Limitations of clinical trials in chronic diseases: is the efficacy of methotrexate (MTX) underestimated in polyarticular psoriatic arthritis on the basis of limitations of clinical trials more than on limitations of MTX, as was seen in rheumatoid arthritis?

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ABSTRACT

Clinical trials are the optimal method to establish efficacy of a drug versus placebo or another drug. Nonetheless, important limitations are seen, particularly in chronic diseases over long periods, although most are ignored. Pragmatic limitations of clinical trials include a relatively short observation period, suboptimal dosage schedules, suboptimal surrogate markers for long-term outcomes, statistically significant results which may not be clinically unimportant and vice versa. Even ideal clinical trials have intrinsic limitations, including the influence of design on results, data reported in groups which ignore individual variation, non-standard observer-dependent interpretation of a balance of efficacy and toxicity, and distortion of a "placebo effect." Limitations are seen in many clinical trials of methotrexate (MTX) in rheumatoid arthritis (RA) and psoriatic arthritis (PsA). The first MTX clinical trial in rheumatology documented excellent efficacy in PsA, but frequent adverse events in 1964, explained by intravenous doses up to 150 kg. MTX was abandoned until the 1980s for RA, while gold salts and penicillamine were termed "remission-inducing," on the basis limitations of clinical trials. In the most recent MTX in PsA (MIPA) trial, all outcomes favoured MTX, but only patient and physician global estimates met the $p<0.05$ criterion. A conclusion of "no evidence for MTX improving synovitis" appears explained by insufficient statistical power, wide individual variation, no subsets, low doses, and other limitations. MTX appears less efficacious in PsA than RA, but may be underestimated in PsA, similar to historical problems in RA, resulting more from limitations of clinical trials than from limitations of MTX.

The randomised, controlled clinical trial is appropriately regarded as the optimal method to establish the efficacy of a drug compared to a placebo or another drug (1). Many physicians and other health professionals apply the term "evidence-based medicine" almost exclusively to randomised controlled clinical trials and meta-analyses of these trials (2, 3). At the same time, important limitations are seen to the clinical trial methodology, as to any scientific method, particularly in chronic diseases over long periods, described in a number of reports (4-20), including previous commentaries by the senior author (21-29). However, most health professionals and the general public continue to ignore limitations of clinical trials.

Increasing attention has been directed to limitations of clinical trials in recent years, including by experts in "evidence-based medicine" (16-20). A member of the Oxford Centre for evidence-based medicine commented that "while they are simple and easy to use, early hierarchies that placed randomised trials categorically above observational studies were criticised (17) for being simplistic (30). In some cases, observational studies give us the 'best' evidence. For example, there is a growing recognition that observational studies – even case-series (31) *and anecdotes* (32) can sometimes provide definitive evidence (17)."

Limitations of clinical trials may be seen in the convoluted history of methotrexate (MTX) for treatment of inflammatory rheumatic diseases since 1964 (33). Indeed, limitations of clinical trials, rather than limitations of MTX, delayed its introduction into management of RA 15–20 years after 1964. In PsA, MTX appears to have limited efficacy for axial manifestations (34), but possi-

Table I. Limitations of clinical trials in rheumatoid arthritis, other diseases, and psoriatic arthritis. MTX *versus* placebo trials.

Pragmatic limitations	Rheumatoid arthritis (RA)	Other diseases	Psoriatic arthritis (PsA)
Relatively short observation period in which short-term efficacy may underestimate or overestimate long-term effectiveness	Meta-analysis that gold, pncamine, Ssz (35), trial of Mtx *vs*. auranofin (65) similar efficacy over one *vs*. 5 years	SLE nephritis trials (36) no effect at 1-4 years seen at 5 years	Most trials – weaker effects of MTX than in observational data
Incorrect, inflexible dosage schedules for test therapy as well as concomitant therapies	Too low for MTX		Too high (33) or often too low (37-39)
Surrogate markers often suboptimal for long-term outcomes	TJC and lab tests less significant than physical function to predict mortality (42) & detect active biological vs control treatment (45)		
Statistically significant may be clinically unimportant and vice versa, due to over or under estimates of insufficient power, wide variation of individual patients	Meta-analyses (35) and trial (65) on similar efficacy of DMARDs to MTX		Insufficient power to recognise differences of MTX & Pbo (33, 37-39)
Variables other than randomisation may affect results		Education in BHAT study (110)	Primary analyses not on subtypes of PsA
Patient selection based on Inclusion and exclusion criteria regardless most patients ineligible	5% of patients eligible for ATTRACT trial (111, 112)		
Intrinsic limitations			
Design of trial influences results – control group does not eliminate bias	Early RA (48, 78, 113) *vs*. long-term, failed MTX (114)		Limited data regarding subsets (33, 37-39)
Data from clinical trials reported in groups – individual variation ignored	Almost all trials other than probability plots (79)		All trials – no probability plots (79)
Balance of efficacy versus adverse effects not standard	All trials	Trials of mammography in women age 40-50 (52)	All trials
"Placebo effect" distorted	All trials		All trials

ble benefits of MTX for synovial manifestations appear underestimated, again possibly due as much to limitations of clinical trials as to limitations of MTX. This article summarises some examples of limitations of clinical trials which may have affected development of MTX for RA or PsA over the last 50 years. All the studies cited were performed according to recognised standards for trial design and clinical care, and there is no intention to criticise any reports or authors cited. On the contrary, we hope these comments concerning MTX in clinical trials as well as observational data, may contribute to optimise therapies for patients with PsA, as well as other rheumatic diseases.

A. Limitations of clinical trials

Limitations of randomised control trials (Table I) include pragmatic and intrinsic limitations (27). Pragmatic limitations could be eliminated, in theory, by changes in design and implementation, while intrinsic limitations exist even in an ideally designed and executed clinical trial. Pragmatic limitations include:

1. A short time frame may limit an opportunity to recognise important trends in the long-term effectiveness, safety and tolerability of a medication. For example, in RA, gold and penicillamine were overestimated, and MTX underestimated in a meta-analysis of clinical trials (35), as most trials were of one year or less, and long-term loss of efficacy and adverse events could not be documented. Another example involved recognition of different outcomes of cyclophosphamide *versus* prednisone in nephritis of systemic lupus erythematosus (SLE), which required 5–10 years of observation, as no differences were seen after 1 year and even 3 years (36).
2. Incorrect and inflexible dosage schedules, as well as concomitant drug therapies; for example, in PsA, doses appear too high in the first methotrexate (MTX) trial (33), while doses appear too low in subsequent PsA clinical trials *versus* placebo (37-39).
3. Surrogate markers may be not be optimal for long-term outcomes or to distinguish active from control treatments; for example, tender joint counts (TJC) are poorly prognostic of severe long-term outcomes of RA, such as work disability (40, 41) or premature mortality (42), but are required to meet ACR criteria for 20%, 50%, and 70% improvement (ACR 20, 50, 70) in clinical trials (43). In addition, TJC is the least efficient of the 7 RA core data set measures (44) to distinguish active from control treatments in clinical trials, as physician and patient global estimates are more efficient than joint

counts or laboratory tests (45), but may be dismissed as "subjective."

4. Statistically significant results may be clinically unimportant and vice versa; many results in PsA trials appear to present clinically important advantages to MTX *versus* placebo (37-39), although they do not meet the $p<0.05$ criterion, in part due to insufficient statistical power and non-stratification of patients regarding the proportion of patients with polyarticular *versus* axial disease.

5. Variables other than randomisation may affect outcome; for example, in the beta blocker to prevent second heart attack trial (BHAT) in patients who had suffered a myocardial infarction, formal education level of the patient was far more significant to predict mortality outcomes than whether the patients were randomised to a beta blocker or placebo (46).

6. Inclusion and exclusion criteria often result in eligibility of only a small minority of patients with a disease; for example, fewer than 10% of people with RA in the authors' care before 2000 were eligible to participate in most trials of biological agents (47).

Intrinsic methodologic limitations of clinical trials are seen even if the trial could be designed and executed ideally:

1. The design of the clinical trial can greatly influence results; a control group does not necessarily eliminate bias. For example, a positive treatment effect to MTX is more likely in patients who had no previous MTX such as in the PREMIER trial (48) compared to patients who "failed" two previous treatments such as in the ARMADA trial (49).

