Commentary

Considerations for Optimal Trial Design for Rheumatoid Arthritis Prevention Studies

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ABSTRACT

The field of rheumatology has made major contributions to medicine through the identification of cellular and molecular targets and with the development of therapies for the treatment of an impressive range of immune-mediated rheumatic diseases. In recent years new milestones have been achieved. These include the recognition of an "at risk" state, defined by distinct clusters of characteristics, including disease-specific autoantibodies in serum and symptom complexes that include inflammatory joint pain. Studies seeking to prevent high-risk individuals from progressing to a state of clinically apparent arthritis have been initiated. Here, exploiting the current evidence base, an experimental framework to inform trial design is described, taking into consideration study patient phenotypes and highlighting the impact of risk stratification and the options available for therapeutic intervention according to the different phases of the preclinical syndrome. Pragmatic primary end points and suggestions for a set of risk-focused trial outcome measures are proposed, including both clinical assessments and patient-reported outcome measures. Rheumatoid arthritis prevention studies provide an important experimental framework for generating deeper insights into risk stratification and for refining trial design in the future. To this end, a research agenda is suggested, together with some considerations for imaging and for biological sampling. This commentary concludes with some of the operational issues that arise from such studies and addresses some of the challenges associated with recruitment and retention of the at-risk trial participant. (*Clin Ther*. 2019;41:1299–1311)

Keywords: Rheumatoid arthritis, Trial design, Clinical trails, Prevention.

INTRODUCTION

What might be the realistic goals for rheumatoid arthritis (RA) prevention, given the current state of knowledge? The answer to this question lies in the definitions of prevention.[1] Primary prevention seeks to avoid a disease from developing. For individuals targeted for primary prevention strategies it is implied that features of the disease are absent. Good examples include vaccination to protect against foreign pathogens or smoking cessation strategies. Secondary prevention applies methods to detect and address an existing disease before the onset of symptoms and before the disease fully develops. The treatment of hypertension and hyperlipidemia are good examples. Tertiary prevention aims to return the patient with established disease to full physical, mental, and social health, reducing the harm of active, symptomatic disease by treatment and rehabilitation. This strategy is central to our approach to managing patients with established RA.[2] As rheumatologists we also recognize the concept of quaternary prevention in which strategies are actively applied to mitigate against the effects of unnecessary or excessive interventions.

With these definitions in mind, what are the options for RA prevention? Primary prevention would necessitate intervention (lifestyle modifications, drug therapy, or otherwise) during the asymptomatic phase before detection of RA-associated autoantibodies.[3–5] Here, risk would be attributable to genetic, demographic, and lifestyle factors, as well as to family history. Defining an optimal duration for intervention, including changes to lifestyle behaviors,[4] becomes

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challenging, where risks of therapeutic intervention need to be weighed against the relatively modest risk of developing disease over extended periods of time. Secondary prevention strategies aim to target the higher risk individual who, in addition to the above risk factors, has joint symptoms and carries serum autoantibodies associated with RA; higher risk is linked to the combination of rheumatoid factor and anti–citrullinated protein antibody (ACPA), or high-titer ACPA,[6] and to subclinical evidence of synovitis or osteitis defined by imaging modalities.[7–10] Targeting a higher risk population might justify more robust therapeutic interventions. Although tertiary prevention is less relevant to the present discussion, concepts of quaternary prevention that address issues around risk and benefit of intervention remain relevant. Thus, from our current knowledge and understanding of RA risk,[11] combined with the lack of reliable immune biomarkers that describe a susceptible immune state, a realistic goal for treating individuals during the preclinical phase of RA most closely aligns with concepts of secondary prevention. The current landscape of prevention trials puts this into context (Fig. 1). With this in mind, the remaining commentary focuses on considerations for optimal trial design to prevent (or delay) the onset of established disease in symptomatic individuals deemed to be at high risk.

KEY CONSIDERATIONS FOR TRIAL DESIGN

The Trial Population: What Does an At-risk Trial Patient Look Like?

