive protein (CRP), and RF. Page 3 (Figure 3) includes a 32 joint count (28 joint count[31] plus hips and ankles as hip involvement conveys a poor prognosis in longterm studies[32]), which incorporates 5 measures: (a) any joint abnormality (to save time if the joint is normal); (b) joint tenderness or pain on motion, which are highly correlated[9]; (c) joint swelling; (d) joint deformity or limited motion, which also are highly correlated with each other and

RA DATABASE

NAME OF PATIENT_____ DOB_____ SS#_____

RECORD NO._____ RA-1ST SYMPTOM (YEAR)_____ RA-DIAGNOSIS (YEAR)_____

FORM COMPLETED BY_____ DATE_____

ARA CRITERIA FOR RA (CIRCLE "Y" OR "N"):

		Ever Present?		Present Now?	
1.	Morning stiffness >1 hr	Y	N	Y	N
2.	Soft tissue swelling of 3 or more joint groups	Y	N	Y	N
3.	Swelling of PIP, MCP, or wrist joints	Y	N	Y	N
4.	Symmetrical swelling	Y	N	Y	N
5.	Subcutaneous nodules	Y	N	Y	N
6.	Rheumatoid factor positive	Y	N	Y	N
	Highest titer_____ Date _____				
7.	Radiograph - Abnormal	Y	N	Y	N
	Erosions	Y	N	Y	N
	Joint space narrowing	Y	N	Y	N

ARA FUNCTIONAL CLASS (AS OF TODAY)
(PLEASE CHECK (√) ONE)

I: _____ II: _____ III: _____ IV: _____

FAMILY HISTORY OF RA ___ No, ___ Yes (If "Yes," Circle one item on each line and # of siblings or children.

Father	Mother		No Parent
Brother #____	Sister #____		No Sibling
Son #____	Daughter #____		No Child

EXTRA-ARTICULAR DISEASE (CIRCLE "Y" OR "N")		If Yes, Ever Present?		Present Now?	
1.	Malaise or weakness	Y	N	Y	N
2.	Clinical pulmonary disease	Y	N	Y	N
	If "Y": _____ Fibrosis _____Nodule, _____Other				
3.	Raynaud's phenomenon	Y	N	Y	N
4.	Sjoegren's syndrome	Y	N	Y	N
	If "Y": Dry eyes	Y	N	Y	N
	Dry mouth	Y	N	Y	N
5.	Clinical pericarditis	Y	N	Y	N
6.	Felty's syndrome, i.e. splenomegaly (See WBC)	Y	N	Y	N
7.	Lymphadenopathy	Y	N	Y	N
8.	Carpal tunnel	Y	N	Y	N
9.	Noncompressive neuropathy	Y	N	Y	N
10.	Vasculitis	Y	N	Y	N
11.	Non-vasculitis skin ulcer	Y	N	Y	N
12.	Scleritis	Y	N	Y	N

COMORBIDITY AND HABITS - HAS PATIENT EVER HAD?
(CIRCLE "Y" OR "N". IF "Y", GIVE YEAR OF ONSET).

Hypertension	Y	N	Year _____
Angina pectoris	Y	N	Year _____
Myocardial infarction	Y	N	Year _____
Peptic ulcer	Y	N	Year _____
Other GI _____	Y	N	Year _____
Renal disease	Y	N	Year _____
Chronic bronchitis	Y	N	Year _____
Diabetes mellitus	Y	N	Year _____
Thyroid disease	Y	N	Year _____
Chronic back pain	Y	N	Year _____
Cancer	Y	N	Year _____
Stroke	Y	N	Year _____
Psychiatric disease	Y	N	Year _____
Abuse alcohol	Y	N	Year _____
Smoke cigarettes - ever	Y	N	# Pk___ Yrs___
now	Y	N	Yr D/C _____
Other _____	Y	N	Year _____
Other _____	Y	N	Year _____
Allergies/Adverse events:	Y	N	Year _____

General	Drugs
_____	_____
_____	_____
_____	_____
_____	_____

JOINT SURGERY - INDICATE # OR IF NONE, CHECK (√) ____

	# of Synovectomies	# of Joint Replacements	# Other	Total #
Hands	____	____	____	____
Knees	____	____	____	____
Hips	____	____	____	____
Other:	____	____	____	____
____	____	____	____	____

RADIOGRAPHIC SCORE
Method Used _____ SCORE_____

LABORATORY FINDINGS (GIVE RESULT AND DATE)

Westergren Sed Rate	Result _____	Date _____
C-Reactive Protein	Result _____	Date _____
Hematocrit	Result _____	Date _____
White blood count	Result _____	Date _____
HLA haplotype_____		Date _____
Other_____	Result _____	Date _____
Other_____	Result _____	Date _____

Figure 2. Standard protocol to evaluate RA. Investigator review. Reprinted with permission.

