

Arthritis, Rheumatism and Aging Medical Information System Post-Marketing Surveillance Program

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ABSTRACT. The Arthritis, Rheumatism, and Aging Post-Marketing Surveillance Program (ARAMIS-PMS) is a collection of multicenter, prospective, noninterventional, observational longitudinal studies of patients with rheumatic diseases. The ARAMIS-PMS program aims to study patients in normal clinical setting to evaluate the real-life effectiveness, toxicity, and cost effectiveness of various medications used to treat rheumatic diseases. (J Rheumatol 2001;28:1174–9)

Key Indexing Terms:

ADVERSE EFFECTS CLINICAL TRIALS ARAMIS POST-MARKETING SURVEILLANCE

The longterm management of patients with rheumatic diseases raises several complex issues, some of which are difficult to answer with randomized clinical trials alone. There are multiple therapies with attendant adverse effects. Treatment is complicated because of the many personal patient attributes that influence outcome, such as age, disease duration, comorbidity, socioeconomic status, and ability to tolerate adverse events. Medications that may demonstrate *efficacy* in a selected group of patients over a short period of time in a clinical trial setting may not prove to have the required *effectiveness* in clinical practice when used in patients who are elderly, have other concomitant illnesses, and are not perfectly compliant. New adverse events that were previously unrecognized in short term clinical trials may be discovered with longterm use. Third party payors, in a struggle to contain rapidly escalating pharmaceutical costs, may look for independent evaluation of the value of different treatments. The Arthritis, Rheumatism and Aging Medical Information System Post-Marketing Surveillance Program (ARAMIS-PMS) was therefore established to explore the real-life effectiveness, toxicity, and value of therapies for rheumatic diseases. We study large cohorts of individuals with rheumatic diseases in an observational, noninterventional protocol driven fashion to answer questions such as: Does this drug work when used outside of clinical trials? Are there any new toxicities? Are patients satisfied with this drug? What is the cost effectiveness of this drug in a real-life setting?

ARAMIS

ARAMIS is the US National Arthritis Data Resource,

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enabled under the Arthritis Act of 1974, funded by the National Center for Health Services Research in 1975 and 1976, and from 1977 to the present by the National Institutes of Health (NIH). ARAMIS includes multiple data bank centers in the United States and Canada, and follows about 17,000 patients with specific arthritis conditions and normal populations of aging seniors. ARAMIS initiated the concept of the chronic disease data bank^{1,2}, in which consecutive patients are enrolled, followed for life, and regularly assessed for multiple factors, including demographics, socioeconomic status, the biology of disease, the influence of comorbidity, the mechanics and setting of care, specific medical and surgical treatments, and associated costs. Over 800 peer-reviewed studies have emanated from the ARAMIS program. An experienced multidisciplinary team includes biostatisticians, epidemiologists, health economists, health services researchers, clinical investigators, and support staff at Stanford and other institutions. The multiple ARAMIS data sets include full clinical data, in addition to systematic outcome assessment and cost data acquired at 6 month intervals.

DATASETS

ARAMIS-PMS data banks currently include complete outcome data on about 5400 patients with rheumatoid arthritis (RA) and 3300 with osteoarthritis (OA). Clinical data banks consist of consecutive patient entry at participating centers and are thereby representative of that clinic or practice without exclusions. The use of multiple data sets with diverse characteristics yet common procedures allows comparisons of outcomes and cost effectiveness between, for example, private and public practices, Black, Hispanic and non-Hispanic white populations, capitated and fee-for-service, and inner city versus more affluent settings. Although ARAMIS data bank centers include a selected group of practices and institutions, characteristics of ARAMIS patients are similar to other patient groups reported in the literature in terms of age (RA: mid 50s, OA: mid 60s), sex (2/3 to 3/4 female), and disease duration, etc. Patients with a wide range of severity are included. Not all

ARAMIS patients have been treated by rheumatologists, and many have received only intermittent care from rheumatologists. Socioeconomic considerations do not appear to have had a major influence on access to rheumatologic care, since many ARAMIS patients have Medicare or Medicaid insurance.

In recent years, we have systematically recruited and followed the Rheumatoid Arthritis National Inception Cohort. This cohort consists of 950 patients with RA seen within the first year of disease onset, and with disease onset between July 1, 1995, and June 30, 1997, recruited from clinical members of the American College of Rheumatology. We collect clinical summary data on these patients from their physicians at yearly intervals, and administer the Health Assessment Questionnaire (HAQ) at 6 month intervals using standard ARAMIS protocols (see below). A serum and DNA data bank on these patients is also maintained.

