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ECHO MODEL FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Assessment of anti-rheumatoid arthritis drugs is possible by employing different parameters. The parameters provide a satisfactory assessment but physicians are always in dilemma regarding the selection of the parameters for rheumatoid arthritis patient. The present article highlights the commonly employed and reliable parameters (Economical, Clinical & Humanistic outcome) for the assessment of anti-rheumatoid arthritis drugs.

Keywords: RA, Rheumatoid arthritis, echo, drugs

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic auto-immune disease, with a main characteristic of persistent joint inflammation that results in joint damage and loss of function (Henk V. 2005). The predominant symptoms are pain, stiffness, and swelling of peripheral joints. The clinical course of the disorder is extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive multi-system inflammation with profound morbidity and mortality. (David M. & Michael E. 2001)

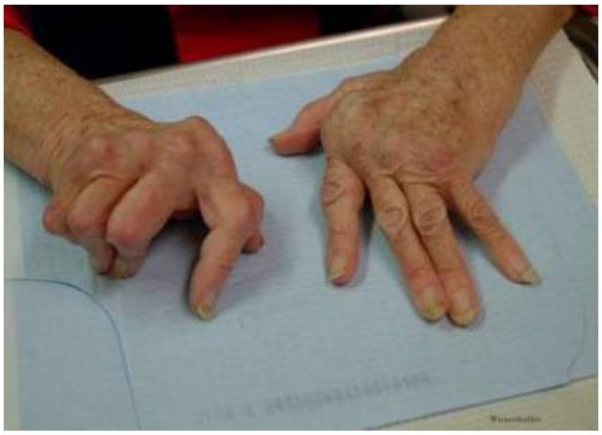

Figure No. 1- Hand deformity of rheumatoid arthritis

Assessment of anti-rheumatoid arthritis drugs is possible by so many parameters. These parameters provide a satisfactory assessment but physicians are always in dilemma for selection of these parameters of rheumatoid arthritis patient. Here the best parameters are mentioned (Economical, Clinical & Humanistic outcome) for best assessment of anti-rheumatoid arthritis drugs.

ECONOMICS OUTCOME

Cost to society:The majority of cost associated with RA is the indirect cost associated with work disability, which increase the disease duration. The average annual indirect costs is US$ 9,700 & direct costs of RA amount to an average of US$ 5,400, per affected individual per year (Yelin, 2003) and are estimated to range from US$ 6,500 to more than US$ 1, 30,000 per affected individual over the course of a lifetime (Wong et al., 2001). Over a lifetime, work disability cost range from US$ 2, 22,500 to US$ 3, 7000 per affected individual (Wong et al., 2001; Gabriel et al., 1999).

The economic evaluation is to identify, measure, value and compare the cost and consequences of the alternatives being considered. The economic evaluation methods include cost-of-illness evaluation, cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. Each method, except cost-of –illness evaluation, is used to compare competing programs or treatment alternatives. The method are all similar in the way they measure cost (dollar/rupees) and different in their measurement of outcomes. Cost effectiveness analysis is therefore used in health economics to compare the financial cost of therapies whose outcome can be measured purely in terms of health effect. The common costs involved in economic outcomes are the following (Wong et al., 2001).

Table no 1: - Common cost involved in economic outcomes.

Sr.no	Cost –Category	Cost
1.	Direct medical cost	Drug, Supplies, Laboratory tests, Health care professional's time, Hospitalization
2.	Indirect non-medical cost	Transportation, Food, Family care, Home aids
3.	Direct non-medical cost	Lost wages [morbidity], Income forgone due to death
4.	Intangible cost	Pain, Suffering, Grief

Direct cost: Direct costs are those directly associated with detection, treatment, and prevention of disease (Eisenberg, 1989). These costs may be disease specific, a direct result of the condition, or disease associated, a consequence of the primary disease or its treatment. Direct costs include costs of physician visits, diagnostic tests, prescription drugs, over-the-counter medication, hospital stay and procedures, aid and devices and outpatient procedures.