2. Data from a clinical trial are reported in groups, and results do not necessarily pertain to all individual patients; for example, in trials to compare acetaminophen to non-steroidal anti-inflammatory drugs (NSAIDs) in osteoarthritis (OA) (50, 51), 55–60% of patients preferred diclofenac/misoprostol, but 20–25% of patients preferred acetaminophen (20–25% reported similar efficacy to both agents) (50). Results in some individuals differ from those in the majority of patients in the majority of clinical trials.

3. A clinical trial cannot definitively estimate adverse events, which may lead to different interpretations of data; for example, clinical trials in mammography in 40–50 year old women can give different interpretations of results, depending on assumptions, say, about the morbidity and mortality of "false positive" biopsies *versus* missed lesions, etc. (52).

4. The placebo effect of treatment is distorted, and may be exaggerated or attenuated when a patient is told that that she/he is receiving a therapy in a "scientific experiment," *versus* the "best therapy" from her/his doctor (14).

B. Underestimation of methotrexate in rheumatology due to limitations of clinical trials: 1964-1985

The first clinical trial of MTX in any rheumatic disease was conducted in patients with PsA and reported in 1964 (33). In this trial, 21 PsA patients were given a course of 3 intravenous MTX injections at 10 day intervals in doses of 1, 2, and 3 mg/kg or 3 placebo injections in a crossover design. All 21 patients had involvement of small joints of the hands, all but one of distal interphalangeal (DIP) joints; 12 had spine involvement, most frequently the cervical spine, and 15 had knee involvement. All but one patient was seronegative for rheumatoid factor, and all but one patient had received systemic glucocorticoid therapy (33).

Significant advantages to MTX *versus* placebo were seen for joint involvement, skin involvement erythrocyte sedimentation rate (ESR), and joint range of motion ($p\leq0.01$) (33). The authors noted that "the clinical response in most patients … was quite impressive … many totally disabled patients were restored to an ambulatory and employable state (33)."

However, adverse events were common, including anorexia in 14 of 21 patients, nausea in 13, burning sensation in the skin in 10, leucopenia in 7, anaemia in 3, transient elevation of transaminase (SGOT) in 3, and thrombocytopenia in 1. One of the 21 patients died, who had been enrolled in the study after having received prednisone 30 mg/day *for 8 months* (33). The patient was then treated with intravenous doses of 50, 100, and 150 mg MTX at 10-day intervals. After the third injection, the patient's while blood cell count fell to 400/cu mm, and platelet count to 18,000/ cu mm. On the 13th post-injection day, he developed haematemesis and died. Autopsy revealed oesophagitis and a pulmonary embolus. Although his bone marrow had recovered fully, his death was attributed to the MTX treatment (33).

The results of the clinical trial were interpreted as indicating efficacy of MTX in psoriasis and PsA, but with many adverse events "suggesting unacceptable toxicity" (39). In retrospect, toxicity appears explained by higher doses of MTX and prednisone 2 to 5 times more than the maximum that would be administered at this time. The patients were not treated with folic acid, as the action of MTX at the time was thought secondary to anti-folate, antimetabolite properties, rather than to anti-inflammatory activity, as recognised today (53, 54).

One response to the results of the 1964 trial might have been an effort to develop a safer regimen of methotrexate, in view of documented significant efficacy (33). However, MTX was largely abandoned by the rheumatology community over the next 15 to 20 years.

MTX was regarded by almost all rheumatologists as a "cancer drug" that was too toxic and unnecessary for RA, while injectable gold salts and penicillamine were considered "remission inducing therapy" as recently as 1985 (55). Ironically, designation of gold salts and penicillamine as "remission-inducing" and rare use of MTX from 1964 to 1979 occurred largely on the basis of limitations in design and interpretation of clinical trials (28, 56), and not on the basis of limitation of MTX.

A few pioneering rheumatologists such as Hoffmeister (57, 58), Scherbel (59), and Zachariae (60) treated patients who had inflammatory rheumatic disease with MTX during the 1970s and 1980s. An abstract presented at the American Rheumatism Association [ARA - now American College of Rheumatology (ACR)] by Hoffmeister in 1972 stated "Twenty-nine patients with classic or definite adult rheumatoid arthritis (RA) have been treated with a single 10 to 15 mg dose [of methotrexate]

once every 7 days. Most were on 5 mg prednisone daily, or less. Average duration of methotrexate therapy was 25.5 months… Improvement of functional capacity was moderate in 7, mild in 15 and absent in 7. Clinical improvement was estimated as major in 11, moderate in 14, and minor or none in 4 (57)." These results 43 years ago appear quite similar to those in contemporary care.

Hoffmeister's observations were not welcomed by the leadership of the rheumatology community (personal communication), in large part as the data were not from a clinical trial. Furthermore, as noted, gold salts and penicillamine were regarded as "remission inducting," largely as a result of interpretation of clinical trials conducted over one year, in which some patients had disappearance of signs of RA (55). However, over the 1970s and 1980s, it was increasingly recognised that gold salts and penicillamine were associated with substantial loss of efficacy over several years, as well as with rare, but serious and sometimes fatal, long-term haematologic, renal, and bone marrow adverse events. Remission over longer than 3 years was seen in fewer than 2% of patients treated with these agents (61), and gold salts and penicillamine are rarely used at this time.

Underestimation of MTX in rheumatology due to limitations of clinical trials: 1985-2000

Two clinical trials were conducted in patients with RA in the 1980s indicating the efficacy and safety of weekly low-dose MTX *versus* placebo (62, 63). These trials followed (rather than preceded) observational data from routine clinical care (57-60) in rheumatology and dermatology (60). For example, MTX had been introduced to treat 35% of patients with RA under care of the senior author by 1985 (Fig. 1) (64). Despite evidence of efficacy from these two clinical trials (62, 63) and observational data (57-60), doubts concerning MTX compared to "remission-inducing" DMARDs continued to be reported to the rheumatology community.

For example, a meta-analysis published in 1990 (Fig. 2) analysed the efficacy and safety in 66 clinical trials of DMARDs that included 117 treatment groups (35). The composite treatment effect of MTX (7 trials) was indistinguishable from sulphasalizine (6 trials), d-penicillamine (19 trials), and parenteral gold (29 trials); antimalarials (11 trials) had a lower treatment effect, with still lower levels for auranofin (oral gold), and lowest for placebo (22 trials). Dropout rates were significantly higher for parenteral gold than all other DMARDs, and the lowest dropout rates (lower than placebo) were seen for anti-malarials and MTX (Fig. 2) (33). Two-thirds of the 66 trials in the meta-analysis were reported during the 1980s, including all 7 involving MTX, indicating that most had been designed after Hoffmeister's 1973 abstract (35).

In 1992, two years after the meta-analysis report, a multicentre clinical trial was conducted to compare MTX, auranofin (oral gold), or the combination of the two drugs in 335 patients over 48

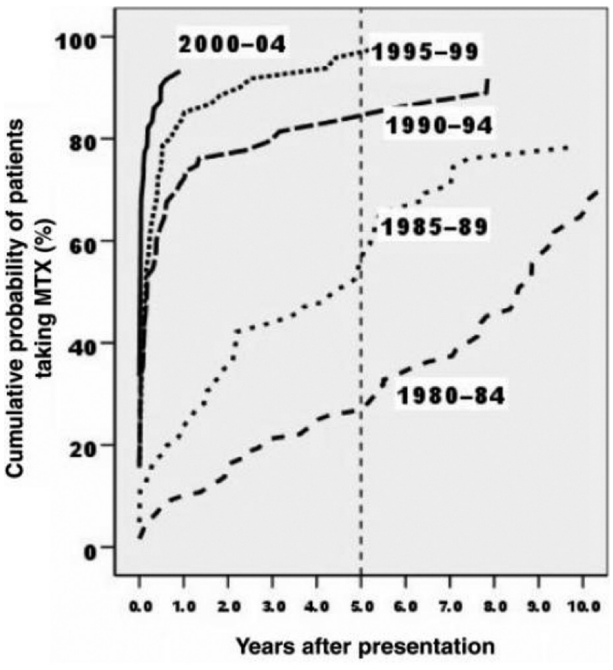

Fig. 1. Interval between patient presentation and initiation of MTX in Nashville, TN between 1980–2005 according to 5-year periods of patient presentation (64).