The contributions of specific factors that confer risk of developing RA have been described in a previous article in this issue,[6] and so they require no further discussion here. Suffice to say that guidelines have been published that describe the essential features of the different phases of the at-risk state, with the intention of harmonizing research studies and clinical trials.[11] Nonetheless, in the setting of recruitment to clinical trials, a robust and systematic assessment of

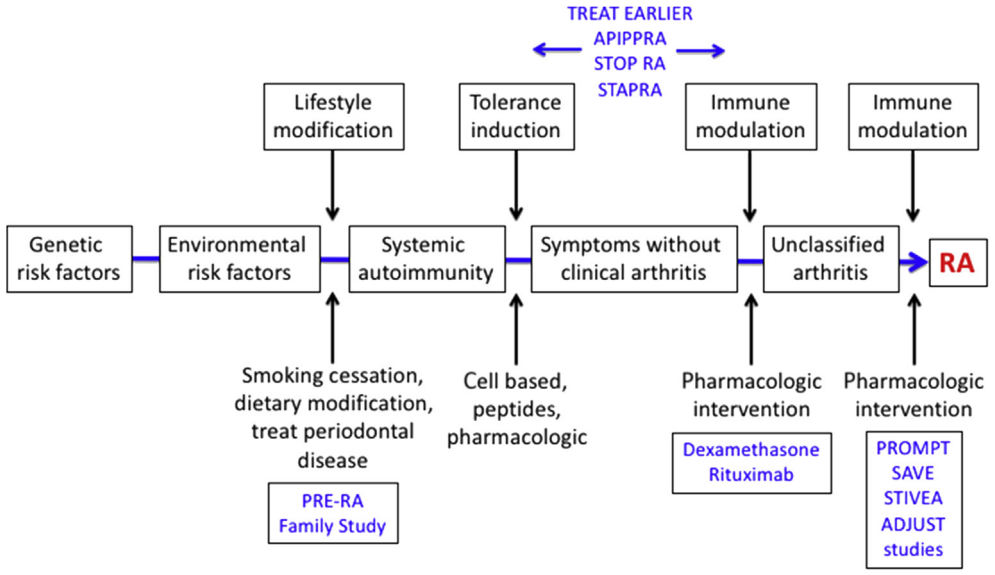

Fig. 1. Overview of strategies for rheumatoid arthritis (RA) prevention. Points of intervention are highlighted (arrows). Completed studies are shown below the boxes, and clinical trials and studies in progress are listed above. ADJUST = Study of Abatacept Versus Placebo to Assess the Prevention of Rheumatoid Arthritis in Adult Patients; APIPPRA = Arthritis Prevention in the Pre-clinical Phase of Rheumatoid Arthritis with Abatacept; PRE-RA = Personalized Risk Estimator for Rheumatoid Arthritis; PROMPT = PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment; SAVE = Stop Arthritis Very Early; STAPRA = Statins to Prevent Rheumatoid Arthritis; STIVEA =Steroids in Very Early Arthritis; STOP RA = Strategy for the Prevention of Onset of Clinically-Apparent RA.

such factors is required to allow the supervising physician to make objective assessments about the phase of RA ("asymptomatic phase" versus "symptomatic phase" versus "onset imminent" versus "very early established RA"), and the level of risk. Assuming that the American College of Rheumatology/European League Against Rheumatism 2010 criteria for the diagnosis are not met[12] and that there is no evidence of clinically apparent synovitis, the absence of these two criteria will best determine whether therapeutic intervention as part of a secondary prevention strategy is appropriate. A robust clinical assessment will also determine whether additional investigations are required or whether a judicious period of monitoring is more appropriate. These key assessments, which can be acquired through structured questionnaires and clinical examination, are summarized in Table I and are informed by published guidelines.[13] This should be viewed as the most basic framework, added to which other variables of risk can be considered. Progression rates ascribed to a range of phenotypes have been described in detail both in this series and elsewhere.[6,10,13]

Refining Risk Stratification for Recruitment to Trials

Risk stratification is discussed in detail in the article by van Boheemen and van Schaardenburg in this issue.[6] In brief, additional assessments can be included, depending on local resources, that may focus on imaging (ultrasonography[9] and magnetic resonance imaging[10]), serology (maturation of the immune response through epitope spreading and isotype usage[14]), and tissue biopsies (lymph node and synovium[15–17]). Algorithms and risk scores, and how they may affect the outcome of interventional studies, have been reported that allow stratification of risk based on likely outcomes over time.[18,19] These can inform discussions with patients, with the caveat that risk strata are based on populations. More precise, personalized risk predictions

Table I. Key assessments for screening at-risk patients.[10]