Indirect cost: Indirect costs are more difficult to measure. Some can be given a monetary value, although this is dependent on local systems of

social support, sickness benefits and pension. Lost of work productivity is important in chronic musculoskeletal conditions but rarely is included in economic evaluations.

Intangible costs: Intangible costs are those associated with loss in function, increased pain and reduced quality of life of patients, families and careers. These include the costs of lost opportunities. These are very important for musculoskeletal conditions, because disability is a significant outcome with limitation in activities of daily living, reduction in leisure and community activities, chronic pain, psychologic problems including depression and anxiety and reduced general health (**Draugalis** *et al*., 1989).

Cost-Effectiveness Analysis - Cost Effectiveness Analysis (CEA) involves comparing programs or treatment alternatives with different safety and efficacy profiles. Cost is measured in rupees and outcomes are often expressed in efficacy unit, a natural unit, or non-rupees units (i.e. lives saved, cases cured, life expectancy, or drop in blood pressure in mm Hg, improved functional ability, disease activity etc) (Bootman *et al*.,1989; Detsky & Nagiie, 1990). The results of Cost Effectiveness Analysis (CEA) are expressed as a ratio – either as an average cost effectiveness ratio (ACER) or as an incremental cost effectiveness ratio (ICER).

An Average CER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the rupees cost per specific clinical outcome gained, independent of comparators (Eisenberg, 1989; Sanchez & Lee, 1994; Detsky & Nagiie, 1990).

ACER = health care cost / Clinical outcome.

An Incremental CEA may be used to determine the additional cost and the effectiveness gained when one treatment alternative (A) is compared with the next best treatment alternative (B).Thus, instead of comparing the average C/E ratio of each treatment alternative, one over another treatment is compared with the additional effect, benefit, or outcome it provides (Eisenberg, 1989).

ICER = cost A – cost B / effect A (%) – effect B (%).

CLINICAL OUTCOME: Clinical outcome are the medical events that occur as a result of disease or treatment (e.g. safety and efficacy end points). The measures of clinical effectiveness in RA are:

DISEASE ACTIVITY - Disease activity in RA is a complex phenomenon, impossible to define and discern. At the present time no single test of disease activity in RA is effective because RA may cause various kinds of symptoms and signs. Thus, the disease activity variables can be considered as surrogate markers for the in-self un-measurable process. Clinical symptoms of disease activity are e.g. morning stiffness, fatigue, pain, impaired function, and psychological and sleep disturbances. Clinical signs include joint swelling and deformity,

reduced objective function, low-grade fever, osteoporosis and weight loss. Some of these symptoms and signs are used to assess disease activity, e.g. the number of swollen and tender joints (Prevoo et al., 1995), graded, ungraded or weighted joint indices (Ritchie et al., 1968; Thompson et al., 1987), pain and fatigue (Ferraz et al., 1990), duration of morning stiffness and different scores for functional decline (Fries et al., 1980; Pincus et al., 1983). The patient's own global assessment of the disease activity is sometimes added. Laboratory markers of disease activity are for instance acute phase proteins and ESR. In some instances, clinical and laboratory markers for disease activity are combined, including the patient's global assessment of disease activity, into compound indices of disease activity, e.g. the disease activity score (DAS) (Van der Heijde et al., 1990), the Stoke index (Davis et al., 1990), Simplified Disease Activity Index (SDAI) and Rheumatoid Arthritis Disease Activity Index (RADAI). The first three instruments includes measurements of clinical and laboratory marker and the patient's and physician's global assessments of disease activity but the last one i.e. RADAI is self-administered questionnaire used by the patient to assess own disease activity.