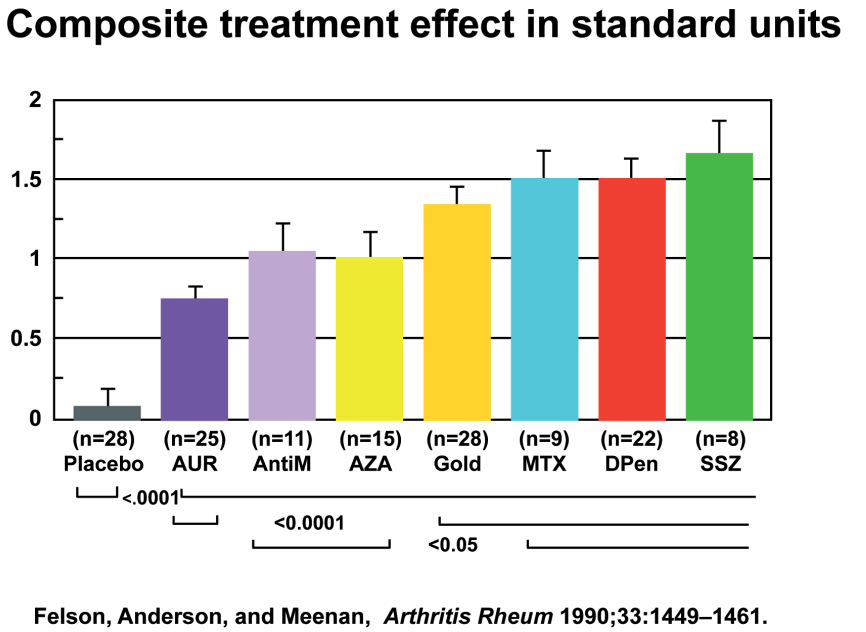

Fig. 2. Meta-analysis to compare standard composite treatment effect of various disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis (51).

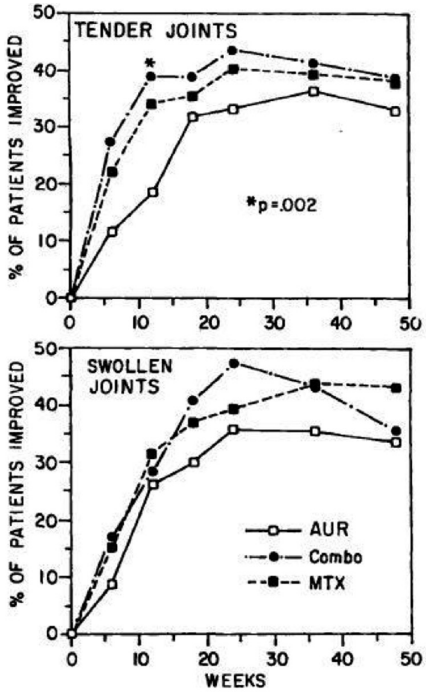

Fig. 3. Percentages of patients with ≥50% improvement in tender joints and swollen joints during treatment with auranofin (AUR), methotrexate (MTX), or auranofin plus methotrexate (Combo) (65).

weeks (65). No significant differences were seen in any clinical or laboratory variable (Fig. 3) (65). The authors tempered their observation of no advantages to either single drug or a combination with a comment "within the time frame of the study (65)."

The conclusions of the meta-analysis and clinical trial in Fig. 2-3 appeared inconsistent with observational data from 7 practices in clinical care, also reported in 1992, concerning continuation of courses of DMARDs in RA patients over 5 years (Fig. 4) (66). Continuation of a therapy may best represent a decision that the short-term efficacy and long-term effectiveness of a therapy justifies issues of tolerability and potential toxicity in analysis of benefit/risk by doctor and patient.

More than 50% of courses of MTX were continued at 60 months (5 years), compared to 20% of courses of hydroxychloroquine, penicillamine, parenteral gold and azathioprine and fewer than 10% of courses of auranofin or oral gold (66) (Fig. 4a) ($p<0.01$). However, a sub-analysis over one year (rather than 5 years) of only the patients who had no prior DMARDS (to simulate clinical trials) indicated no clinically or statistically significant differences between MTX, hydroxychloroquine, penicillamine, parental gold, azathioprine, or oral gold (Fig. 4b).

These analyses indicated that results over one year in clinical trials, including the extensive meta-analysis, are also seen in actual care, but the results are not applicable to data over 5 years in clinical care. Further observational studies indicated that continuation of courses of weekly low-dose MTX is almost always longer than seen for any therapy for rheumatic diseases, other than possibly prednisone (67), including biological agents (68).

Perhaps the most instructive example of the need for long-term observations in rheumatology clinical trials is the "exception that proves the rule," a trial of nephritis associated with systemic lupus erythematosus (SLE) performed at the National Institute of Health (NIH) during the 1970s and 1980s (36). In this trial, renal survival was 90% over 5–10 years in patients who took cyclophosphamide *versus* 30% in patients who took only glucocorticoids (Fig. 5). However, after 1 year, and indeed after 3 years, no differences were seen between prednisone monotherapy and cyclophosphamide (Fig. 5) (36).

This trial is one of the few rheumatology clinical trials conducted over as long as 3 years, and indicates the need for long term observations to recognise certain treatment effects in chronic diseases. Cyclophosphamide might not have been established as the standard of care over the next 2 or 3 decades for the treatment of SLE nephritis if the trial had been terminated after one or even 3 years.

The problem of short time frame may be relevant to many rheumatology clinical trials over the years, including at this time, which appear to indicate negative or equivocal results. Of course, many therapies that do not differ from placebo or another therapy after one year also will not differ over longer periods. Nonetheless, Figure 5 might be recalled when similar results are seen over one year for a therapy *versus* another therapy or placebo in a rheumatic disease, including PsA (33, 37-39, 69, 70), as well as SLE (71, 72), systemic sclerosis (73-75), and other rheumatic diseases. These trials often are regarded as "failed," but interpretation of results may be complex.

This concern may be particularly relevant when many measures indicate advantages to a therapy which is not statistically significant according to the $p<0.05$ criterion, as seen in 3 of 4 PsA trials (37-39) [other than the first trial (33) in which difference between MTX and placebo were significant, but the dose was far too high]. MTX became the standard of care for RA and emerged as the "anchor drug" for RA over the last decade (76, 77), and is recommended for PsA (34), in part because of clinical trials, but largely by overcoming limitations of clinical trials and interpretations of results.

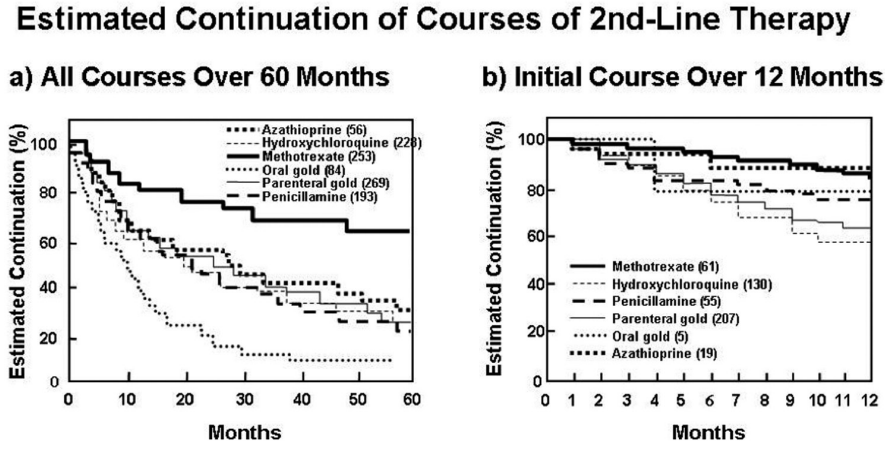

Fig. 4. Estimated continuation of courses of 6 DMARDs in 477 patients with rheumatoid arthritis in 7 rheumatology practices (4): **a)** 532 courses over 5 years; **b)** 477 initial courses over 1 year (66).

