

Canadian Recommendations for Clinical Trials of Pharmacologic Interventions in Rheumatoid Arthritis: Inclusion Criteria and Study Design

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ABSTRACT. Objective. Current clinical trial designs for pharmacologic interventions in rheumatoid arthritis (RA) do not reflect the innovations in RA diagnosis, treatment, and care in countries where new drugs are most often used. The objective of this project was to recommend revised entry criteria and other study design features for RA clinical trials.

Methods. Recommendations were developed using a modified nominal group consensus method. Canadian Rheumatology Research Consortium (CRRC) members were polled to rank the greatest challenges to clinical trial recruitment in their practices. Initial recommendations were developed by an expert panel of rheumatology trialists and other experts. A scoping study methodology was then used to examine the evidence available to support or refute each initial recommendation. The potential influence of CRRC recommendations on primary outcomes in future trials was examined. Recommendations were finalized using a consensus process.

Results. Recommendations for clinical trial inclusion criteria addressed measures of disease activity [Disease Activity Score 28 using erythrocyte sedimentation rate (DAS28-ESR) > 3.2 PLUS ≥ 3 tender joints using 28-joint count (TJC28) PLUS ≥ 3 swollen joint (SJC28) OR C-reactive protein (CRP) or ESR > upper limit of normal PLUS ≥ 3 TJC28 PLUS ≥ 3 SJC28], functional classification, disease classification and duration, and concomitant RA treatments. Additional recommendations regarding study design addressed rescue strategies and longterm extension.

Conclusion. There is an urgent need to modify clinical trial inclusion criteria and other study design features to better reflect the current characteristics of people living with RA in the countries where the new drugs will be used. (J Rheumatol First Release July 15 2011; doi:10.3899/jrheum.110188)

Key Indexing Terms:

RHEUMATOID ARTHRITIS CLINICAL TRIALS METHODOLOGY ELIGIBILITY

The randomized controlled trial (RCT) is the standard for drug evaluation used by regulatory agencies and bodies deciding on drug reimbursement, such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Clinical

Excellence (NICE) in the United Kingdom. Coincident with the reliance on well-executed RCT has been a considerable decline in recruitment in established sites with clinical trial experience and a shift to sites in countries with less developed medical research infrastructure^{1,2,3}. Concerns regard-

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ing research proficiency in sites with less clinical trial expertise are reflected in the variability in efficacy results and placebo response rates that have been observed globally^{4,5,6,7}. Additional challenges include the ability to collect informed consent from illiterate and vulnerable populations, and the ethics of testing drugs that will not be available to the host nation once the study is completed^{4,5}. Because of these factors there is an increasing concern that the globalization of clinical trials may impede the development of new therapies, not only in rheumatology, but across many diseases.

In rheumatology, substantial variation in the incidence of infectious adverse events has been observed from country to country, and this has influenced the withdrawal of new drugs⁸. There is also evidence demonstrating that differences in baseline characteristics of patients with rheumatoid arthritis (RA) globally are related to the economic wealth of countries^{9,10,11,12,13,14}. As a result, RA populations in developing countries have a much higher level of RA disease activity than those in wealthier countries. This disparity calls into question the generalizability of research findings from studies where most participants have been recruited from developing countries, a point that is not lost on regulatory agencies or payers^{1,5}.

The globalization of clinical trials was in response to several factors including increasing costs and bureaucratic challenges in North America and Western Europe^{1,15}. Trial design is also affected by ethical and methodological requirements in countries that adhere to the International Conference on Harmonization guidelines for clinical trials of pharmaceuticals for human use¹⁶. However, the need remains to test new therapies for RA. This can be facilitated by changing trial inclusion and exclusion criteria to better reflect the characteristics of RA populations in the countries where the drugs will most often be used.