HEALTH ASSESSMENT QUESTIONNAIRE

The Health Assessment Questionnaire (HAQ) and the Childhood Health Assessment Questionnaire (CHAQ) are outcome assessment instruments developed by and deployed throughout ARAMIS³⁻⁶, and widely used throughout the world. The HAQ forms the basis of most data in the ARAMIS-PMS program. Two recent reviews discuss over 200 publications on the reliability, validity, and application of the HAQ^{7,8}. At present, over 500 such studies have been published (review in preparation) and the HAQ has been validated in over 25 languages. The CHAQ has been translated into 9 different languages, and other studies have been published on its reliability and validity. The HAQ conceptualizes patient outcome in the 5 dimensions of (1) mortality, (2) disability, (3) pain and other symptoms, (4) adverse effects of treatment, and (5) economic impact⁹. The HAQ has been administered by mail, in the clinical setting, or by telephone interview, and serves as a mechanism both for collecting relevant variables for ARAMIS-PMS studies and for maintaining high levels of followup in data banks over extended periods of time. The HAQ has been employed in ARAMIS studies regularly since 1979, with over 200,000 assessments to date, and provides up to 21 years of longitudinal cost and utilization data through this study period⁸.

DATA COLLECTION PROCEDURES

Data elements. Data collection protocols are followed by all data bank centers. About 1200 variables are assessed, including demographic data derived from a Background Information Questionnaire (BIQ), full clinical data, the HAQ, mortality data, and data bank-specific data. Data are longitudinal. An average of 10 and 5 observation points are available for RA and OA patients, respectively.

Patients are recruited by a data bank network physician or staff member at first clinic visit as a part of usual care at

that clinic. Over 95% of patients accept. After patients agree to participate and provide informed consent, they complete a BIQ, which establishes the patient's demographic profile and drug history. Once enrolled, study participants complete the HAQ every 6 months. The HAQ covers multiple dimensions including: disability, general health status, pain, and the presence of about 60 disease symptoms. The HAQ also includes items on medication use (about 35 rheumatic disease-specific medications and 15 classes of other medications), drug side effects, hospitalizations, comorbid conditions, health behaviors, and health care utilization.

Items from the Medical Outcome Survey Short Form-36 (SF-36)^{10,11} have recently been incorporated into the HAQ. The SF-36 includes dimensions of general health, physical functioning, pain, mental health, and social functioning. The HAQ also includes items derived from the Self-Efficacy Scale¹² and derived from a patient preference "feeling thermometer"¹³. It now includes the RADAR self-administered joint count techniques¹⁴. We have also incorporated the Arthritis Impact Measurement Scales anxiety and depression scales¹⁵ and the Center for Epidemiologic Studies Depression Scale¹⁶. Patients are also asked to provide periodic updates on demographic variables such as their employment status and living arrangements. Further information on many hospitalizations and some outpatient procedures is requested from providers. Ascertainment of information regarding deaths is facilitated by the use of the National Death Index.

Successive data collection cycles each 6 months are designated numerically. The January 2001, cycle is designated the 40th cycle. The HAQ is a dynamic instrument that is revised every 6 months, as needed, to include new questions of interest. These procedures have been in place for 20 years.

Every 6 months, the list of drug variables is reviewed, and additions and deletions are made. For example, over the years, all new nonsteroidal antiinflammatory drugs (NSAID), methotrexate, and other new agents have been added. The most recent additions were minocycline, celecoxib, rofecoxib, meloxicam, leflunomide, etanercept, and infliximab. In contrast, ARAMIS dependent variables and definitions of existing variables remain the same; the HAQ disability index, pain scale, and patient global, for example, have been used in the same form since 1983. After review, changes are made to the data dictionary and to the data collection forms. Sometimes new rheumatic disease drugs are added to the HAQ while the drug is still in clinical trials. When a patient is enrolled in a clinical trial, the study drug is entered but coded for the study (e.g., STUDY43). After study close, the actual drug is retrospectively entered as appropriate. Sometimes a drug is approved for use in Canada before receiving US Food and Drug Administration (FDA) approval (e.g., arthrotec). In these cases, we collect data on the new drug at our Canadian centers so that we

already have substantial data before the drug is approved in the US.