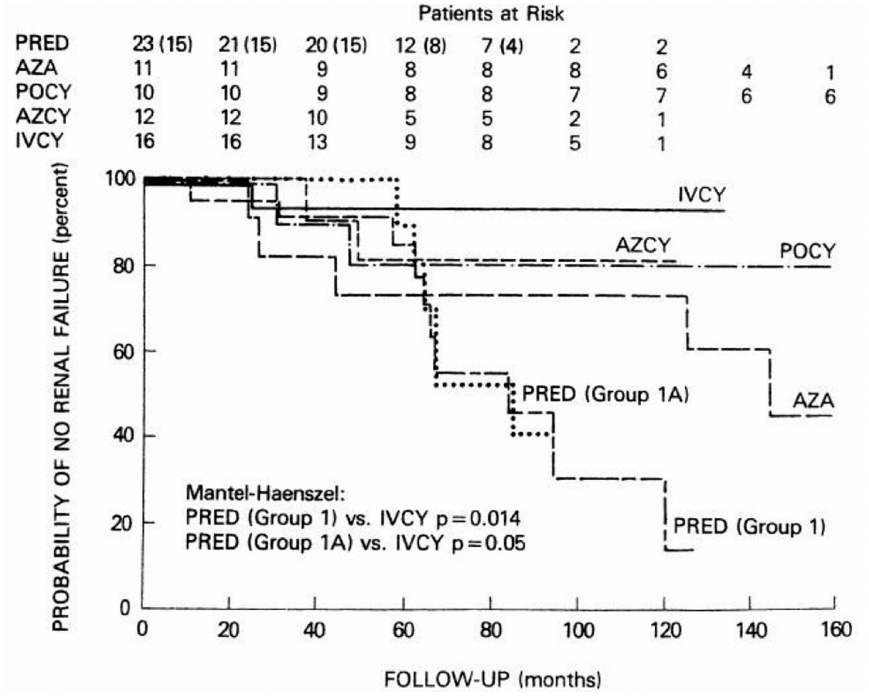

Fig. 5. Estimated probability of renal failure in patients with nephritis associated with systemic lupus erythematosus over 10 years according to treatment with prednisone (PRED), ayalluoprine (AZA), asclophophamine by mouth (POCY) in combination with ayathip[rine (AZCY), or intracenously (IVCY) (36).

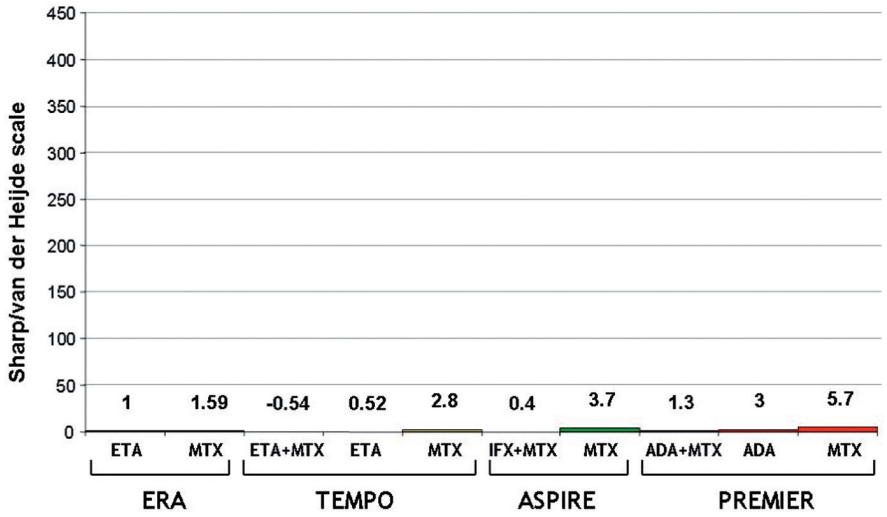

Fig. 6. Radiographic outcomes, expressed as changes in Sharp/van der Heijde radiographic scores (0–448), in 4 randomised controlled trials with methotrexate-naïve patients (103). Data are compared from the ERA (65), TEMPO (102), ASPIRE (108) and PREMIER (109) trials. ADA: adalimumab; ETA: etanercept; IFX: infliximab; MTX: methotrexate (56).

Of course, it is not possible to maintain randomisation over 5–10 years in symptomatic patients with RA, PsA, or any chronic disease, for ethical reasons, not to mention costs. However, open-label extensions for indefinite periods to analyse outcomes such as renal failure, joint replacement, work disability or death are possible at low costs using, the internet, telephone, or mail, without a need for costly patient visits. Consent for and implementation of such long-term extensions might be required in clinical trials of all chronic diseases.

C. Underestimation of MTX in rheumatology due to limitations of clinical trials: 2000-2010

In the early 2000s, several clinical trials were conducted by pharmaceutical companies to compare radiographic progression in patients treated with biologic agents or MTX or a combination of MTX and the biological agent. For example, the TEMPO trial of early RA patients indicated radiographic progression of 3.34 units over 2 years in patients randomised to MTX, compared to 1.15 in patients randomised to etanercept, and 0.56 in patients randomised to the combination of MTX and etarnercept (78).

These differences are statistically significant. However, a change of 3.34 units is less than 0.5% of the total number of units in a Sharp/van der Heijde score of 448 (79) (Fig. 6). Patients rarely develop more than 50% of the maximum score and it may be suggested that maximum scores actually are 224, or 50% of maximum. Nonetheless, 3.4 units over 2 years would not be detectable in an individual patient (80), and a clinically detectable change of 17 units (5 x 3.4) would be seen only after 10 years would not be useful in actual patient care.

Furthermore, hand radiographs are limited as predictors of severe RA outcomes such as work disability (40, 41) or mortality (42). A review of all 53 reports which described long-term predictors of premature mortality in RA indicated that functional status was significant in analyses in 17 of 18 studies, while hand radiographs were significant in 5 of 18 studies (42) (Fig. 7). Although structural damage is correlated significantly with functional disability, the levels of r=0.3–0.5 indicate that radiographs explain less than 25% of variation in functional disability (81).

Results similar to TEMPO are seen for many biologic agents (Fig. 6) (56), with statistically significant differences between the biological agent and MTX in early RA patients, which would be clinically undetectable in individual patients (56). Moreover, MTX inhibits radiographic progression considerably (82) and remains the mainstay therapy for RA, taken by far more patients than any DMARD or biological therapy, despite observations of radiographic differences *versus* biological agents (83).

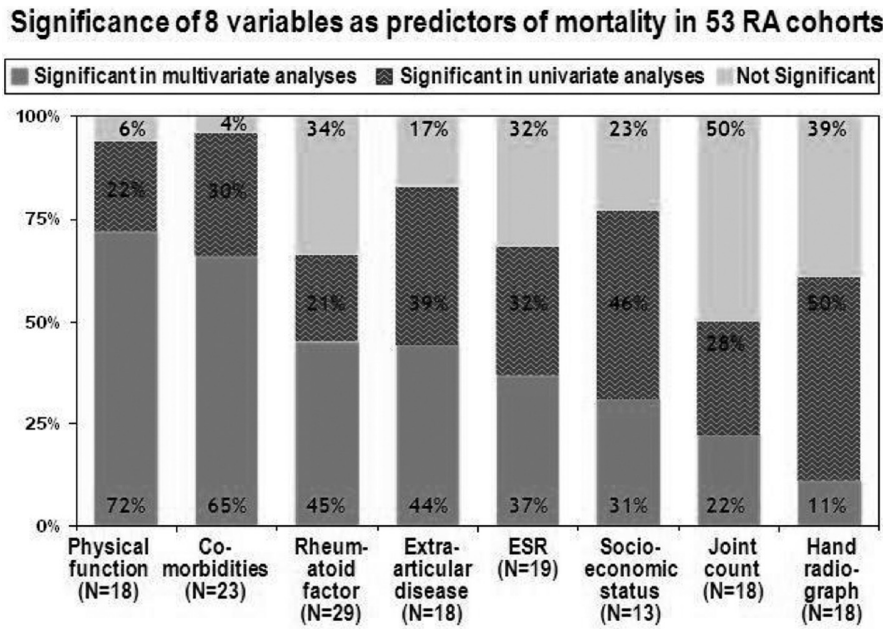

Fig. 7. Significance of 8 variables as predictors of mortality in 53 RA cohorts in multivariate, or in univariate analyses, or not significant (115).

D. Underestimation of MTX in rheumatology due to limitations of clinical trials since 2010

The largest placebo-controlled study of MTX *versus* placebo in the medical literature is the MTX in PsA (MIPA) trial reported in 2012 (39). The investigators enrolled 221 MTX-naïve patients with PsA at 22 centers in Europe over 5 years; 109 received MTX and 112 placebo over 6 months. Patients could take concomitant non-steroidal anti-inflammatory drugs (NSAIDS), but not systemic glucocorticoids. Responses were assessed at 3 and 6 months (39).