DISEASE ACTIVITY RESPONSE CRITERIAS: - There are three standard response criteria being used widely in clinical trial of RA are (Gestel et al., 1996; Lipsky et al., 2000):

i) American college of rheumatology (ACR) criteria (Felson, 1993; Arnett, 1988)

ii) European League Against rheumatism (EULAR) criteria (DAS-28 score)(Prevoo, 1995; Gestel, 1996))

iii) Paulus criteria (Paulus, 1990)

i) American college of Rheumatology (ACR) criteria - Overall patient's clinical response of therapy is assessed by ACR improvement criteria. The ACR20 criterion is developed to define improvement in rheumatoid arthritis. The primary efficacy variable is rate at which the intention to treat sample achieves 20% improvement in ACR core set variables (ACR20). To be considered an ACR20% responder, a subject has to show a 20% improvement in tender & swollen joints count and 20% improvement in at least three of the following five criteria: patient global assessment, physician global assessment, pain intensity, physical function or disability (e.g. HAQ) and level of acute-phase reactant or erythrocyte sedimentation rate (Felson et al., 1995).

Count of tender joints is based on 68 joints assessments by pressure and joint manipulation on physical examination, and count of swollen joint is based on 66 joint assessments. Percentage changes in the tender joint and swollen joint counts are based on the number of valuable joints at a visit. Physician and patient assessment of global RA disease activity is based on a ten-point (10 cm line) non-anchored horizontal visual analogue scale (VAS) ranging from 1(very good) to 10 (very poor) &

pain intensity assessment is based on a visual analogue scale (VAS), made up of a 10 cm line which also ranges from 0 (no pain) to 10 (severe pain) point scale.

Sixty-Eight Joint counts: Sixty eight joint are Metacarpophallenges (MCP-10), Metatarsophallenges (MTP-10), Distalinterphallenges (DIP-8), Proximalinterphallenges (PIP-20), wrist (2), elbow (2), shoulder (2), knee (2), Hip (2), ankle (2), Subtalar (2), Temporomandibular (2), Sternoclavicular (2) and Acromioclavicular (2)

Secondary outcome included in ACR are ACR50 and ACR 70 responder rates. The ACR50 and ACR70 are defined as at least 50% and 70% improvement, respectively, assessed by the same criteria used to calculate ACR20 response (Van der Heijde et al., 1990; Felson et al, 1995).

ii) European League of Association against Rheumatism (EULAR) – The EULAR criteria is based on both an improvement and the achievement of a low disease activity state, as measured by the DAS-28 (Prevoo, 1995). Disease Activity Score involving 28 joints (DAS28). It is a linear sum of four outcome parameters: tender joint count, swollen joint count, Patients' global assessment of disease activity and a level of C – reactive proteins or Erythrocyte sedimentation rate (ESR) (**Van Gestel *et al.*, 1996**).

DAS-28 = 0.56√TJC + 0.28√SJC + 0.70[ln ESR] + 0.014 (VASGH)

TJC = Tender joint Count

SJC = Swollen Joint Count

ESR = Erythrocyte Sedimentation Rate in mm first hour.

VASGH = Patient global assessment of general health.

Disease activity by DAS scores is interpreted as:

DAS < 3.2 = mild disease activity.

DAS 3.2-5.1 = moderate disease activity

DAS > 5.1 = severe disease activity

Twenty-Eight Joint counts: Twenty-eight joints are MCP (10), PIP (10), wrist (2), elbow (2), shoulder (2) and knee (2) joints are examined for the presence or absence of tenderness or pain on motion, swelling, or deformity (Smollen *et al.*, 1995).

Patient's global assessment of disease activity: It represents patients overall assessment of how the arthritis is doing. Patients are asked to mark a cross on a 0 to 10 cm scale (Visual analogue scale) for how well he/she is doing by considering all the ways the arthritis affect the life.

Change of DAS score from Baseline is categorized as good improvement if DAS change ≥ 1.2, moderate > 0.6 but ≤ 1.2, & no improvement ≤ 0.6 (Van Gestel et al., 1998). The Disease Activity Score is widely used to quantify disease activity and gauge the response to treatment. A rather complex calculation conceals the relative contribution of each measure to the composite score.

iii) Paulus – The Paulus response criteria is based on 20% improvement in 4 of 6 measures: Joint tenderness score, joint swelling scores, physician's global assessment, patient's global assessment, ESR, and morning stiffness (Paulus, 1990).