Screening assessment for RA prevention trial participants	Tasks
History taking	Joint symptoms of recent onset (<12 months)
	Symptoms localized to MCP joints
	Duration of morning stiffness $\geq$ 60 min
	More severe symptoms present in the early morning
	First-degree relative with RA
	Demographic factors (smoker, body mass index)
	No current immunomodulatory drugs or regular use of corticosteroids
Physical examination	Distribution of tender joints
	Difficulty making a fist
	Positive MCP joint squeeze test
	Tenosynovitis
	Absence of joint swelling
	Absence of signs suggestive of other rheumatic diseases (eg, psoriasis, diffuse tender points, advanced degenerative disease in hands)
Imaging (optional)	Evidence of tenosynovitis
	Evidence of gray scale synovitis with power Doppler signal
	Absence of frank tissue damage (eg, erosions)
Laboratory investigations	High titre anti-CCP antibodies (ACPA) and rheumatoid factor
	Evidence of autoantibodies to multiple antigenic epitopes

CCP = cyclic citrullinated peptide; MCP = metacarpophalangeal joint; RA = rheumatoid arthritis.

are likely to be forthcoming when the immunobiology of the preclinical phase and its transition to established disease is better understood. In operational terms, degree of risk will guide the intensity and exposure of the intervention under investigation. It should be born in mind that incorporation of multiple risk factors has the inevitable effect of reducing the pool of potentially eligible patients.

What Are the Characteristics of Patients Likely to Be Less Suitable for RA Prevention Studies?

Experienced physicians recognize new-onset RA when they see it. With the use of the same intuitive processes, specialists have developed a good feel for individuals presenting to their early arthritis clinics with signs and symptoms indicative of a pre-RA inflammatory state.[6,11,13] This RA prodrome may feature a wide spectrum of characteristics, changing over time.[11] Even in the absence of clinically apparent joint swelling, an alert physician will also recognize a state of imminent RA (progression to RA likely in weeks rather than months), perhaps reflected in the severity of symptoms, such as joint pain or fatigue, or the distribution and number of symptomatic joints. Random assignment of extremely high-risk patients to the placebo arm of a clinical trial would be a potential concern. It could also confound evaluation of the therapeutic agent under investigation under circumstances in which the investigational medicinal product (IMP) is not known to elicit rapid clinical responses. This would be as relevant to slow-acting disease modifying antirheumatic drugs as it would to the biologic agents currently licensed for use in established RA, let alone the more experimental tolerance-inducing interventions that lack anti-inflammatory activity in the conventional sense.

In marked contradistinction to the imminent RA group, other groups may be less suitable for prevention studies. For example, risk scores take duration of symptoms into account, and data suggest that patients with arthralgia for >12 months may be at lower risk than patients with symptoms of shorter duration.[18] Whether this points to a distinct subtype of joint pain or to symptoms that are unrelated to an inflammatory process is not entirely clear. In addition, patients also present with more chronic widespread pain, in whom joint assessments could be challenging, especially in the case of symptoms that are clearly unrelated to an inflammatory process. A history suggestive of palindromic symptoms can be trickier to evaluate, given the wide variation in duration and frequency of symptomatic episodes. Rheumatologists have taken the view that in the absence of joint swelling and prior exposure to disease-modifying drugs or corticosteroids, then such individuals might be considered for inclusion. Indeed, published prediction rules for the development of arthritis indicate that intermittent symptoms confer higher risk.[18]

Finally, a common consideration for inclusion into trials of patients with established RA relates to comorbidities. Historically, this has had as much to do with tolerability than anything else. In the context of a prevention trial consideration needs to be given to avoiding treatment of comorbid conditions that could also influence progression of joint signs and symptoms. The intermittent use of corticosteroids for exacerbations of asthma or chronic obstructive pulmonary disease is one example. In the Arthritis Prevention in the Pre-clinical Phase of Rheumatoid Arthritis with Abatacept (APIPPRA) trial we also have been uncompromising about the inclusion of patients with ACPA + arthralgia who have a history of crystal arthropathies, acknowledging that swollen joints attributed to a gout flare could trigger a per protocol primary end point assessment, albeit inadvertently.

Strategies for Identification and Recruitment of the At-risk Patient?

A growing appreciation of the at-risk phenotype prompts two questions. First, has the rheumatology community reached a stage at which active screening to identify at-risk patients in the community should be encouraged? Second, what pathways would allow rheumatologists to capture at-risk individuals in the most time and cost-effective way? These questions are of particular relevance to the clinical trial setting in which the recruitment of at-risk individuals to RA prevention studies is a major challenge. For simplicity, I focus here on the at-risk patient defined simply as an individual positive for ACPA with inflammatory joint pain, because these individuals form the core target population from which a more refined cohort of study patients might be recruited.