The results indicated odds ratios for MTX-treated *versus* placebo-treated patients of 1.77 (p=0.06) for the primary outcome, the psoriatic arthritis response criteria (PsARC) index (84). Odds ratios were 2.00 (p=0.23) and 1.70 (p=0.10), respectively, for the 2 secondary outcomes of ACR 20% improvement criteria (ACR 20) and disease activity score 28 (DAS28) (39). Each of the 7 individual RA core data set measures favoured MTX numerically, although the only statistically significant differences according to the criterion of p<0.05 were the assessor and patient global estimates of status (39).

The authors concluded "that there is presently no evidence that MTX improves inflammatory synovitis in active PsA; this would be required for a true disease-modifying effect. However, MTX did significantly improve assessors' and patients' global estimates, suggesting it may have symptom-modifying effects. It also showed a positive effect on psoriasis skin scores, consistent with its known efficacy in psoriasis" (39). The authors further stated that "As MTX is not licensed for PsA and two RCTs have now provided insubstantial evidence of its benefit for treating synovitis, we therefore believe PsA is best managed using effective licensed conventional drugs like LEF or biologics. We also think that guidelines for treating PsA need to be revisited so that the sequencing of conventional drugs before biologics are used is re-evaluated (39)".

The conclusion of the abstract states that "This trial of active PsA found no evidence for MTX improving synovitis and consequently raises questions about its classification as a disease-modifying drug in PsA". The 3 "key messages for rheumatologists" were:

a) "Low-dose oral MTX does not improve synovitis in active PsA."

b) "MTX has borderline symptom-modifying properties."

c) "There is insufficient evidence to support the use of MTX as a standard treatment for PsA" (39).

The observation in MIPA that 2 of the 7 ACR Core Data Set measures indicated statistically significant advantages to MTX over placebo, *i.e*. physician global estimates and patient global estimate. This finding was interpreted as "symptom-modifying," as the more "objective" measures of laboratory tests and joint counts, as well as indices, were not statistically significant in differences between MTX and placebo (39). However, physician and patient global estimates are most likely among the 7 RA Core Data Set to discriminate active from control treatment in clinical trials of biological agents, which document disease-modifying activity, defined as radiographic progression (45). Therefore, differences according to the global measures in the MIPA study may have some clinical significance (in contrast to statistical significance), may be more than acknowledged.

Analyses of data from all 9 clinical trials in which relative efficacies of core data set measures to distinguish active from control treatments have been computed (of MTX, leflunomide, adalimumab, abatacept, and infliximab) indicates that physician global estimate and patient global estimate are the most efficient measures (Fig. 8) (45). Analyses of 4 studies involving adalimumab, ARMADA, DE011, STAR, and DE019 (85), indicated that physician global estimate had the highest relative efficiency to distinguish active from control treatments (45). In 3 studies of MTX or leflunomide *versus* placebo (86, 87), and infliximab *versus* MTX (45, 88), patient global estimate had the highest relative efficiency to distinguish active from control treatments (45).

The measures among 7 RA Core Data Set measures that were among the 3 highest in relative efficiencies in the 9 studies for which data have been analysed, which might be chosen for an optimal index to assess improvement in clinical trials (89), were physician global estimate in 7/9 (78%), patient global estimate, pain, and HAQ function in 5/9 (56%), SJC and ESR/CRP in 3/9 (33%), and TJC in none (Fig. 8A) (45). Analyses only of 3 measures, one from each category of the core data set – laboratory, assessor, and patient,

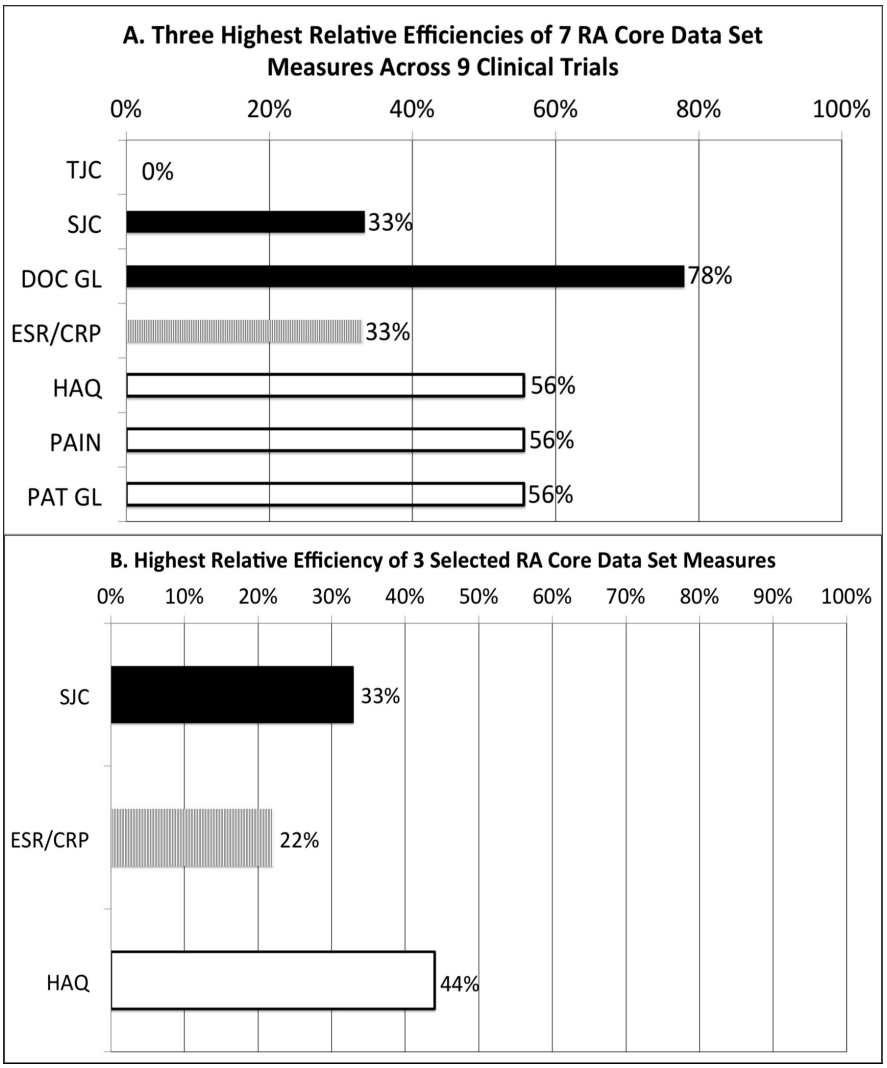

Fig. 8. Relative efficiencies of the 9 Core Data Set measures, tender joint count (TJC), swollen joint count (SJC), physician global estimate of status (DOCGL), erythrocyte sedimentation rate or C-reactive protein (ESR/CRP), health assessment questionnaire (HAQ), physical function, pain, and patient global estimate of status (PATGL) in 9 clinical trials involving methotrexate, leflunomide, adalumimab, abatacept, and infliximab. Top panel A indicates the proportion of studies in which each measure was among the 3 with the highest relative efficiencies. Lower panel B indicates only each of three measures: ESR/CRP (the only laboratory test), swollen joint counts (the more efficient of joint count measures), and HAQ physical function (which is thought to be the least responsive of all 7 Core Data Set measures in the 9 clinical trials). Physical function (HAQ) was at least as likely to have highest relative efficiency in the trials compared to SJC and ESR/CRP (45).

included the single laboratory test – ESR or CRP, whichever had the *higher* efficiency if both were available, SJC -the joint count measure with higher relative efficiency (*vs*. TJC), and HAQ physical function – which is regarded as the least likely among RA Core Data Set measures to be reversible (90, 91). In these analyses, HAQ physical function was most efficient (Fig. 8B) (45), although each was significant in more than one of 9 trials, indicating the need for an index.

An emphasis on radiographic scores and joint counts over functional disability as a primary outcome measure in clinical trials reflects dominance of a "biomedical model" (92, 93) in contemporary medicine. A major feature of this model is that "objective" data from high technology sources or detailed examinations are more important than data from a patient. The importance of a "biomedical model" is seen in dismissal of statistically significant differences between MTX and placebo in patient and physician global assessment as "subjective" in the MIPA trial (39).

Another example of the preeminence of a biomedical model in rheumatology may be seen in a requirement for 20%, 50%, and 70% improvement in TJC and SJC *versus* only 3 of the other 5 RA core data set measures to meet ACR 20, 50, and 70 responses (43). Therefore, TJC and SJC are weighted as "objective" measures higher than a physician global estimate or patient self-report scores. More recently, an ACR/EULAR committee to establish new criteria for remission in early RA made an *a priori* decision that any criteria for remission must include a TJC, SJC, and laboratory tests (94).