The Canadian Rheumatology Research Consortium (CRRC) is a network of rheumatology trialists and other experts from across Canada. CRRC members have seen unprecedented changes in the clinical trials arena over the past decade. Earlier diagnosis and access to biologics in North America and Europe, coupled with the common use of higher doses of methotrexate (MTX), limits patient eligibility for trials. In addition, markers of disease activity for many patients have decreased overall, yet inclusion criteria for many trials continue to require high numbers of tender and swollen joints and high eligibility limits for laboratory values. This creates a critical situation by greatly reducing the number of Canadian patients enrolled in the studies that will be used to provide evidence to inform the availability and access to therapies and guide overall rheumatology care in Canada.

In the context of this dynamic international environment, the CRRC undertook a study to inform recommendations for the entry criteria and other design considerations to be used in clinical trials in RA.

MATERIALS AND METHODS

The CRRC recommendations were developed using a modified nominal group consensus method¹⁷. CRRC members were polled using a questionnaire to rank the greatest challenges to clinical trial recruitment in their practices. A followup questionnaire was administered (with a very limited response period) to collect additional information about problematic trial eligibility criteria. Initial recommendations were developed by an expert panel of rheumatology trialists and other experts affiliated with the CRRC. A scoping study methodology was then used to examine the evidence available to support or refute each initial recommendation¹⁸. Key steps are outlined in Table 1. The potential effects of CRRC recommendations on primary outcomes in future trials were considered. We examined the primary outcome variables from RCT using similar inclusion criteria to determine if there was any significant influence on expected short-term and long-term outcomes for American College of Rheumatology (ACR) response¹⁹, European League Against Rheumatism (EULAR) response²⁰, and radiographic progression. Recommendations were finalized using a consensus process.

RESULTS

There are 63 CRRC members representing 38 distinct clinical sites. Twenty-eight sites (74%) completed the initial questionnaire, which addressed overall challenges to clinical trial recruitment. Fifteen of 63 (24%) CRRC members completed a followup questionnaire specifically targeting trial entry criteria. The low response rate is attributed to the limited response window, as it was circulated just prior to the 1-day workshop. Ten Canadian rheumatologists participated on the expert panel and prepared preliminary recommendations, reviewed current literature, and participated in the final consensus process. Resulting recommendations for study inclusion criteria addressed measures of disease activity and previous and concomitant RA treatments. Additional recommendations regarding study design features that may affect patient recruitment were also identified. Issues related to the limitations of traditional and current clinical trial design and RA outcomes and endpoints were the subject of much discussion and are the focus of a current CRRC scoping study. Along with the specific recommendations to improve trial recruitment, evidence-informed discussion points have been reported where appropriate.

Inclusion and exclusion criteria.

Confirmed diagnosis of RA. Recommendation: (future) clinical trials should use the 2010 ACR and EULAR classification criteria for RA.

The ACR and EULAR have collaborated to devise new RA classification criteria to replace the existing RA classification criteria^{21,22}. The 2010 RA classification criteria will not affect the inclusion of patients with established RA but may be important for studies of interventions for early RA to ensure the homogeneity of study populations. New analyses with these criteria have demonstrated that increased numbers of patients qualify as RA and this will enhance recruitment, and given weighting on seropositivity, will likely increase specificity of disease at entry²³.

Disease activity. Recommendation: (a) (At the least) moderate disease at baseline defined by a Disease Activity Score 28 using erythrocyte sedimentation rate (DAS28-ESR) > 3.2

Table 1. Scoping study methodology used to inform Canadian recommendations for entry criteria and study design features of clinical trials of pharmacologic interventions in rheumatoid arthritis (RA).