WEIGHT: HEIGHT: BP:

32 JOINT COUNT Patient Name_____, Record #_____, Date_____

SCORE EACH JOINT AS: "+" or "POSitive" or "ABNormal" versus "-" OR "NEGative" or "NORMal"

	? Abnormal¶	Tender or pain on motion	Swollen	Limited motion or deformed	# Surgeries§		? Abnormal¶	Tender or pain on motion	Swollen	Limited motion or deformed	# Surgeries§
R-PIP1						L-PIP1					
R-PIP2						L-PIP2					
R-PIP3						L-PIP3					
R-PIP4						L-PIP4					
R-PIP5						L-PIP5					
R-MCP1						L-MCP1					
R-MCP2						L-MCP2					
R-MCP3						L-MCP3					
R-MCP4						L-MCP4					
R-MCP5						L-MCP5					
R-WRIST(0-1)						L-WRIST(0-1)					
R-ELBOW(0-1)						L-ELBOW(0-1)					
R-SHOULDER(0-1)						L-SHOULDER(0-1)					
R-HIP(0-1)						L-HIP					
R-KNEE(0-1)						L-KNEE(0-1)					
R-ANKLE(0-1)						L-ANKLE					
						TOTAL #/32					

¶ = tenderness, pain on motion, swelling, limited motion, deformity and/or surgery

§ - S = Synovectomy J = Total Joint Replacement (TJR)
O = Other

Total # joints with TJR _____, Total # synovectomies_____, Total # joint surgeries _____

Description only - not in formal joint count

NECK ___ _____ FEET ___ _____

BACK ___ _____ OTHER ___ _____

PHYSICAL RHEUMATOLOGY FUNCTION TEST MEASUREMENTS (NOTE EXACT INSTRUCTIONS):

1. ASK: "Are you right-handed or left-handed?" R _____ L _____
2. SAY: "Let's begin with your R _____ L _____ hand."
3. BUTTON TEST – READ: "When I tell you to do so, using one hand only, please unbutton and then button the 5 buttons on this board. You may use your other hand to steady the frame. I will time you while you do this."

   R (secs) _____ L (secs) _____ Unable to do _____ (Score as 201 secs)
4. GRIP STRENGTH (Inflate cuff to 30 mmHg encased in black fabric container) – READ: "When I tell you to do so, please squeeze the cuff as hard as you can." (Measure grip strength for each hand three times and record each measurement)

   R (mmHg) _____ _____ _____ L (mmHg) _____ _____ _____ Unable to do ___ ___ (Score as 30 mmHg)
5. WALKING TIME – read: "When I tell you to do so, please walk from here to me." (Show patient starting and stopping points for 25-foot course). "Walk as though you are going somewhere. I will time you while you do this."

   _____ (secs) Unable to do _____ (Score as 21 secs)

Figure 3. Standard protocol to evaluate RA. Physical measures review. Reprinted with permission.

with radiographic damage[9]; and (e) joint surgeries, to incorporate this information. This joint count requires 5–10 minutes and includes assessment of joint damage such as joint deformity. The form also includes a review of physical measures of functional status termed "rheumatology function tests."[33] Page 4 (Figure 4) includes a review of medications and work history. Costs may be computed from the collected data, although improved pragmatic approaches to assess more detailed cost data are needed and remain under development by ourselves and others.