Clinical and laboratory information for study participants are collected from the medical record for each clinic visit. Most centers use chart forms adapted from the Stanford Rheumatic Disease Chart, which in turn was derived from the Uniform Database for the Rheumatic Diseases¹⁷. This ensures that the most important signs and symptoms, functional measurements, laboratory variables, and treatment variables are collected in a standard manner across centers, while allowing the centers the flexibility to collect additional variables specific to a given disease or research question.

Because ARAMIS-PMS projects typically rely on observational data, many of the results need to be adjusted for differences in patient characteristics across groups that result from non-random assignment. A large number of control variables are collected including: age, sex, ethnicity, disease duration, comorbidity, educational level, prednisone use, prior use of NSAID or disease modifying antirheumatic drugs (DMARD), etc. These variables are used as covariates or as stratification variables as needed.

Data quality control. Rigorous protocols standardize data collection and maximize data quality. Uniform outcome assessment scanning and clinical abstracting manuals are used to ensure document consistency and quality of project data. Pilot studies of instruments test the clarity and consistency of the data, the suitability of abstracting, coding, and entry procedures and forms, and the reliability and validity of the instruments (e.g., test-retest reliability, validation against a gold standard, etc.). Instruments, procedures, and manuals are revised regularly to clarify procedures or coding rules, add new items of interest, update medication lists, etc.

New outcome assessors spend a one-week formal training period where they learn data coding, patient followup, database management, clinical data abstraction, and scanning data entry. For at least one questionnaire cycle, questionnaires coded by a beginning assessor are recoded by the Outcome Coordinator or an experienced assessor to identify systematic errors or confusion. Trainees are given detailed feedback, and the procedures are monitored to ensure that they remain at an acceptable level. Similar procedures are followed with respect to clinic abstracting. Core staff make site visits to the centers to ensure that procedures are maintained, that clinical forms are completed correctly, and to meet with the center investigators. Outcome assessors, center coordinators, and investigators attend the yearly Data Bank Network symposium at Stanford for updated training.

Procedures to monitor the quality of clinical and laboratory data are handled on a center-by-center basis. For many data banks, monitoring of quality control is conducted by Stanford on a regular basis (monthly for clinic data, at the end of each 6 month phase for questionnaire data).

A copy of the data bank and a set of randomly selected questionnaire or clinic forms are forwarded to Stanford. The questionnaires or clinic forms are “blinded” (by covering original coding strips) for recording and reentry using software programs that identify any discrepancies. After all selected questionnaires or clinic visits have been recoded and reentered, the quality control staff categorize errors as: (1) coding errors, (2) entry errors, or (3) recoding errors by core staff (the latter are not included in the error rate).

An error tally program then tallies the errors according to variable type (e.g., medications), and the errors are reviewed to determine whether there are any systematic errors (specific items or sections of the questionnaire or clinic forms that cause repeated discrepancies). Each center receives a copy of its error tally with the coding and entry error rates for that phase. Systematic errors are discussed with the assessor, and manuals are revised to clarify any problem areas. The results of the quality control checks are included in a manual maintained at Stanford and at each site. The errors can also be tallied across data bank centers or over time to look for patterns of errors.

The acceptable error rate for each data bank for coding and entry are usually set at 0.5 to 1.0%, depending on the nature of the data. In the unusual cases where this rate is exceeded, all the questionnaires (or other forms) coded and entered for that cycle are forwarded to Stanford for recoding and reentry. The procedures and protocols have evolved over 2 decades.

Outcome assessment and followup. Systematic followup and standardized outcome assessment are essential elements for longterm studies. Vigorous followup identifies the outcome status of participants and minimizes the loss of the study population. Pairing of questionnaire administration and followup procedures efficiently accomplishes both goals.

The outcome assessment core unit coordinates the administration of outcome assessment studies and followup across the different populations of the data bank network. It is also responsible for the training of new outcome assessors, revising the protocols and coding manuals, and monitoring compliance with study protocols. Outcome assessors for each study have responsibility for questionnaire administration, processing, followup, entry, and data bank management.

Procedures involved with mailing the questionnaire at 6 month or yearly intervals are standardized, although modifications are made to accommodate specific study needs. A Spanish speaking outcome assessor will be responsible for all non-English speaking Hispanic patients at all ARAMIS data bank centers and the inception cohort. Stanford interpreters are used to handle other non-English speaking patients (e.g., Asians), and telephone interviews are conducted with patients with low literacy levels. For some data bank centers, questionnaires are administered at clinic

visits instead of, or in addition to, mailed questionnaires. If patients prefer, they may complete the questionnaire during a telephone interview.