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| Expert panel convened | Ten Canadian rheumatologists with expertise in the design and implementation of Phase I to IV clinical trials of pharmacologic treatments for RA and/or other inflammatory diseases |
| Needs assessment | Survey of 63 CRRC members (representing 38 clinical sites) to determine and rank challenges to clinical trial recruitment in their practices. Results discussed and prioritized in a 1-day workshop |
| Priority questions identified and preliminary recommendations developed | Preliminary recommendations addressed eligibility criteria and study design. Inclusion criteria: disease activity and duration (DAS, TJC, SJC, APR, functional classification, disease duration), concurrent conditions (laboratory abnormalities, infections, tuberculosis screening and treatment), previous and concurrent RA medications, methotrexate, other DMARD and oral corticosteroids at baseline, washout period, number of prior conventional DMARD, prior biologics. Study design: rescue, intraarticular steroid rescue, longterm extension, timing of study visits |
| Literature search | A systematic search of Medline, Embase, and Cochrane Central Register of Controlled Trials to September 2010 was carried out by research support staff using search strategies designed by research librarians. The search strategy included MeSH terms, keywords, and text words related to RA and RCT of DMARD and biologic treatment. To supplement these electronic bibliographic databases, abstracts from annual scientific meetings were also searched (ACR and EULAR). Additional literature considered for this project included very recent diagnosis and treatment guidelines (published later than 2008), systematic reviews and metaanalyses, longitudinal cohorts, and postmarketing surveillance or registry data. Recent critical reviews and narrative reviews by experts in the field were also considered |
| Relevance screening | Independent review of abstracts by research support team. Inclusion criteria included: population (RA), drug (DMARD and/or biologics for RA), primary and secondary outcomes reported. Quality assessment is not completed in a scoping study |
| Data extraction | Reports from relevant studies were pulled. For RCT, the following variables were extracted: first author, year, trial acronym, phase, investigational agent, control agent, eligibility criteria for: disease activity and duration inclusion criteria, concurrent conditions, previous and concurrent RA medications, rescue (including joint injection), timing of primary outcome, ACR response, EULAR response, and radiographic progression for the experimental and control group(s) at all timepoints reported |
| Key informant input | Key informants were asked to identify any additional literature or current research that should be included in the scoping study |
| Data review | Data were reviewed by the Expert Panel and preliminary recommendations were revised |
| CRRC recommendations finalized | Consensus method used to finalize CRRC recommendations. Recommendations to be vetted by the international rheumatology community and other stakeholders |

ACR: American College of Rheumatology; APR: acute-phase reactants; CRRC: Canadian Rheumatology Research Consortium; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; RA: rheumatoid arthritis; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count.

PLUS 3 or more tender joints using the 28-joint count (≥ 3 TJC28) PLUS 3 or more swollen joints using the 28-joint count (≥ 3 SJC28), OR, (b) C-reactive protein (CRP) greater than upper limit of normal ($> \text{ULN}$) according to the centralized reference laboratory OR ESR $> \text{ULN}$ using a licensed independent laboratory PLUS ≥ 3 TJC28 PLUS ≥ 3 SJC28.

Entry criteria for RA RCT have traditionally included a specific number of tender joints (TJ) and swollen joints (SJ)

using the 68/66 joint count and specified levels for acute-phase reactants (APR). Recent changes include the move to the 28-joint count as used by the DAS²⁴ and a baseline DAS28 to set the disease activity entry criterion^{25,26,27}. Kingsley, *et al*²⁸ have demonstrated that the DAS28 may better identify trial-ready patients in clinical cohorts. The use of specific cutoff criteria for ESR and/or CRP is being reconsidered. There is mounting evidence that APR levels

may not be elevated in many patients, normal ranges may be declining in those who are diagnosed and treated early with conventional disease-modifying antirheumatic drugs (DMARD), and levels may not change at all in some patients despite the effectiveness of treatment^{29,30,31,32}. The new EULAR/ACR revised RA classification criteria²² do not contain specific laboratory values, but instead use normal and abnormal ratings as determined by local laboratory standards. The terminology “elevated ESR or CRP” without a value specified is starting to be used in RCT and takes into account the differences in laboratory reference rates³³. The CRP can be processed in a centralized laboratory, which is particularly important for international RCT. To improve reliability, we recommend that ESR not be done in the office of the investigator, rather that they be read by a licensed local independent laboratory. Differences in DAS28 classifications using ESR vs CRP have recently been examined^{34,35}. The DAS28 using CRP has not been validated for use in RCT. There is sufficient evidence from recent clinical trials that using a CRP ≥ 1 mg/dl or \geq ULN and ESR \geq ULN has not affected the ability to achieve a significant clinical or radiographic outcome^{33,36,37,38,39,40,41,42,43,44,45,46,47}.