However, no "evidence" is available that favourable values for joint count or laboratory tests are more prognostic of long-term outcomes such as work disability or premature death, or more likely to distinguish active from control treatment more effectively than the other 4 RA core data set measures, *i.e*. 3 patient self-report measures of physical function, pain, patent global assessment and physician global assessment in clinical trials. The decisions concerning ACR improvement and remission criteria are not "evidence-based" from the standpoint of long-term outcomes or clinical trial results. However, these decisions may be appropriate on the basis of clinical considerations.

To their credit, the authors of the MIPA trial present several supplementary tables, as well as a candid description of possible limitations of their study. An analysis of completers only (rather than all participants in "intention to treat" analyses, as was presented in the report) indicated a statistically significant advantage to MTX according to the PsARC primary outcome (95), as well as higher odds ratios according to the ACR 20 and DAS28 secondary outcomes (39). However, the authors point out that the intent to treat analyses in the published report are preferable methodologically, which is technically correct, but completer analyses may be preferable in some instances (perhaps in MIPA) because of issues of statistical power, short time-frame, and absence of PsA subset analyses.

Indeed, another supplementary table classifies participants into two catego-

ries, oligoarticular (79 patients) and polyarticular (142 patients), including a further subset of polyarticular termed "RA equivalent" (37 patients). The differences between MTX and placebo-treated patients were considerably greater in the polyarticular, than oligoarticular patient group and dramatically different in the "RA-equivalent" group (39). The authors commented that "interpretation of these data is fraught with difficulty and requires extreme caution as the analyses were not predetermined, the groups were very small, the confidence intervals are large. Nevertheless, we have included the data online for interest" (39). Perhaps, it would have been desirable that these analyses would have been included in the main report, rather than as a supplementary table; perhaps they were included in the initial submission, and changes were made during the editorial process.

The authors also discussed possible limitations of MIPA, suggesting that "it is possible that MTX might be effective in some circumstances in patients with PsA" (39). The first involved possible higher doses of MTX for longer periods, which was not thought important as "placebo-controlled RCTS show 15 mg weekly or less MTX is effective within three months" (39). The second was that inclusion criteria allowed patients with fewer active joints than other PsA trials, but this was not regarded as a problem since "most patients were more active than the minimum requirement and MIPA was designed as a pragmatic trial" (39). Thirdly, there is a concern regarding sample size, which is explained by other trials having higher odds ratios using the imputation methodology in this study. The MIPA authors suggest that studies with apparently conflicting results concerning MTX efficacy may have included a greater proportion of patients with RA-like PsA (39).

The report of the MIPA trial notes five previous clinical trials involving MTX in PsA, 3 *versus* placebo and 2 *versus* cyclosporine, as supporting the absence of MTX efficacy in PsA. However, each of these 5 trials showed meaningful efficacy of MTX. The first trial (33) as discussed above, was noted to have "unacceptable toxicity", but no comment was made that the doses were 2–5 times more the maximum at this time of 30 mg/wk. A second trial included 37 patients (37); as in MIPA, physician global assessment and skin psoriasis were improved at a significantly statistical level, and all measures other than TJC showed an advantage to MTX. A third trial of 35 patients with early PsA, all of whom were described as "belonging to the oligoarthritic subset" showed statistically significant advantages to MTX for SJC, TJC, patient and physician global estimates, and pain visual analogue scale (38). The other two clinical trials documented similar improvement with cyclosporine and MTX (70). The MIPA discussion also commented that systematic reviews also are consistent with a "paucity of evidence" concerning possible efficacy of MTX in PsA (96, 97).

Several rheumatologists also questioned some interpretations of findings in MIPA. An editorial in the same issue of *Annals of Rheumatic Diseases* pointed out that "such negative results are not in line with the physicians' views", and points to problems with inclusion criteria, the choice of the primary outcome and study duration (98). The editorial appears to accept the idea that MIPA is the "third negative placebo-controlled trial of MTX *versus* placebo," but suggested that since the number of involved joints was low, a more informative outcome measure might have been the number of patients with no swollen joints.

A letter to the editor in a subsequent issue (99) also raised issues with the inclusion criteria, suggesting that the CASPAR criteria (100) might have led to a different outcome. Several reviews specifically pointed out issues with MIPA, including a channeling bias for milder patients, low MTX dose, long period to dose escalation, insufficient statistical power to recognise differences between MTX and placebo, and high dropout rate (101-103). An article in an earlier Supplement in this series concerning MTX concluded that "it seems that MTX does have an important role in the management of PsA" (97).

The MIPA authors responded that the number of patients with no joint swelling was similar in both groups and that the same result would have been seen using the CASPAR criteria (104). They also suggested that physicians' acceptance of MTX as beneficial may be explained by "regression to the mean" (104).

An open-label study of 115 PsA patients who had not received MTX found ACR20 responses in 67% receiving MTX only compared to 86% of patients who received infliximab plus MTX (105). Treatment was more efficacious in the infliximab group (as expected); however, 67% ACR 20 responses is in the range seen in the treatment arm of RA clinical trials. It may be noteworthy that the initial SJC and TJC, as well as ESR and CRP, were higher than in the MIPA trial (39, 105).

In the tight control of inflammation in early PsA trial (TICOPA) (106), advantages were seen to the tight control group. MTX monotherapy was continued in 27% patients in tight control group and 60% in the standard care group. No differences were seen in radiographic progression, which was quite low in both groups, suggesting that MTX is "disease-modifying" in PsA as in RA. The TICOPA authors noted that "MTX is often the first drug to be used in PsA at doses that are considerably higher than in the MIPA trial, with 82% in the tight control group taking 25 mg weekly by 12 weeks" (106).

A study from Norway reported in 2009, indicated comparable improvements in 330 patients with PsA compared to 929 with RA, with no significance difference in SJC, ESR, CRP, or Physician global VAS, and somewhat greater in TJC (3.9 *vs*. 3.2) and DAS 28 (1.38 *vs*. 1.13). Drug retention was similar in both groups at two years with 65% and 66% continuing MTX therapy in PsA and RA respectively (107).

Concluding comments

The randomised controlled clinical trial remains the most effective approach to distinguish an active treatment from a placebo or other treatment. However, clinical trials have a number of limitations as do all scientific methods. Further refinement of clinical trials over the last few decades has been focused more on statistical methodology than on clinical relevance, and the possibil-

ity that results may be misleading despite a control group and excellent statistical methods.

Possible advantages of a treatment *versus* a placebo which does not meet the $p<0.05$ criterion, as seen in most trials of MTX in PsA (37-39), may not necessarily indicate the absence of a treatment effect. The findings may result from limitations of the clinical trials, including inadequate statistical power, selection of patients with mild disease, low doses and slow escalation of MTX, and the absence of pre-specified stratification of patients regarding primarily axial, oligoarticular, symmetrical, or polyarticular presentation.

A negative interpretation of MTX efficacy in a clinical trial in 1964 (33) was a major contributor to 15–20 years in which patients with RA, PsA and other rheumatic diseases were not routinely treated with MTX, the current standard of care for RA. In PsA, MTX appears less effective than RA, as axial disease usually does not respond. Nonetheless, the efficacy of MTX in PsA may be underrated in polyarticular arthritis, although polyarticular arthritis in PsA differs from RA (108).

Observational data may provide insights not available from clinical trials, particularly when all consecutive patients seen are captured in the data set (109), which may be enhanced with electronic data capture for patients. Data from patients appear as informative as data from physical examination, imaging, and laboratory to distinguish active from control treatments in RA and to predict severe long term RA outcomes such as work disability and mortality.

Although many rheumatology talks about treatment of most diseases often end with a suggestion of a need for (more) clinical trials, most problems in rheumatic diseases have not been and will not be solved through clinical trials, due to costs and other pragmatic limitations. The rheumatology community has ethical and intellectual responsibilities to attempt optimal capture of data from routine care to improve therapies toward better outcomes for our patients with all rheumatic diseases, most of which will not be derived from clinical trials.