Questionnaires are mailed to all participants with a stamped return envelope. Vigorous followup is done for those patients who do not respond within the initial 2 week period. A timed sequence of reminders is carried out including post cards, telephone calls, and additional questionnaire mailings. Nonresponders are traced and deaths are followed up using standard procedures (see below.) At the end of each questionnaire cycle, all participants are classified according to their study status: ongoing, dead, lost or unable to contact, withdrawn for personal reasons, or administratively withdrawn (a change in diagnosis, entrance into a clinical trial).

All returned questionnaires are checked for completeness, ambiguities, or inconsistencies, and patients are contacted for clarification. Questionnaires are coded using the HAQ manual. Medical records pertaining to all hospitalizations, surgeries, emergency room visits, and nursing home care are obtained from the providers and the patient and are reviewed, coded, and entered.

For patients who do not return the questionnaire, an initial attempt to recover the patient is made at the patient's last address. If this is unsuccessful, additional attempts are made through the contacts given by the participant, the referring physician, the Department of Motor Vehicles, post office tracing, and death registries. The National Death Index is used to ensure completeness of records of deaths including patients who are not currently enrolled in the study. Patients who are recontacted through these means after previously withdrawing from the study are invited to re-enroll and the previously described procedures initiated. For patients who have died, information is requested from the family, attending physician, and hospital including copies of the death certificate, discharge summary, and/or autopsy report, if applicable. These procedures result in 98 to 99% followup per cycle.

Although clinical data are collected at a large number of sites, and self-report data are collected in multiple settings (clinic, mail, telephone), the site or method of data collection does not influence the results of ARAMIS research studies. Extensive validation studies have established congruence across sites and by methods of administration. Reliability and validity have been documented for all HAQ variables, including utilization variables such as number of hospital days and number of doctor visits⁸.

PREVIOUS WORK

ARAMIS and ARAMIS-PMS have conducted studies directed at establishing the natural history of rheumatic diseases, identifying the factors that predict adverse outcomes, and working systematically toward approaches to improve these outcomes over the past 25 years. The chronic

disease data bank model initiated by ARAMIS provided a means for enrolling a large number of patients with arthritis from first appearance at a data bank center or by an inception cohort and then following these patients for the remainder of their lives^{1,2,9}. In this section, we provide some highlights of our more recent work.

ARAMIS, ARAMIS-PMS, and Stanford Arthritis Center projects developed the concept of assessment of longterm outcomes in RA and use of patient outcome measures, such as disability, pain, and costs, as primary dependent variables in clinical studies. The development of the Health Assessment Questionnaire (HAQ)^{3,4,7,8} and its application throughout ARAMIS data sets beginning in 1980 provided the basis for subsequent work. The CHAQ permitted a similar evaluation in children^{5,6}. ARAMIS studies of mortality in RA confirmed and extended observations of an increase in standardized mortality rates of 2-fold or more^{18,19}. The consistent development of disability in RA over time was quantified in a number of studies^{20,21}. Longterm disability outcomes were found to be a function of many variables, and early persistent DMARD use was established as superior to NSAID based strategies, reducing disability over the long term by one-third to one-half^{22,23}. The toxicity profiles of different DMARD were compared, and longterm toxicity of immunosuppression assessed^{24,25}. ARAMIS epidemiologic and pharmacoeconomic studies in RA have contributed substantially to our knowledge of major adverse effects of medications and costs²⁶⁻²⁸.

Several pharmacoeconomic studies in RA and OA have been completed²⁶⁻³⁷. Costs models for treatment of RA have been built^{32,36}. We have established that the disability index is a strong determinant of costs of care in RA, and that early aggressive interventions can lead to possible cost savings^{30,32}. Cost effectiveness models for the new biological agents are being developed³⁷.

A toxicity index for quantitating drug toxicity that aggregates adverse symptoms, laboratory tests, and hospitalizations into a single value has been developed and used to analyze NSAID and DMARD therapy³⁸⁻⁴¹. A separate gastrointestinal toxicity index has also been developed⁴¹. Using the toxicity index, DMARD were shown to have similar toxicity to NSAID⁴⁰ without a clear safety advantage for either group. A methodology for comparing treatment effectiveness in the domains of disability, pain, and patient global assessment, based upon the HAQ, has been developed^{42,43}.