PROPOSED PRINCIPLES FOR LONGTERM OBSERVATIONAL STUDIES

The development of a SPERA to assess both inflammatory activity and joint damage presents certain implications for clinical research in RA (Table 3):

(A) The emphasis should be on rigorous data collection rather than on a specific hypothesis, with an implicit hypothesis that these efforts will enhance the capacity of clinicians to develop improved approaches to patients with chronic diseases[22]. For example, a study with a plausible hypothesis that reversal of abnormalities in the Ritchie Index or ESR might ameliorate work disability over 5–10 years would likely prove relatively uninformative without baseline measures of damage such as joint deformity and radiographic progression, although these measures may have appeared irrelevant to the primary hypothesis at the time the study was initiated. Evidence that patient questionnaire

PATIENT _____ VUH # _____ DX _____ ONSET _____ DATE _____

Name of Drug or Medicine	Ever taken, (Y=Yes, N=No, ?orU=Unknown)	If taken in past or now, please indicate: Mo/Yr begun	Mo/Yr discontinued	Taking at this time (✓)	# years-months on drug	Efficacy[1]	Toxicity[2]	If discontinued, reason[3]
hydroxychloroquine (Plaquenil™)								
gold pills (Ridaura™)								
gold injections (Circle one: Myochrysine™ or Solganal™)								
penicillamine (D-Pen™, Cuprimine™)								
sulfasalazine (Azulfidine™)								
azathioprine (Imuran™)								
methotrexate (Rheumatrex™)								
cyclosporine (Sandimmune, Neoral™)								
cyclophosphamide								
prednisone (Medrol™, corticosteroid)								
Other: _____								

[1]Efficacy Codes: 0=N=No Benefit, 1=S=Some Benefit, 2=M=Much Benefit, 3=R=Remission, 4=W=Worse, 9=U=Unknown
[2]Toxicity Codes: 0=N=None, 1=G=GI, 2=S=Skin, 3=H=Heme, 4=R=Renal, 5=L=Liver, 8=O=Other(Specify), 9=U=Unknown
[3]Reason for Discontinuation: 0=N=No efficacy, 1=T=Toxicity(specify code), 2=L=Less of efficacy, 3=R=Not Needed, 4=O=Other, 5=M=MD stopped drug, 9=U=Unknown

Costs: Work status at onset of RA: Check (✓) all that apply:
___Working full time ___Retired
___Working part time ___Student
___Homemaker-full time ___Disabled
___Other (describe)_____

Number of years of formal education completed:
Please circle the number of years of schooling
1 2 3 4 5 6 7 8 9 10
11 12 13 14 15 16 17 18 19 20

Work status at present: Check (✓) all that apply:
___Working full time ___Retired
___Working part time ___Student
___Homemaker-full time ___Disabled
___Other (describe)

If working at onset or while having RA:
changes of work duties after onset due to RA: _____
changes of job after onset due to RA: _____
years after onset before discontinuing work: _____
years after onset before disability payments: _____

Comments: _____

Figure 4. Standard protocol to evaluate RA. Medication review. Reprinted with permission.

data[17,32] or formal education level[5,24,32,34] predict mortality in RA more effectively than laboratory data or radiographs[5] would not have been detected through a baseline hypothesis. However, these observations have been documented through data collected at baseline 5–15 years earlier to study longterm outcomes. The Framingham database[35] is perhaps the most prominent example of a longitudinal database without an explicit baseline hypothesis; it has proven highly effective to analyze chronic diseases.

(B) All patients should be included in a database to avoid patient selection[22]. This goal can be accomplished most easily through distribution of a patient questionnaire to each patient at each visit[36]. If the patients are selected according to any criterion, that compromises substantially the value and generalizability of the data. For example, it may appear plausible to include in a database only patients with a diagnosis of RA at baseline. However, patients who may appear to have reactive arthritis, fibromyalgia, or other diagnoses at one point may ultimately be found to have RA. If data collection in clinical settings is restricted only to certain patients, the data are inevitably not as informative for later analyses.

(C) Patient questionnaires should meet psychometric criteria for validity and reliability. However, the primary basis for inclusion should be their feasibility for use in routine clinical settings and documented clinical value, such as capacity to predict outcomes such as work disability[16,18] or mortality[5,17,32]. The goal of feasibility requires that

Table 3. Proposed principles for optimal protocols for longitudinal studies.

a. Emphasize rigorous data collection rather than specific hypotheses
b. Include or account for *all* consecutive patients over a given time period
c. Measures should be valid and reliable, but emphasis should be on documented clinical value and feasibility — measures should be as simple as possible
d. A comprehensive protocol should be followed for data to be collected at baseline concerning each patient
e. Include measures of inflammatory activity, irreversible joint damage, and longterm outcomes
f. Recognize that disease progression from inflammation to damage to poor outcomes is not linear in groups or in individual patients
g. A system should be in place for periodic monitoring in the clinic and every 6 months monitoring of patients who do not return

A simple 2 page patient questionnaire provides the most feasible approach to meet all the above objectives, and ironically may provide optimal data for studies of longterm outcomes.