References

1. POCOCK SJ: Clinical trials: a practical approach 2013.
2. SACKETT DL, ROSENBERG WM, GRAY JA, HAYNES RB, RICHARDSON WS: Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71-2.
3. GUYATT G, GUTTERMAN D, BAUMANN MH *et al*.: Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest* 2006; 129: 174-81.
4. SACKETT DL, GENT M: Controversy in counting and attributing events in clinical trials. *N Engl J Med* 1979; 301: 1410-2.
5. HUSKISSON EC: Important factors in the success and failure of clinical trials (closing remarks). *Agent actions Suppl* 1980; 7: 323-4.
6. FREIREICH EJ: The randomized clinical trial as an obstacle to clinical research. Varco RL DJ (Eds.) Philadelphia: W.B. Saunders; 1983.
7. BOMBARDIER C, TUGWELL P: Controversies in the analysis of longterm clinical trials of slow acting drugs. *J Rheumatol* 1985; 12: 403-5.
8. GOTZSCHE PC: Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Control Clin Trials* 1989; 10: 31-56.
9. 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.
10. HAWLEY DJ, WOLFE F: Are the results of controlled clinical trials and observational studies of second line therapy in rheumatoid arthritis valid and generalizable as measures of rheumatoid arthritis outcome: analysis of 122 studies. *J Rheumatol* 1991; 18: 1008-14.
11. GOTZSCHE PC, HANSEN M, STOLTENBERG M *et al*.: Randomized, placebo controlled trial of withdrawal of slow-acting antirheumatic drugs and of observer bias in rheumatoid arthritis. *Scand J Rheumatol* 1996; 25: 194-9.
12. FEINSTEIN AR, HORWITZ RI: Problems in the "evidence" of "evidence-based medicine". *Am J Med* 1997; 103: 529-35.
13. HORWITZ RI, SINGER BH, MAKUCH RW, VISCOLI CM: Clinical versus statistical considerations in the design and analysis of clinical research. *J Clin Epidemiol* 1998; 51: 305-7.
14. KAPTCHUK TJ: Powerful placebo: the dark side of the randomised controlled trial. *Lancet* 1998; 351: 1722-5.
15. KAPTCHUK TJ: The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? *J Clin Epidemiol* 2001; 54: 541-9.
16. IOANNIDIS JP, TRIKALINOS TA: An exploratory test for an excess of significant findings. *Clin Trials* 2007; 4: 245-53.
17. HOWICK J: The Philosophy of Evidence-Based Medicine: Oxford: Wiley-Blackwell; 2011.
18. MORRIS AH, IOANNIDIS JP: Limitations of medical research and evidence at the patient-clinician encounter scale. *Chest* 2013; 143: 1127-35.
19. EBRAHIM S, SOHANI ZN, MONTOYA L *et al*.: Reanalyses of randomized clinical trial data. *JAMA* 2014; 312: 1024-32.
20. GREENHALGH T, HOWICK J, MASKREY N; EVIDENCE BASED MEDICINE RENAISSANCE GROUP: Evidence based medicine: a movement in crisis? *BMJ* 2014; 348: g3725.
21. PINCUS T: Rheumatoid arthritis: disappointing long-term outcomes despite successful short-term clinical trials. *J Clin Epidemiol* 1988; 41: 1037-41.
22. PINCUS T: Limitations of randomized clinical trials to recognize possible advantages of combination therapies in rheumatic diseases. *Semin Arthritis Rheum* 1993; 23 (2 Suppl. 1): 2-10.
23. PINCUS T, STEIN CM: What is the best source of useful data on the treatment of rheumatoid arthritis: clinical trials, clinical observations, or clinical protocols? *J Rheumatol* 1995; 22: 1611-7.
24. 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): S27-38.
25. PINCUS T, SOKKA T: Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? *Ann Rheum Dis* 2004; 63 (Suppl. 2): ii32-ii9.
26. PINCUS T, SOKKA T: Clinical trials in rheumatic diseases: designs and limitations. *Rheum Dis Clin North Am* 2004; 30: 701-24, v-vi.
27. PINCUS T, YAZICI Y, SOKKA T: Are excellent systematic reviews of clinical trials useful for patient care? *Nat Clin Pract Rheumatol* 2008; 4: 294-5.
28. PINCUS T, FURER V, SOKKA T: Underestimation of the efficacy, effectiveness, tolerability, and safety of weekly low-dose methotrexate in information presented to physicians and patients. *Clin Exp Rheumatol* 2010; 28 (Suppl. 61): S68-79.
29. PINCUS T, CASTREJON I: Evidence that the strategy is more important than the agent to treat rheumatoid arthritis - data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. *Bull Hosp Jt Dis* (2013). 2013; 71 (Suppl. 1): 33-40.
30. SMITH GC, PELL JP: Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003; 327: 1459-61.
31. GLASZIOU P, CHALMERS I, RAWLINS M, MCCULLOCH P: When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007; 334: 349-51.
32. ARONSON JK, HAUBEN M: Anecdotes that provide definitive evidence. *BMJ* 2006; 333: 1267-9.
33. BLACK RL, O'BRIEN WM, VANSCOTT EJ, AUERBACH R, EISEN AZ, BUNIM JJ: Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. *JAMA* 1964; 189: 743-7.
34. GOSSEC L, SMOLEN JS, GAUJOUX-VIALA C *et al*.: European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological

therapies. *Ann Rheum Dis* 2012; 71: 4-12.
35. FELSON DT, ANDERSON JJ, MEENAN RF: The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. *Arthritis Rheum* 1990; 33: 1449-61.
36. AUSTIN HA, 3RD, KLIPPEL JH, BALOW JE *et al*.: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 314: 614-9.
37. WILLKENS RF, WILLIAMS HJ, WARD JR *et al*.: Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984; 27: 376-81.
38. SCARPA R, PELUSO R, ATTENO M *et al*.: The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clin Rheumatol* 2008; 27: 823-6.
39. KINGSLEY GH, KOWALCZYK A, TAYLOR H *et al*.: A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* (Oxford) 2012; 51: 1368-77.
40. 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.
41. PUOLAKKA K, KAUTIAINEN H, MOTTONEN T *et al*.: Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. *Ann Rheum Dis* 2005; 64: 130-3.
42. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S35-61.
43. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
44. FELSON DT, ANDERSON JJ, BOERS M *et al*.: The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993; 36: 729-40.
45. PINCUS T, RICHARDSON B, STRAND V, BERGMAN MJ: Relative efficiencies of the 7 rheumatoid arthritis Core Data Set measures to distinguish active from control treatments in 9 comparisons from clinical trials of 5 agents. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): 47-54.
46. RUBERMAN W, WEINBLATT E, GOLDBERG JD, CHAUDHARY BS: Psychosocial influences on mortality after myocardial infarction. *N Engl J Med* 1984; 311: 552-9.
47. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
48. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al*.: The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
49. WEINBLATT ME, KEYSTONE EC, FURST DE *et al*.: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
50. PINCUS T, KOCH GG, SOKKA T *et al*.: A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001; 44: 1587-98.
51. PINCUS T, KOCH G, LEI H *et al*.: Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004; 63: 931-9.
52. GOTZSCHE PC, JORGENSEN KJ: Screening for breast cancer with mammography. *The Cochrane Database Syst Rev* 2013; 6: CD001877.
53. CRONSTEIN BN, NAIME D, OSTAD E: The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. *J Clin Invest* 1993; 92: 2675-82.
54. CRONSTEIN B: How does methotrexate suppress inflammation? *Clin Exp Rheumatol* 2010; 28 (Suppl. 61): S21-3.
55. KELLEY WN, HARRIS ED, RUDDY S, SLEDGE CB: Textbook of Rheumatology. 2 ed: W.B. Saunders Company; 1985.
56. YAZICI Y, YAZICI H: Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 449-52.
57. HOFFMEISTER RT: Methotrexate in rheumatoid arthritis [abstract]. *Arthritis Rheum* 1972; 15: 114.
58. HOFFMEISTER RT: Methotrexate therapy in rheumatoid arthritis: 15 years experience. *Am J Med* 1983; 75: 69-73.
59. WILKE WS, CALABRESE LH, SCHERBEL AL: Methotrexate in the treatment of rheumatoid arthritis; pilot study. *Cleve Clin Q* 1980; 47: 305-9.
60. KRAGBALLE K, ZACHARIAE E, ZACHARIAE H: Methotrexate in psoriatic arthritis: a retrospective study. *Acta Derm Venereol* 1983; 63: 165-7.
61. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12:245-52.
62. WILLIAMS HJ, WILLKENS RF, SAMUELSON CO, JR *et al*.: Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. *Arthritis Rheum* 1985; 28: 721-30.
63. WEINBLATT ME, COBLYN JS, FOX DA *et al*.: Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985; 312: 818-22.
64. SOKKA T, PINCUS T: Ascendancy of weekly low-dose methotrexate in usual care of rheumatoid arthritis from 1980 to 2004 at two sites in Finland and the United States. *Rheumatology* (Oxford) 2008; 47: 1543-7.
65. WILLIAMS HJ, WARD JR, READING JC *et al*.: Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. A controlled clinical trial. *Arthritis Rheum* 1992; 35: 259-69.
66. PINCUS T, MARCUM SB, CALLAHAN LF: Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. *J Rheumatol* 1992; 19: 1885-94.
67. YAZICI Y, SOKKA T, KAUTIAINEN H, SWEARINGEN C, KULMAN I, PINCUS T: Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. *Ann Rheum Dis* 2005; 64: 207-11.
68. DUCLOS M, GOSSEC L, RUYSSEN-WITRAND A *et al*.: Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. *J Rheumatol* 2006; 33: 2433-8.
69. SPADARO A, RICCIERI V, SILI-SCAVALLI A, SENSI F, TACCARI E, ZOPPINI A: Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol* 1995; 13: 589-93.
70. FRASER AD, VAN KUIJK AW, WESTHOVENS R *et al*.: A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005; 64: 859-64.
71. MERRILL JT, NEUWELT CM, WALLACE DJ *et al*.: Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; 62: 222-33.
72. WOFSY D, HILLSON JL, DIAMOND B: Abatacept for lupus nephritis: alternative definitions of complete response support conflicting conclusions. *Arthritis Rheum* 2012; 64: 3660-5.
73. SMITH V, PIETTE Y, VAN PRAET JT *et al*.: Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. *J Rheumatol* 2013; 40: 52-7.
74. POORMOGHIM H, REZAEI N, SHEIDAIE Z *et al*.: Systemic sclerosis: comparison of efficacy of oral cyclophosphamide and azathioprine on skin score and pulmonary involvement-a retrospective study. *Rheumatology Int* 2014; 34: 1691-9.
75. JORDAN S, DISTLER JH, MAURER B *et al*.: Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. *Ann Rheum Dis* 2015; 74: 1188-94.
76. PINCUS T, YAZICI Y, SOKKA T, ALETAHA D, SMOLEN JS: Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S179-85.
77. PINCUS T, GIBSON KA, CASTREJON I:

Update on methotrexate as the anchor drug for rheumatoid arthritis. *Bull Hosp Jt Dis* (2013). 2013; 71 (Suppl. 1): 9-19.
78. KLARESKOG L, VAN DER HEIJDE D, DE JAGER JP *et al*.: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; 363: 675-81.
79. VAN DER HEIJDE D, LANDEWÉ R, KLARESKOG L *et al*.: Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. *Arthritis Rheum* 2005; 52: 49-60.
80. BRUYNESTEYN K, VAN DER HEIJDE D, BOERS M *et al*.: Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. *Arthritis Rheum* 2002; 46: 913-20.
81. 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.
82. PINCUS T, FERRACCIOLI G, SOKKA T *et al*.: Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. *Rheumatology* (Oxford) 2002; 41: 1346-56.
83. NARANJO A, SOKKA T, DESCALZO MA *et al*.: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008; 10: R30.
84. FRANSEN J, ANTONI C, MEASE PJ *et al*.: Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. *Ann Rheum Dis* 2006; 65: 1373-8.
85. PINCUS T, AMARA I, SEGURADO OG, BERGMAN M, KOCH GG: Relative efficiencies of physician/assessor global estimates and patient questionnaire measures are similar to or greater than joint counts to distinguish adalimumab from control treatments in rheumatoid arthritis clinical trials. *J Rheumatol* 2008; 35: 201-5.
86. STRAND V, COHEN S, SCHIFF M *et al*.: Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. *Arch Intern Med* 1999; 159: 2542-50.
87. TUGWELL P, WELLS G, STRAND V *et al*.: Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. Leflunomide Rheumatoid Arthritis Investigators Group. *Arthritis Rheum* 2000; 43: 506-14.
88. MAINI R, ST CLAIR EW, BREEDVELD F *et al*.: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.
89. BERGMAN MJ, REISS W, CHUNG C, WONG P, TURPCU A: Composite Indices Using 3 or 4 Components of the Core Data Set Have Similar Predictive Ability to Measure Disease Activity in RA: Evidence from the DANCER and REFLEX Studies. *Autoimmune Dis* 2013; 2013: 367190.
90. ALETAHA D, SMOLEN J, WARD MM: Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. *Arthritis Rheum* 2006; 54: 2784-92.
91. ALETAHA D, ALASTI F, SMOLEN JS: Chronicity of rheumatoid arthritis affects the responsiveness of physical function, but not of disease activity measures in rheumatoid arthritis clinical trials. *Ann Rheum Dis* 2015; 74: 532-7.
92. ENGEL GL: The need for a new medical model: a challenge for biomedicine. *Science* 1977; 196: 129-36.
93. MCCOLLUM L, PINCUS T: A biopsychosocial model to complement a biomedical model: patient questionnaire data and socioeconomic status usually are more significant than laboratory tests and imaging studies in prognosis of rheumatoid arthritis. *Rheum Dis Clin North Am* 2009; 35: 699-712, v.
94. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63: 573-86.
95. CLEGG DO, REDA DJ, MEJIAS E *et al*.: Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; 39: 2013-20.
96. RAVINDRAN V, SCOTT DL, CHOY EH: A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Ann Rheum Dis* 2008; 67: 855-9.
97. CEPONIS A, KAVANAUGH A: Use of methotrexate in patients with psoriatic arthritis. *Clin Exp Rheumatol* 2010; 28 (Suppl. 61): S132-7.
98. DOUGADOS M: Methotrexate in peripheral spondyloarthritis including psoriatic arthritis: a need for further evaluation. *Rheumatology* (Oxford) 2012; 51: 1343-4.
99. SATHI N, GLADSTON-CHELLIAH E, CHATTOPADHYAY C: Comment on: A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* (Oxford) 2013; 52: 761.
100. HELLIWELL PS, TAYLOR WJ, GROUP CS: Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. *J Rheumatol* 2008; 35: 472-6.
101. MEASE P: Update on treatment of psoriatic arthritis. *Bull NYU Hosp Jt Dis* 2012; 70: 167-71.
102. MEASE PJ: Spondyloarthritis: Is methotrexate effective in psoriatic arthritis? *Nat Rev Rheum* 2012; 8: 251-2.
103. MEASE P: Methotrexate in psoriatic arthritis. *Bull Hosp Jt Dis* (2013). 2013; 71 (Suppl. 1): S41-5.
104. KINGSLEY GH, SCOTT DL: Comment on: A randomized placebo-controlled trial of methotrexate in psoriatic arthritis: reply. *Rheumatology* (Oxford) 2013; 52: 761-2.
105. BARANAUSKAITE A, RAFFAYOVA H, KUNGUROV NV *et al*.: Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann Rheum Dis* 2012; 71: 541-8.
106. COATES L, MOVERLEY A, MCPARLAND L *et al*.: Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015 Sep 30. pii: S0140-6736(15)00347-5 [Epub ahead of print].
107. LIE E, VAN DER HEIJDE D, UHLIG T *et al*.: Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 671-6.
108. HELLIWELL PS, PORTER G, TAYLOR WJ, GROUP CS: Polyarticular psoriatic arthritis is more like oligoarticular psoriatic arthritis, than rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 113-7.
109. MOSES LE: The series of consecutive cases as a device for assessing outcomes of intervention. *N Engl J Med* 1984; 311: 705-10.
110. PINCUS T: Psychosocial influences and mortality: Ruberman *et al*. (1984). *Adv Mind Body Med* 2001; 17: 24-7.
111. SOKKA T, PINCUS T: Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 313-8.
112. YAZICI Y, ERKAN D: Eligibility of rheumatoid arthritis patients seen in clinical practice for rheumatoid arthritis clinical trials: comment on the article by Sokka and Pincus. *Arthritis Rheum* 2003; 48: 3611; author reply 3-5.
113. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al*.: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-93.
114. WEINBLATT ME, KREMER JM, BANKHURST AD *et al*.: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.
115. ABELSON B, RUPEL A, PINCUS T: Limitations of a biomedical model to explain socioeconomic disparities in mortality of rheumatic and cardiovascular diseases. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S25-34.