A series of ARAMIS-PMS studies quantitated the magnitude of the epidemic of NSAID gastropathy, documenting the patient and societal costs. Singh, *et al*⁴⁴⁻⁵⁵, Wolfe, *et al*⁵⁶, and Fries⁵⁷, among others, quantitated frequencies of hospitalizations and deaths, and differentiated the risks of different NSAID. Singh, *et al*^{54,55} developed a quantitative model called SCORE (standardized calculator for risk for events) for prediction of individual risks of serious gastrointestinal

toxicities. This instrument is widely used to identify patients who are appropriate candidates for the newer safer NSAID.

Our recent work has focused on the incidence of serious infections in patients with RA, and patient characteristics that may increase this risk^{58,59}. Other studies have documented the longterm toxicities associated with steroid use, even in low doses^{60,61}.

Our group has used the ARAMIS model of embedding randomized trials in ongoing prospective longitudinal studies in several randomized trials. This model permits increased efficiency, reduced costs, larger patient numbers, and perhaps increased validity, compared with standard designs. We have just completed a large clinical trial comparing a selective cyclooxygenase-2 inhibitor to a “usual care” approach in managed care settings. The primary outcomes include patient satisfaction with therapy and discontinuations. Detailed health care resource utilization data has also been collected. Another clinical trial on the clinical and economic outcomes of viscosupplementation in knee OA is in progress.

FUNDING AND COLLABORATIONS

The ARAMIS-PMS program depends on and is made possible by US National Institutes of Health support to the ARAMIS project. Supplemental funding is obtained from multiple pharmaceutical companies and the FDA.

ARAMIS-PMS program works with various individuals and organizations on projects of mutual interest. We have worked extensively with the OMERACT group and the FDA in quantitating drug toxicities and measuring patient satisfaction. There are several ongoing programs with large managed care organizations, aimed at optimizing formulary decisions. A collaborative program with the Institute of Rheumatology at Tokyo Women’s Medical University led to the start of J-ARAMIS (Japan ARAMIS)⁶². Almost 4000 patients with RA have been enrolled in the J-ARAMIS program. Similar collaborative endeavors are continuing in many other countries.