The current standards of disease activity indices for clinical trials are the EULAR Disease Activity score (DAS) (appendix 1) and the ACR 20% response criteria (appendix 1 & 2).

DISABILITY - Disability in RA is associated with the extent of joint damage, and influenced by factor such as age, female gender, low socio economic status, income and educational level, and pain & depression (Fries et al., 1982). The effects of disability have a substantial impact on individuals and their role, and on their families. Disability influences psychosocial function and can lead to anxiety, depression and fatigue. Health assessment Questionnaire- Disability index (HAQ-DI) (Chopra, 2004) and Global function performance (GPF) (Agustin et al., 2004) is expressed as measure of disability.

Health Assessment Questionnaire (HAQ) - A new approach to assess disability in RA was introduced by Fries *et al.,* 1980, the Stanford Health Assessment Questionnaire (HAQ) (see Appendix. 3). They developed a structure of patient outcome measurement representing five separate dimensions: Death, Disability, Discomfort, Drug (therapeutic) toxicity and Dollar cost. The Full HAQ assesses all the above mentioned five dimensions of health outcome. The Short HAQ questionnaire that only assesses disability (HAQ Disability Index, HAQ-DI) is often used by itself, and is here referred to as HAQ (Bruce & Fries, 2003). The HAQ-DI was originally developed and validated for English speaking populations in the United States and Canada, and has since been translated or culturally adapted into more than 60 different languages or dialects, often with only minor changes (Bruce & Fries, 2003). HAQ is a self administered questionnaire, with one or more specific questions on each of eight dimensions of activities of daily life (dressing and grooming, arising, eating, walking, hygiene, reach, grip and outdoor activities). Each question is scored on a scale of 0 to 3, according to the following performance status: functions that can be performed without difficulty = 0; any function performed with some difficulty = 1; functions performed with great difficulty = 2; and inability to perform a function = 3. The item with the highest score within each dimension is the score for that dimension. The scores for the eight different dimensions are added and divided by eight to get the mean value, i.e. the HAQ score. The eight category scores are averaged into an overall HAQ score on a scale from 0 to 3 (0 indicating no disability & 3 indicating complete disability (Chopra, 2004). The disability assessment component of the full HAQ and HAQ-DI assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotors

activities of the lower extremity, and activities that involve both upper and lower extremities (Fries *et al*., 1982). It can be self-administered in 5 minutes and scored in less than one minute. In a recent analysis of 1817 RA patients from leflunomide trials, it was suggested that HAQ is a relatively good indicator of disease activity in groups of patients given DMARDs, and that changes in HAQ scores mainly reflect changes in pain and other subjective measures of disease activity (Scott and Strand, 2002). In addition to HAQ, there are several other self-reported instruments to assess the physical function in RA; Arthritis Impact Measurement Scale (AIMS) (Meenan et al., 1980), Nottingham Health Profile (NHP) (Hunt et al, 1981), and McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), have all been shown to be effective to monitor patient status in clinical trials (Houssien *et al*., 1997; Haavardsholm *et al*., 2000; Verhoeven *et al*., 2000). However, they are rather comprehensive and time consuming. The simpler HAQ seems to be the instrument of choice for standard clinical trials and clinical care. Some study shows that the Indian HAQ is a reliable, sensitive and valid instrument for measuring functional disability in RA. It can be self-administered in English or Hindi (Chopra, 2004).

Global Function Performance (GFP) - Measurement of physical functional limitations in patients with rheumatoid arthritis (RA) is a time-honored strategy to assess the disease's outcome. Performance based tests of physical function such as grip strength and walking velocity over 50 feet; and the timed shirt button test provide reproducible, quantitative information about a patient's current status and about the prognosis (Agustin *et al*., 2004).