Another challenge to trial recruitment in recent years is the significant reduction of actively inflamed joints seen in patients in usual care. In a cross-sectional analysis of 3 RA cohorts at 3 timepoints, contemporary cohorts had smaller numbers of tender and swollen joints⁴⁸. In Canada, the Canadian Early Arthritis Cohort (CATCH) is a recently established cohort of adults with early RA. In a recent analysis of 886 patients in CATCH, the median TJC28 and SJC28 was 2 at 12 weeks from consult (when patients would first be approached for RCT), and after therapy initiation (CATCH investigators, personal communication). A sub-analysis was recently completed to examine cohort eligibility for 312 CATCH patients receiving MTX, assessed at 6 months after initiation of treatment. The authors report that reducing joint criteria from 6 to 4 of 28 joints (in combination with elevated APR vs absolute cutoff criteria) resulted in a 25% increase in eligible patients; 40% of these subjects would be trial-eligible⁴⁹. Greenberg, *et al*⁵⁰ recently used the 28-joint validation study by Smolen, *et al*⁵¹ to estimate equivalents for 66-joint count thresholds and mapped 6 of 66 active joints to 4 of 28 active joints to determine the trial readiness of 2 US cohorts for biologics trials. While our recommendation is based on an estimation to the equivalent of 6 active joints using a 66-joint count⁵⁰, there are now published examples of RA RCT that specified very low active joint counts (< 6 on either the 66-joint count or 28-joint count) at baseline^{6,37,52,53,54,55}. Zhang, *et al*⁵⁶ have recently analyzed the data from 6 multicenter trials (N = 2002) and determined that subtrials of subjects with lower TJC had much higher sensitivity to change than those of subjects with higher TJC across all trials and outcome measures (results were not consistent for SJC subgroups). The concordance of the DAS28

with other recommended criteria for joint activity and APR is highlighted in the following example. A patient with a TJC of 3, SJC of 3, ESR 18 mm/h, and a patient global assessment of 30/100 would have a DAS28 of 3.9.

All joint assessments should be performed by a trained, independent blinded joint assessor and the same assessor should be used for all assessments during the trial, if possible^{57,58,59}. Assessor training with ongoing inter- and intratester reliability testing (and retraining) is recommended⁶⁰.

ACR functional classification. Recommendation: Participant must be ambulatory.

The 1991 ACR functional classification criterion is too restrictive because it excludes patients needing any assistance with usual activities of daily living⁶¹. We recommend use of the original ACR functional class criteria⁶² or exclude only bedridden subjects^{45,63,64,65}.

Disease duration. Recommendations: (a) minimum disease duration for established RA: 6 months or more after symptom onset; (b) minimum disease duration for early RA: 8 to 12 weeks after symptom onset and 6 weeks after symptom onset if protocol is targeting very early RA; (c) maximum disease duration for early RA: 1 to 2 years after symptom onset.

Disease duration continues to be a negotiated category as current efforts focus on identifying patients at the earliest possible timepoint and examining the importance of potential risk factors with radiographic disease progression. The ACR has stratified its treatment guidelines using a minimum duration of 6 months⁶⁶ and this limit has been used in recent trials^{45,47,67,68,69,70,71,72}. Duration of symptoms has recently been defined as patient self-report of the duration of signs and symptoms of synovitis of joints that are clinically involved at the time of assessment, regardless of treatment status²². Very few recent RCT limited the length of the disease duration unless they were targeted to early RA^{25,26}.

Concomitant RA medications at baseline. Recommendations: (a) Phase I: stable MTX or monotherapy without MTX background; (b) Phase II: stable MTX or MTX plus hydroxychloroquine; and (c) Phase III to IV: stable DMARD (monotherapy or combination).

There are 3 distinct cohorts of patients with RA available for clinical trials: patients who are naive to DMARD therapy, DMARD-inadequate responders and biologic-inadequate responders⁷³.