In addressing the first question one is minded of the World Health Organisation's guidelines for screening or "Wilson's Criteria," in which strategies focus on identifying the possible presence of an as yet

undefined disease.[20] Although a screening approach may be "universal" (targeting all patients in a certain category) or "case finding" (involving a smaller group of individuals deemed to be at risk), the principles and practice of screening for disease, published by the World Health Organisation in 1968, remain the same. These principles were revised in 2008 with advanced molecular and genomic technologies in mind (Table II).[21]

These guidelines highlight some of the challenges faced by establishing such a screening program. Perhaps the most important, highlighted in Table II, are that there should be a treatment for the condition and an agreed policy on whom to treat. With respect to the preclinical phase of RA these are two areas for which there remains no consensus, and so, for these reasons alone, it would seem premature at this time to consider population-based screening policies. Nonetheless, a systematic approach to identifying robust blood biomarkers as predictors in cohorts of asymptomatic individuals enriched for risk is likely to reap dividends. Whether this would take the form of a whole blood transcriptomic signature, early epigenetic changes to chromatin configurations, or a profile of emerging autoantibodies will require further investigation.

Table II. World Health Organisation guidelines for screening.[20]

Guidelines for Screening
The screening program should respond to a recognized need.
The objectives of screening should be defined at the outset.
A target population should be defined.
Scientific evidence of screening program effectiveness is needed.
The program should integrate education, testing, clinical services, and program management.
Quality assurance, with mechanisms to minimize potential risks of screening, is needed.
The program should ensure informed choice, confidentiality, and respect for autonomy.
The program should promote equity and access to screening for the entire target population.
Program evaluation should be planned from the outset.
The overall benefits of screening should outweigh the harm.

The second question addresses pathways to capture individuals for assessment of risk. This can be achieved in a number of ways, without the need for a formal screening process. Given that the task of identifying at-risk patients and their subsequent assessment should be undertaken by experts in the diagnosis and treatment of patients with inflammatory arthritis, it is logical that early arthritis clinics would operate as the coordinating unit for such activity. Experience suggests that the flow of at-risk patients would likely arise through, or be influenced by, one or more of the following routes. (1) Early arthritis clinics: this route is deemed opportunistic. Referrals from family practitioners in primary care would be enriched for patients with inflammatory joint pain. Some will have tested positive for rheumatoid factor, some for anti–cyclic citrullinated peptide, and some will have tested positive in both assays. (2) Active engagement with primary care: an increased awareness of the concept of the preclinical phase of RA, and the phenotypes of at-risk individuals, has already begun to influence the threshold for rheumatoid factor and/or anti–cyclic citrullinated peptide testing in the community. (3) Primary care database searches: databases in primary care provide ideal platforms to screen for patients with joint pains. Search strategies can be stratified by sex, age, and, if already available, positive testing for RA-associated autoantibodies. At the same time concurrent medications will identify patients who have already been given a diagnosis of RA or other form of inflammatory arthritis. This approach has already been applied successfully to recruitment in the clinical trial setting. (4) Screening of clinical laboratory results: autoantibody tests are provided by most National Health Service Trusts in the United Kingdom. Some of the larger and more specialized clinical immunology laboratories, often those affiliated with a clinical immunology service, may serve multiple hospitals. Depending on the unit, laboratories may run many thousands of tests per year, including but certainly not confined to requests from local rheumatology services. Experience suggests that positive results commonly arise through testing initiated outside the rheumatology setting, such as from the emergency department or form other medical specialties. Picking up these results and engaging with

the supervising physician can be helpful, and invariably patients benefit. (5) Education and public engagement: concepts of screening and prevention for cardiac disease and cancer are better appreciated than those emerging for rheumatic disease. Campaigns aimed at educating the public about rheumatic symptoms increase awareness of risk and will prompt assessments in primary and secondary care. RheumaBus and Health Fairs provide good examples, specifically focused on screening for patients with inflammatory-sounding joint pains "on the high street."[22] Thus, pathways for identifying patients at risk of developing RA depend not only on awareness of primary and secondary care physicians but also on at-risk individuals themselves.