HUMANISTIC OUTCOME: Humanistic outcome are the consequences of disease or treatment on patient functional status or quality of life. Quality of life is a descriptive term that refers to people's emotion, social and physical well being and their ability to function in the ordinary tasks of living (Whalley et al., 1997). Several instruments such as Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Health Assessment questionnaire (HAQ), European Quality of life (EuroQoL) and Short Form (SF)-36 have been designed in an attempt to go beyond measurement of physical impairment and disability by addressing more emotional and social aspect of a condition.

Short Form-36 (SF-36) – The Short Form-36 (SF-36), a general health status questionnaire designed in the USA, has been shown to be both valid and acceptable in a normal healthy population and reliable across diverse patient groups. The SF 36 assesses eight areas of general health as follows (Table No.2): limitations in physical activities caused by the disease, limitations in the social functioning of patients as a result of physical and/or emotional problems, limitations in the usual role

functioning (work or other daily activities) as a result of emotional problems, limitations in the usual role functioning as a result of physical health problems, bodily pain, general mental health (feelings of well being \ depression etc), vitality (energy and fatigue) and general health perceptions. Scores in the range 0-100 are calculated for each of these different aspects of health, with a high score indicating better health and a low score indicating worse health. However, the SF-36 may also be converted to two summary scales: the physical and mental component summary scales (Figure no: 2) (Brazier *et al.,* 1992). The two SF-36 physical and mental component summary scales are reliable, valid and responsive measures of health status in patients with RA. Six of the eight subscales meet standards required for comparing groups of patients, and the physical function and general health scales may be suitable for monitoring individuals. The two scales measuring role limitations have poor measurement characteristics. The SF-36 pain and physical function scales may be suitable for use as patient self-assessed measures of pain and physical function within the ACR core disease activity set (Talamoa *et al.,* 1997; Ruta *et al*., 1998).

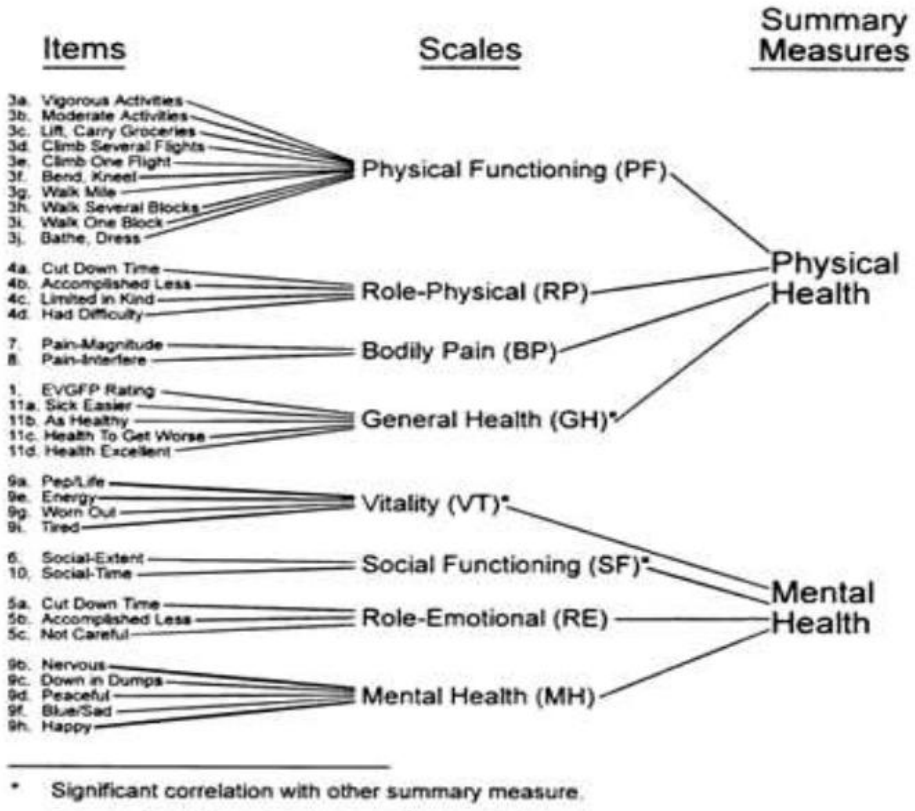

Figure no: 2-Diagrammatic overview of Short form-36 (Eight areas of general health)