REFERENCES

1. Fries JF, McShane DJ. ARAMIS: A prototypical national chronic-disease data bank. *West J Med* 1986;145:798-804.
2. Fries JF. The ARAMIS (American Rheumatism Association Medical Information System) post-marketing surveillance program. *Drug Information J* 1985;19:257-62.
3. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
4. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789-93.
5. Singh G, Athreya BA, Fries JF, Goldsmith DP. Measurement of functional status in juvenile rheumatoid arthritis. *Arthritis Rheum* 1994;37:1761-9.
6. Singh G, Brown B, Athreya B, et al. Functional status in juvenile rheumatoid arthritis: sensitivity to change of the Childhood Health Assessment Questionnaire [abstract]. *Arthritis Rheum* 1991;34 Suppl:S81.
7. Ramey DR, Raynauld JP, Fries JF. The Health Assessment Questionnaire 1992: status and review. *Arthritis Care Res* 1992;119-29.
8. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 – status and review. Chapter 25. In: Spiker B, ed. *Pharmacoeconomics and quality of life in clinical trials*. 2nd ed. New York: Raven Press; 1995.
9. Fries JF. Toward an understanding of patient outcome measurement. *Arthritis Rheum* 1983;26:697-704.
10. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions: Results from the Medical Outcomes Study. *JAMA* 1989;262:907-13.
11. Ware JE, Sherbourne CD. The MOS 36-item Short-form Health Survey (SF-36). *Med Care* 1992;30:473-83.
12. Lorig K, Ung E, Chastain R, Shoor S, Holman H. Development and evaluation of a scale to measure the perceived self-efficacy of people with arthritis. *Arthritis Rheum* 1989; 32:37-44.
13. Torrance GW. Measurement of health state utilities for economic appraisal: a review. *J Health Economics* 1986;5:1-30.
14. Mason JH, Anderson JJ, Meenan RJ, Haralson KM, Lewis-Stevens D, Kaine JL. The rapid assessment of disease activity in rheumatology (RADAR) questionnaire – validity and sensitivity to change of a patient self-report measure of joint count and clinical status. *Arthritis Rheum* 1992;35:156-62.
15. Wolfe F, Hawley DJ. The relationship between clinical activity and depression on rheumatoid arthritis. *J Rheumatol* 1993;20:2032-7.
16. Blalock SJ, DeVellis RF, Brown GK, Wallston KA. Validity of the Center for Epidemiological Studies depression scale in arthritis populations. *Arthritis Rheum* 1989;32:991-7.
17. Fries JF, Hess EV, Klinenberg JR. A uniform database for rheumatic diseases. *Arthritis Rheum* 1976;19:645-8.
18. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37:481-94.
19. Matsuda Y, Wang W, Fries F, Singh G. Mortality in RA in a contemporary cohort: analysis of 918 deaths in 4628 patients (25,814 patient years) [abstract]. *Arthritis Rheum* 2000;43 Suppl:S183.
20. Sherrer YS, Bloch DA, Mitchell DM, Young DY, Fries JF. The development of disability in rheumatoid arthritis. *Arthritis Rheum* 1986;29:494-500.
21. Sherrer Y, Bloch DA, Mitchell DM, Roth SH, Wolfe F, Fries JF. Disability in rheumatoid arthritis: Comparison of prognostic factors across three populations. *J Rheumatol* 1987;14:705-9.
22. Fries JF, Williams CA, Morfeld D, Singh G, Wolfe F, Sibley J. Reduction in long-term disability in rheumatoid arthritis by DMARD-based treatment strategies. *Arthritis Rheum* 1996; 39:616-22.
23. Fries JF, Williams CA, Singh G, Ramey DR. Response to therapy in rheumatoid arthritis is influenced by immediately prior therapy. *J Rheumatol* 1997;24:1697-702.
24. Singh G, Fries JF, Williams CA, Zatarain E, Spitz PW, Bloch DA. Toxicity profiles of disease-modifying antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 1991;18:188-94.
25. Singh G, Fries JF, Spitz PW, Williams CA, Bloch DA. Toxic effects of azathioprine in rheumatoid arthritis: a national post-marketing perspective. *Arthritis Rheum* 1989;32:837-43.
26. Lubeck DP, Spitz PW, Fries JF, Wolfe F, Mitchell DM, Roth SH. A multicenter study of annual health service utilization and costs in rheumatoid arthritis. *Arthritis Rheum* 1986;29:488-93.
27. Singh G, Ramey DR, Fries JF. The costs of immunosuppressive therapy for rheumatoid arthritis [abstract]. *Arthritis Rheum* 1993;36 Suppl:S178.
28. Singh G, Ramey D, Morfeld D, Shi H, Fries J. The clinical and economic consequences of NSAID therapy [abstract]. *Arthritis*