Some trials, particularly those in very early RA, will continue to require patients to be DMARD-naive and/or not receiving any DMARD at baseline^{25,26,53}.

Methotrexate (MTX) add-on trials. Recommendations: Duration of MTX at baseline: (a) For a 3-month primary endpoint: 12 weeks of stable MTX. (b) For a 6-month primary endpoint: 8 weeks of stable MTX.

MTX monotherapy, or in combination with other DMARD, is now often the standard of care. Because patients can improve taking MTX over 3 to 6 months, the

dose and route of administration should be stable to avoid what could be a high placebo response^{54,74}. We recommend that patients should have received some dose of MTX for at least 6 months prior to trial enrollment. To truly identify the MTX-inadequate responders, baseline MTX dosing should be 20 to 25 mg/week (oral or subcutaneous) if tolerated and supported by local guidelines^{75,76}. Doses < 20 mg/week are acceptable to avoid intolerance and toxicity. Optimal dosing ranges and options for managing common side effects are now outlined in the most current treatment guidelines^{66,77,78,79,80}. Folate supplementation should be used according to local guidelines^{76,81}.

Other DMARD add-on trials. Recommendation: If DMARD other than MTX are allowed to continue, the patient should have been taking each DMARD for at least 12 weeks and receiving a stable dose within local treatment guidelines for at least 4 weeks prior to initiation of study drug.

Patients taking a stable single or multiple DMARD should be allowed entry into trials unless there is a concern that there could be an unwanted drug interaction with a specific DMARD and the study medication. There are some people who cannot tolerate MTX or have contraindications to its use and they are often excluded from RA trials. In a real-world Canadian RCT only 70% of patients were currently taking MTX when a biologic was initiated⁸². Newer trials have allowed the inclusion of other or combination stable DMARD as concomitant therapies and have demonstrated the efficacy of other DMARD in the optimal treatment of RA, in addition to MTX and biologics. Katchamart, *et al*⁸³ recently completed a systematic review of RCT comparing MTX monotherapy vs MTX combined with other nonbiologic DMARD in adult RA populations. Nineteen trials, totaling 2025 patients, were reviewed. Ma, *et al*⁸⁴ completed a metaanalysis of RCT to determine how combination DMARD therapies (including some biologics) plus MTX affect clinical and radiological outcomes compared to MTX therapy alone in early active RA. Fifteen RCT, totaling 4200 randomized patients, were included in the review. The CRRC supports the use of stable combination DMARD as opposed to discontinuing all DMARD except MTX. However, stratification for MTX alone vs other DMARD alone or in combination should occur to correct for potentially different response rates and toxicities between the underlying treatment groups. We recommend against the use of combination MTX and leflunomide in a clinical trial due to the increased risk of side effects⁸⁵ and the recent finding from the Canadian RA treatment guidelines team that it has no added benefit relative to other DMARD combinations⁷⁹.

Oral corticosteroids at baseline. Recommendation: If low-dose oral corticosteroids are allowed, the patient must be on stable dosing for at least 4 weeks prior to initiation of study drug. "Low-dose" is considered < 10 mg/day.

Low-dose oral corticosteroids have been proven an effective therapy in the treatment of signs and symptoms of RA

and may also improve radiographic outcomes^{86,87,88}. RA RCT allow the use of stable low-dose oral corticosteroids as a concomitant therapy^{26,38,39,42,45,46,47,55,69,72}. Hoes, *et al*⁸⁸ have recently reviewed RCT of glucocorticoid cotherapy with DMARD in RA, and summarized the evidence to support low to medium doses (well under 10 mg/day). If a remission criterion stricter than the DAS remission is to be a study outcome, especially in trials of early RA, a mechanism will be required to taper and discontinue steroids. Stratification by use of steroids at baseline should likely be performed as the treatment effect could be different (as well as the severity of subjects taking steroids).