TABLE NO-2: SHORT FORM-36 (EIGHT DIMENSIONS)

AREA	DIMENSION	NO OF QUESTION
FUNCTIONAL STATUS	PHYSICAL FUNCTIONING	10
	SOCIAL FUNCTIONING	2
	PHYSICAL PROBLEM	4
	EMOTIONAL PROBLEM	3
WELLBEING	MENTAL HEALTH	5
	VITALITY	4
	PAIN	2
OVERALL EVALUATION	GENERAL HEALTH PERCEPTION	5
	HEALTH CHANGE*	1

*THIS ITEM IS NOT INCLUDED IN THE EIGHT DIMENSIONS NOR IS IT SCORED

References

1. Henk V. Early diagnosis of rheumatoid arthritis. *Best Prac. Res. Clin. Rheumatol.* 2005; **19**:55–72.
2. David, M.L., Michael E.W. Rheumatoid arthritis. *Lancet* 2001; **358:**903–911.
3. Yelin, E. Cost of musculoskeletal: impact of work disability and functional decline. *J.Rheumatol.* 2003; **68**:8-11.
4. Wong, J.B., Ramey, D.R., Singh, G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. *Arthritis Rheum*. 2001; **44**:2746-9.
5. Gabriel, S., Tugwell, P., O'Brien, B., Yelin, E., Drummond, M., Ruff, B. Report of the OMERACT task force on economic evaluation outcome Measures in Rheumatology. *J. Rheumatol*. 1999; **26**:203-206.
6. Eisenberg, J.M. Clinical economics: A guide to economic analysis of clinical practices. *JAMA* 1989; **262**:2879-2886.
7. Bootman, J.L., Larson, L.N., McGhan, W.F., Townsend, R.J. Pharmaeconomic research & clinical trial: concepts and issue. *DICP Ann. Pharmacother*. 1989; **23**:693-697.
8. Detsky, A.S., Nagiie, I.G. A clinician's guide to cost effectiveness analysis. *Ann. Med.*, 1990; **113:**147-154.
9. Sanchez, L.A., Lee, J.T. Use and misuse of pharmacoeconomic terms. *Top Hosp. Pharm. Manage*. 1994; **13**:11-22.
10. Prevoo, M.L., van't Hof, M.A, Kuper, H.H., Van, L.M.A., Van de Putte, L.B. Van Riel, P.L. Modified disease activity scores that include twenty-eight-joint counts: Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995; **38**:44-48.
11. Ritchie, D.M., Boyle, J.A., McInnes, J.M., Jasani, M.K., Dalakos, T.G., Grieveson, P. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *J. Med*. 1968; **37**:393-406.
12. Thompson, P.W., Silman, A.J., Kirwan, J.R., Currey, H.L. Articular indices of joint inflammation in rheumatoid arthritis. Correlation with the acute-phase response. *Arthritis Rheum*. 1987; **30**:618-23.
13. Ferraz, M.B., Quaresma, M.R., Aquino, L.R., Atra, E., Tugwell, P., Goldsmith, C.H. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. *J. Rheumatol.* 1990; **17**:1022-4.