- Rheum 1995;38 Suppl:S206.
29. Singh G, Ramey D, McGuire J. Costs of medical care for patients with rheumatoid arthritis: an 11-year study [abstract]. *Arthritis Rheum* 1995;38 Suppl:S225.
 30. Fries JF, Williams C, Ramey D, Singh G. Medical costs are strongly associated with disability levels in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1995;38 Suppl:S187.
 31. Singh G, Ramey D, Terry R, Wolfe F, Fries J. Costs of medical care for patients with osteoarthritis and rheumatoid arthritis: a 13 year study [abstract]. *Arthritis Rheum* 1996;39 Suppl:S71.
 32. Singh G, Ramey D, Terry R, Wolfe F, Fries J. Long-term medical costs and outcomes are significantly associated with early changes in disability in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S318.
 33. Singh G, Ramey D, McGuire J. Secular trends in the outpatient costs of care for RA: an 11-year study [abstract]. *Arthritis Rheum* 1996;39 Suppl:S383.
 34. Singh G, Ramey D, Terry R, Wolfe F, Fries J. Costs of medical care for patients with osteoarthritis and rheumatoid arthritis: a 13 year study [abstract]. *Arthritis Rheum* 1996;39 Suppl:S71.
 35. Singh G, Ramey DR, Terry R. Direct costs of medical care in rheumatoid arthritis: Patterns and role of rheumatology care [abstract]. *Arthritis Rheum* 1996;39 Suppl:S170.
 36. Wong JB, Ramey DR, Singh G. The morbidity, mortality and economics of rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S389.
 37. Wong JB, Singh, G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S144.
 38. Fries JF, Spitz PW, Williams CA, Singh G, Bloch DA, Hubert HB. A toxicity index for comparison of side effects among different drugs. *Arthritis Rheum* 1990;33:121-30.
 39. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1991;34:1353-60.
 40. Fries JF, Williams CA, Ramey DR, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. *Arthritis Rheum* 1993;36:297-306.
 41. Singh G, Williams C, Ramey DR, Fries JF. A toxicity index for comparison of gastrointestinal toxicity of non-steroidal anti-inflammatory drugs [abstract]. *Arthritis Rheum* 1996;39 Suppl:S178.
 42. Singh GS, Ramey DR, Fries JF. Non-analgesic approaches to pain management in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S379.
 43. Singh GS, Morfeld D, Shi H, Ramey DR, Fries JF. Effectiveness and toxicity profiles of drug treatment in RA [abstract]. *Arthritis Rheum* 1996;39 Suppl:S196.
 44. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum H, Fries JF. Gastrointestinal complications of non-steroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. *Arch Intern Med* 1996;156:1530-6.
 45. Singh G, Ramey Dr, Terry R, Khraishi M, Triadafilopoulos G. NSAID-related effects on the GI tract: An ever widening spectrum [abstract]. *Arthritis Rheum* 1996;39 Suppl:S93.
 46. Singh G, Terry R, Ramey DR, et al. Comparative GI toxicity of NSAIDs [abstract]. *Arthritis Rheum* 1996;39 Suppl:S115.
 47. Singh G, Terry R, Ramey DR, Triadafilopoulos G, Brown BW. Epidemiology of serious NSAID-related complications: A prospective multivariate lifetable analysis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S213.
 48. Singh G, Ramey DR, Balise R, Triadafilopoulos G. Epidemiology of NSAID-related GI complications in patients with osteoarthritis: a 13 year prospective study [abstract]. *Arthritis Rheum* 1996;39 Suppl:S180.
 49. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105:31S-38S.
 50. Singh G, Rosen Ramey D. NSAID induced gastrointestinal complications: the ARAMIS perspective—1997. *Arthritis, Rheumatism and Aging Medical Information System. J Rheumatol* 1998;25 Suppl 51:8-16.
 51. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol* 1999;26 Suppl 56:18-24.
 52. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol* 1999;26:18-24.
 53. Singh G, Ramey D, Triadafilopoulos G. Early experience with selective COX-2 inhibitors: Safety profile in over 340,000 patient years of use [abstract]. *Arthritis Rheum* 1996;39 Suppl:S296.
 54. Singh G, Terry R, Ramey DR, Triadafilopoulos G, Brown BW. GI score: A simple self-assessment instrument to quantify the risk of serious NSAID-related GI complications [abstract]. *Arthritis Rheum* 1996;39 Suppl:S93.
 55. Singh G, Ramey DR, Triadafilopoulos G, Brown BW, Balise RR. GI score: A simple self-assessment instrument to quantify the risk of serious NSAID-related complications in RA and OA [abstract]. *Arthritis Rheum* 1996;39 Suppl:S75.
 56. Wolfe MM, Lichtenstein D, Singh G. Gastrointestinal complications of non-steroidal anti-inflammatory drugs. *N Engl J Med* 1999;340:1888-99.
 57. Fries J. Toward an understanding of NSAID-related adverse events: the contribution of longitudinal data. *Scand J Rheumatol* 1996;102 Suppl:3-8.
 58. Singh G, Ramey D, Rausch P, Schettler J. Serious infections in rheumatoid arthritis: relationship to immunosuppressive use [abstract]. *Arthritis Rheum* 1996;39 Suppl:S242.
 59. Ramey D, Rausch P, Schettler J, Singh G. Serious infections in rheumatoid arthritis: what is the scope of the problem? [abstract]. *Arthritis Rheum* 1996;39 Suppl:S279.
 60. Singh G, Schettler JD, Ramey D, Wong JB. Prednisone use significantly increases the risk of cataracts in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S135.
 61. Schettler J, Wong J, Ramey D, Singh G. Prednisone use significantly increases the risk of hip fractures in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1996;39 Suppl:S136.
 62. Yamanaka H, Singh G, Matsuda Y, Saito T, Hara M, Kamatani N. Does NSAID-induced GI disease exist in Japan: a cross sectional study in 8,948 patients [abstract]. *Arthritis Rheum* 1996;39 Suppl:S146.