Exclusion criteria. Studies have suggested that the majority of exclusion criteria are not directly related to drug safety, but they impair trial recruitment and generalizability⁸⁹. In most trials, patients with significant comorbidities, older age, and past cancer have been excluded⁹⁰. It is important to balance safety with generalizability of the data from an ideal population to the real world. Only exclusion criteria that address the safety of a product should be considered, but not necessarily past treatments or remote (cured) cancers.

Study design.

Rescue therapy. Recommendations: (a) rescue to the active drug should be allowed if the trial continues longer than 12 weeks, with criteria for rescue defined as failure of the patient to improve TJC and SJC by 20% or more or a DAS28 response less than 1.2. Failure to achieve an ACR20 criteria response should not be used as a rescue criterion; (b) change to active agent in Phase II and III trials.

Improvements in overall outcomes for patients over the past decade may be as attributable to the strategy of treatment as to the agent used⁹¹. Rescue of participants with an inadequate response to their current regimen within an RCT is increasingly being included as a standard component of study design. However, the timing of rescue, and how it is measured, may affect withdrawal rates from trials, and these results may be misinterpreted by those conducting systematic reviews and guideline development. For example, in 2 RCT of certolizumab pegol the majority of participants receiving placebo (62.8% and 79.5%) were rescued at Week 16^{68,72}. Of significance, the criteria for rescue likely accounted for the high withdrawal rate in these 2 studies. Thus, instead of the criterion of failing to achieve a 20% improvement in the TJC and SJC, participants failing to achieve an ACR20 response were rescued. Upon further analysis, the primary reason for failing to achieve the ACR20 response related to patient-reported outcomes, not physician or laboratory outcomes (E.C. Keystone, personal communication). This result is consistent with other studies of ACR20 nonresponders⁹². It is also important to note that if there is rescue therapy at 12 weeks, then the maximal ACR response scores could be blunted, as even with fast-acting agents ACR70 improvements usually occur beyond 12 weeks⁹³.

Despite the significant outlay of time and resources to

complete RCT, CADTH, a national body that provides Canada's federal, provincial, and territorial healthcare decision-makers with evidence-based information about the effectiveness and efficiency of drugs, recently excluded certolizumab pegol trials from its metaanalysis and subsequent recommendations for biologics use in Canada⁹⁴. CADTH excluded the certolizumab pegol trials because of the high rate of withdrawals, without fully taking into account the finding that the rescue strategy, and not traditional reasons for withdrawal, influenced the primary results (CRRC, personal communication). Adaptive designs and clinical trial efficiency are considered a current challenge for rheumatology trials^{73,95}.

A high rate of withdrawal is of particular concern when regulatory agencies require radiographic evidence at 52 weeks in order to demonstrate proof of structural improvements in RA trials^{96,97}. In countries such as Canada, defined options for rescue (either blinded or open-label) are increasingly considered necessary by ethics review boards (CRRC, personal communication). In an era of early, rapidly escalated treatment and tight monitoring, it may be time to reassess the optimal use and timing of radiographic outcomes in the context of emerging trial designs^{98,99,100}.

Intraarticular steroid rescue for trials of 6 months or longer. Recommendations: (a) 1 large joint: methylprednisolone acetate 40 mg to 80 mg, triamcinolone acetonide 40 mg, and triamcinolone hexacetonide 40 mg may be given more than 8 weeks from significant endpoints or assessments; and (b) eliminate the injected joint from both clinical and radiographic assessment if intraarticular steroids are given at any time after baseline.

Limited intraarticular injections have been added to RCT as a strategy to retain patients in the trial. The steroid affects the injected joint but also has a systemic impact; a single injection may have a substantial effect on the disease activity state for several weeks^{88,101}.

Longterm extension. Recommendation: Phase IIb, Phase III (and potentially some Phase IV) trials: Participants should be eligible for longterm extension if the experimental product moves forward in development with no safety issues for the patient after the trial closes. The extension should occur at a timepoint most appropriate for the investigational drug to ensure optimal safety and effectiveness for the patient. A statement to this effect should be included in the consent form.