14. Fries, J.F. *et al*. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;**23**: 137-145.
15. Pincus, T., Summey, J.A., Soraci, S.A., Wallston, K.A., Hummon, N.P. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum*. 1983; **26**:1346-53.
16. Van der, H. *et al*. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann. Rheum. Dis*., 1990; **9**:916-920.
17. Davis, M.J. *et al.* Comparison and evaluation of a disease activity index for use in patients with rheumatoid arthritis. *Br. J. Rheumatol*. 1990; **29**:111-115.
18. Gestel, A.M. *et al*. Development and validation of European League against Rheumatism response criteria for rheumatoid arthritis. *Arthritis Rheum*. 1996; **39**:34-40.
19. Lipsky, P.E. *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343**:1594-602.
20. Felson, D.T., Anderson J.J., Boers, M., Bombardier, C. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum.* 1993; **36**:729-740.
21. Arnett, F.C. *et al*. The American Rheumatoid Association 1987 revised criteria for classification of rheumatoid arthritis. *Arthritis Rheum*. 1988; **31**:315-324.
22. Paulus, H.E., Egger, M.J., Ward, J.R., Williams, H.J. Analysis of improvement in individual rheumatoid arthritis patients treated with disease modified anti rheumatoid drugs, based on the findings in patients treated with placebo. *Arthritis Rheum.* 1990; **33**:477-84.
23. Felson, D.T., *et al.* American college of rheumatology; Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 1995; **38**:727-735.
24. Smollen, J.S. *et al.* Validity and reliability of the twenty eight joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum*.1995; **38**:38-43.
25. Fries, J.F., Spitz, P.W., Youg, D.Y. The dimension of health outcome: the health Assessment Questionnaire, disability and pain scales. *J. Rheumatol*. 1982; **9**:789-793.
26. Agustin, E., Roy, W.H., Rincon, I.D. Measurement of global functional performance in patient with rheumatoid arthritis using rheumatology function tests. *Arthritis Res. Ther.* 2004; **6**: R315-R325.
27. Bruce, B., Fries, J.F. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol*. 2003; **30**:167-78.

28. Chopra, A. Rheumatology: Made in India. *J. Indian Rheumatol. Assoc*. 2004; **12:**43-53.
29. Scott, D.L. Strand, The effects of disease-modifying anti-rheumatic drugs on the Health Assessment Questionnaire score. Lessons from the leflunomide clinical trials database. *Rheumatology (Oxford)* 2002; **41**:899-909.
30. Meenen, R.F., Gertman, P.M., Mason, J.H. Measuring health status in arthritis: t he arthritis impact measurement scale. *Arthritis Rheum.* 1980; **23**:146-152.
31. Houssien, D.A., McKenna, S.P., Scott, D.L. The Nottingham Health Profile as a measure of disease activity and outcome in rheumatoid arthritis. *Br. J. Rheumatol*. 1997; **36**:69-73.
32. Hunt, S., McKenne, S.P., McEwan, J. The Nattinghan Health Profile: subjective health status and medical consultations. *Soc. Sci. Med.* 1981; **15**:221-229.
33. Haavardsholm, E.A., Kvien, T.K., Uhlig, T., Smedstad, L.M., Guillemin, F. A comparison of agreement and sensitivity to change between AIMS2 and a short form of AIMS2 (AIMS2-SF) in more than 1,000 rheumatoid arthritis patients. J. Rheumatol. 2000; **27**:2727-2730.
34. Verhoeven, A.C., Boers, M., van der Liden, S. Validity of the MACTAR questionnaire as a functional index in a rheumatoid arthritis clinical trial. *Arthritis. J. Rheumatol*. 2000; **27**:2801-2809.
35. Whalley, F. *et al*. Quality of life in rheumatoid arthritis. *Br. J. Rheumatol*. 1997; **25**:773-777.
36. Brazier, J.E., Harper, R., Jones, N.M.B. Validation the SF-36 health survey questionnaire: new outcome measure for primary care. *Br. Med. J.* 1992; **305:**160-164.
37. Talamoa, J., Frater, A., Gallivan, S., young, A. Use of the short form 36 (SF-36) for health status measurement in rheumatoid arthritis *Br. J. Rheumatol*. 1997; **36**:463-469.
38. Ruta, D.A., Hurst, N.P., Kind, P., Hunter, M., Stubbings, A. Measuring health status in British patients with rheumatoid arthritis: reliability, validity and responsiveness of the short form 36-item health survey (SF-36). B*r. J. Rheumatol*. 1998; **37**:425–436.