measures should be as simple as possible, seen in reduction of the HAQ from 20 activities of daily living to an 8 activity modified HAQ[11]; or simplifying the joint count from 70 to 28 joints[37], although we advocate here inclusion of 32 joints (28 joint count plus hips and ankles) for longterm studies. We also advocate inclusion of joint deformity or limited motion in addition to joint tenderness and swelling in the joint count[5], but include a simple notation that a joint is normal. Simple measures collected in all patients are much more valuable than complex measures collected in only a few patients. Nonetheless, it may be desirable to collect more complex data on a subset of patients, who can be selected from the entire sample and/or compared for their representative nature.

(D) It is necessary to include multiple types of measures of activity, damage, and outcomes in a longitudinal study, as it is not possible to know which measures will prove optimal over 5–20 years. Furthermore, disease progression may be described differently according to different measures. For example, 2 of the most widely used measures in clinical studies of RA, the Ritchie Index (or joint tenderness) and radiographic damage, are not associated at all in cross sectional studies[9]. Radiographic change is associated at higher levels with HLA haplotype, RF, ESR, CRP, and duration of disease, than with functional status and age[9,11,38]. By contrast, joint tenderness is associated at higher levels with functional status and pain than with acute phase reactants and duration of disease[9,11,38]. Therefore, it is desirable to include different types of measures in a database to characterize clinical status.

(E) It is also desirable to have a system to monitor patients over long periods. A simple 2 page patient questionnaire provides the most feasible approach to monitoring and meeting all of the above objectives[5,17,24,32,34,39]. Ironically, a patient questionnaire may provide not only the most easily collected, but also the most predictive, data for studies of longterm outcomes. Some patients may ultimately require a telephone contact, which may be arranged.

(F) Disease progression from inflammation to damage to poor outcomes generally is not linear, but occurs at different rates in individual patients and in the same patient over time. However, an assumption of linearity underlies most longitudinal studies in which duration of disease is regarded as a continuous variable. Thus, analyses of, say, 100 patients over 0–5 years versus 10–15 years would yield apparently identical 500 patient years of analyses. However, measures of damage such as joint deformity and outcomes such as joint replacement and premature mortality are not usually seen in most patients until after 5–20 years of disease, so that this apparent numerical identity does not necessarily indicate identity of clinical phenomena under study. Interpretation of longitudinal data requires knowledge of the observation period in disease course and measures of damage and outcomes.

Of course, limitations are seen in longterm observational studies, even when conducted according to a rigorous protocol as described here, primarily inevitable biases in treatment assignment when patients are not randomized, and longterm losses to followup. Nonetheless, limitations are seen in any type of clinical study, including clinical trials. The goal of all clinical research is to develop better treatments and better outcomes for people with a disease, using many types of approaches. We hope that the 30–45 minute SPERA described here to assess activity, damage, and outcomes will contribute to that goal.

REFERENCES

1. Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? Rheum Dis Clin North Am 1993;19:123-51.
2. Wolfe F. The natural history of rheumatoid arthritis. J Rheumatol 1996;23 Suppl 44:13-22.
3. van Leeuwen MA, van Rijswijk MH, van der Heijde DMFM, et al. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. Br J Rheumatol 1993;32:9-13.
4. Pincus T, Callahan LF. Prognostic markers of activity and damage in rheumatoid arthritis: why clinical trials and inception cohort studies indicate more favorable outcomes than studies of patients with established disease. Br J Rheumatol 1995;34:196-9.
5. Callahan LF, Pincus T, Huston JW III, Brooks RH, Nance EP Jr, Kaye JJ. Measures of activity and damage in rheumatoid arthritis: depiction of changes and prediction of mortality over five years. Arthritis Care Res 1997;10:381-94.
6. 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.
7. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989;16:585-91.
8. Forre O. Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: results of a 48-week multi-center study comparing low-dose cyclosporine with placebo. Arthritis Rheum 1994;37:1506-12.