Industry sponsors are increasingly providing open-label access to new drugs after primary endpoints are assessed under randomized and blinded conditions. The utility of open-label studies is currently being addressed in the literature^{102,103,104}. The extension should be timed to ensure optimal safety and effectiveness for trial participants while not jeopardizing blinding or measurement of primary endpoints. Access to efficacious medications that are otherwise unavailable or unaffordable can be an important motivator for patients to participate in clinical trials^{105,106}. A CRRC

needs assessment found that recruitment to RCT without an open-label extension is becoming quite difficult (CRRC, personal communication).

Most regulatory bodies require longterm safety and effectiveness data prior to licensing a new therapeutic agent^{96,97}. In addition, longterm experience is gained by the investigators for the product and provides important information on durability (sustained or improved response, dropout rate due to loss of effectiveness or adverse events), so the risk-to-benefit of a product can be determined over a longer period of time.

DISCUSSION

In recent years, RCT in rheumatology have become increasingly complicated. At the same time, participant recruitment at established rheumatology research sites is increasingly difficult. This situation has created an urgent impetus to modify traditional RCT design. This crisis has been addressed in the literature^{28,49,50,56,73,74,93,95,107,108,109,110,111,112,113,114,115,116,117,118,119}. However, there has been little effect of this body of work on RCT designed and sponsored by the pharmaceutical industry and required by regulators and payers.

The changes that we have outlined should increase the pool of appropriate trial participants by taking into consideration the baseline clinical characteristics of current patients with RA. There is now adequate literature to support these changes based on more recent studies that have generated similar clinical outcomes compared to more standard designs. More studies with these designs are needed to demonstrate comparable radiographic outcomes.

Of significance, the characteristics of patients entering trials with current designs generate results that do not reflect those of clinical practice in the real world^{28,49,50,112,113,114,115,116,117,118,119}. Thus, the lower disease activity of patients in practice may not result in treatment responses (as determined by ACR or EULAR DAS responses) as high as those in clinical trials, but do improve the proportion of patients achieving a low disease state or remission. It is time to adapt clinical trial outcomes to reflect disease states achieved, rather than treatment responses. The use of less stringent inclusion criteria in trials in concert with changes in primary outcomes would go a long way toward improving the generalizability of clinical trials to clinical practice in countries with established rheumatology infrastructure, while at the same time improving the participation of countries where therapies are most utilized.

We also proposed changes in trial design that would enhance the interpretation of the results. Among them is assuring stability of background DMARD to avoid a high placebo response rate, and utilizing higher doses and parenterally administered MTX to identify true MTX inadequate responders. We discussed the challenges of rescue strategies. Such strategies are important to enhance patient

acceptance of participation in a study but may have had unforeseen consequences of inappropriately high withdrawal rates leading to difficulties in the interpretation of results. In particular, short duration on placebo makes the interpretation of radiographic data very difficult and the timing of radiographic endpoints and the interpretation of their clinical significance may need to be reevaluated. It is a useful reminder that the original US Food and Drug Administration guidance document to industry for the acceptance of an indication for prevention of radiographic progression suggested placebo-controlled trials of 2 to 5 years⁹⁶.

We have not addressed many other barriers to clinical trial recruitment such as changing procedures to make trials more attractive to patients. CRRC members have reported that patients who are approached about enrolling in a clinical trial are often frightened by highly legalistic consent forms and inordinate time commitments (CRRC, personal communication). Increasing the number of centers doing trials could improve recruitment, but becoming a successful trialist can be a daunting and expensive task. Nevertheless, if the expertise in conducting clinical trials that has developed over the past 2 decades in established sites is to remain engaged, changes have to be considered. There are many important therapeutic questions remaining to be answered. A move to innovative trial designs is currently being discussed to address a similar crisis in cancer research¹⁵.

There is an urgent need to modify RCT inclusion criteria and other study design features such as primary outcomes to better reflect the current characteristics of people living with RA in the countries where the new drugs will be used. Regulators, scientists, and others involved must address this crisis before we lose our capacity to participate in clinical trials that are relevant to the optimal treatment of our patients.

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