9. Fuchs HA, Callahan LF, Kaye JJ, Brooks RH, Nance EP, Pincus T. Radiographic and joint count findings of the hand in rheumatoid arthritis: related and unrelated findings. Arthritis Rheum 1988;31:44-51.
10. 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.
11. 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; 110:259-266.
12. Pincus T, Callahan LF. Quantitative measures to assess, monitor and predict morbidity and mortality in rheumatoid arthritis. Bailliere's Clin Rheum 1992;6:161-91.
13. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997;24:43-8.
14. Gordon DA, Stein JL, Broder I. The extra-articular features of rheumatoid arthritis: a systematic analysis of 127 cases. Am J Med 1973;54:445-52.
15. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously — predictive markers, socioeconomic status and comorbidity. J Rheumatol 1986;13:841-5.
16. Yelin E, Meenan R, Nevitt M, Epstein W. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med 1980;93:551-6.
17. 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.
18. Callahan LF, Bloch DA, Pincus T. Identification of work disability in rheumatoid arthritis: physical, radiographic and laboratory variables do not add explanatory power to demographic and functional variables. J Clin Epidemiol 1992;45:127-38.
19. Pincus T, Stein CM. Why randomized controlled clinical trials do not depict accurately long-term outcomes in rheumatoid arthritis: some explanations and suggestions for future studies. Clin Exp Rheumatol 1997;15 Suppl 17:S27-S38.
20. Pincus T. Analyzing long-term outcomes of clinical care without randomized controlled clinical trials: the consecutive patient questionnaire database. Advances in Mind-Body Medicine 1997;13:3-32.
21. Duthie JJR, Brown PE, Truelove LH, Baragar FD, Lawrie AJ. Course and prognosis in rheumatoid arthritis: a further report. Ann Rheum Dis 1964;23:193-204.
22. Moses LE. The series of consecutive cases as a device for assessing outcomes of intervention. New Engl J Med 1984;311:705-10.
23. Felson DT, Anderson JJ, Meenan RF. Time for changes in the design, analysis, and reporting of rheumatoid arthritis clinical trials. Arthritis Rheum 1990;33:140-9.
24. Callahan LF, Cordray DS, Wells G, Pincus T. Formal education and five-year mortality in rheumatoid arthritis: mediation by helplessness scale scores. Arthritis Care Res 1996;9:463-72.
25. Hawley DJ, Wolfe F. Sensitivity to change of the Health Assessment Questionnaire and other clinical and health status measures in rheumatoid arthritis: results of short term clinical trials and observational studies versus long term observational studies. Arthritis Care Res 1992;5:130-6.
26. Mulherin D, Fitzgerald O, Bresnihan B. Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that pathogenesis of synovial inflammation and articular erosion may differ. Br J Rheumatol 1996;35:1263-8.
27. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. Br J Rheumatol 1996;35:1106-15.
28. Porter DR, McInnes I, Hunter J, Capell HA. Outcome of second line therapy in rheumatoid arthritis. Ann Rheum Dis 1994;53:812-5.
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. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498-502.
31. Pincus T, Callahan LF, Brooks RH. Quantitative nonlaboratory measures to monitor and predict the course of rheumatoid arthritis. In: Ehrlich GE, editor. Rehabilitation management of rheumatic conditions. 2nd ed. Baltimore: Williams & Wilkins, 1986:45-63.
32. Pincus T, Brooks RH, Callahan LF. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann Intern Med 1994;120:26-34.
33. Pincus T, Callahan LF. Rheumatology function tests: grip strength, walking time, button test and questionnaires document and predict longterm morbidity and mortality in rheumatoid arthritis. J Rheumatol 1992;19:1051-7.
34. Pincus T, Callahan LF. Formal education as a marker for increased mortality and morbidity in rheumatoid arthritis. J Chronic Dis 1985;38:973-84.
35. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis: the Framingham Study. Ann Intern Med 1988;109:18-24.
36. Pincus T. Documenting quality management in rheumatic disease: are patient questionnaires the best (and only) method? Arthritis Care Res 1996;9:339-48.
37. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531-7.
38. Olsen NJ, Callahan LF, Brooks RH, et al. Associations of HLA-DR4 with rheumatoid factor and radiographic severity in rheumatoid arthritis. Am J Med 1988;84:257-64.
39. Pincus T, Callahan LF, Vaughn WK. Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatol 1987;14:240-51.
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. Arthritis Rheum 1993;36:729-40.
41. Tugwell P, Boers M. OMERACT Committee. Proceedings of the OMERACT Conferences on outcome measures in rheumatoid arthritis clinical trials, Maastricht, Netherlands. J Rheumatol 1993;20:527-91.
42. van Riel PLCM. Provisional guidelines for measuring disease activity in clinical trials on rheumatoid arthritis [editorial]. Br J Rheumatol 1994;31:793-4.