Some Reflections on Communicating Risk in the Clinic

Risk is associated with the disease itself, as well as the intervention being introduced to prevent it. Discussing new diagnoses with patients has been the work of physicians for centuries. With few exceptions, physicians are much less familiar with communicating concepts of risk before the disease has started, because, until relatively recently, this has been the domain of the clinical geneticist. It can be useful when confronted with an individual deemed to be at high risk of RA to provide examples of preventative medicine, especially at the time when individuals are considering consenting to participate in a clinical trial. At a follow-up APIPPRA study investigator meeting in May 2017, the attendees, who included patient experts, were invited to suggest suitable examples of prevention strategies for discussion with the at-risk patient. They were encouraged to explore interventions that encompassed lifestyle changes, as well as examples of oral and parenteral medication. Popular and rather obvious suggestions included weight loss, smoking cessation, the use of medications for control of hypertension and hypercholesterolemia to prevent future cardiovascular events, the use of daily injections of insulin for glycemic control, and the self-administration of low molecular weight heparin for prophylaxis against venous thromboembolism. Although simple in concept, these examples resonate with many individuals, especially those with first- or second-hand experience of such strategies. In our unit, we have found this approach helpful when recruiting at-risk study patients to trials. Notwithstanding this, perceptions of risk differ between individuals, rather like financial risk, with ethnic and cultural differences, age, as well as personal experiences associated with family history, all playing an important role in the decision-making process.

Patients recognize concepts of "harm," and so a discussion about how disease-associated immune reactions (eg, ACPAs) can be harmful to joint and bone tissues might be appropriate for some at-risk individuals.[23,24] Useful analogies might include the pain, inflammation, and damage associated with periodontal disease and the development of dental caries, or the immune reactions that destroy insulin-producing β-islet cells in patients with type 1 diabetes.

As rheumatologists, we are more familiar with communicating risks associated with therapy.[25] During the consenting process, an open discussion will need to address risks versus benefits associated with lifestyle versus medication and those risks associated with the spectrum of conventional and biologic drugs. The value of evidence acquired from after-marketing surveillance and biologics registries in communicating safety profiles cannot be underestimated,[26] because they give reassurance to the at-risk patient and some confidence to the prescribing physician. The more experimental interventions, be they first-in-disease or first-in-man, inevitably present different challenges. Thus, there is value in collecting data on perceptions of risk in the trial setting.

Duration of Therapy and Follow-up

A major challenge rheumatologists face in prevention trials is to limit exposure to the study drug to the minimum period of time that permits a strong likelihood of evaluating the degree of benefit, based on the mechanism of action of the study drug, without unnecessary exposure and its associated risks. The second challenge depends on the specific question the clinical trial seeks to address. If the study is more exploratory, investigating symptom control or modification of pathogenic immune responses in an at-risk population, then the period of exposure might be considerably shorter (eg, 3−6 months) than a trial aimed at prevention requiring complete suppression of the evolving pathology. Furthermore, if the study seeks to prevent disease progression, or even reversal toward a healthy state, then after an appropriate period of study IMP, a defined period off the study drug will be necessary. Recent and currently recruiting

RA prevention trials have adopted similar approaches, in which the period of follow-up is determined to an extent by the impact of the intervention and the primary outcome (Table III). When end points are directly associated with disease progression, then the period of follow-up will be determined by the risk state and its associated progression rate.

These trial designs highlight the relationship between drug mode of action and sample size, as well as the follow-up period, and clearly differ from contemporary approaches for preventing cardiovascular disease. Time will tell as to whether RA prevention adopts the fixed period approach associated with cancer remission-inducing protocols or whether they morph into chronic therapy, rather like antihypertensive agents. The potential for reversibility of harmful autoimmune reactions by inducing immune tolerance at different stages of pre-RA will undoubtedly influence the approaches used. Opportunities for reducing disease-associated comorbidities at the same time is tantalizing because, by preventing progression of systemic inflammatory responses, there may be additional benefits such as prevention of cardiovascular disease. Ultimately, the type of therapy, the mode, frequency, and duration of administration must be acceptable to patients.[27]

What Do At-risk Patients Stand to Gain From Participating in RA Prevention Trials?

Patients increasingly recognize the concept that research can be good for your health, and many find the opportunity to participate in studies that would benefit individuals in the future rewarding. This can be for a multitude of reasons, including access to expert clinicians in secondary care, access to new therapies, opportunities to experience more comprehensive clinical assessments, regular follow-up with the same clinical assessors, and prompt access to study teams as and when required. Accepting that standard of care is equivalent to best care and that there are no accepted guidelines for either the treatment or follow-up of patients at high risk of RA, offering regular follow-up and detailed assessments in a specialist unit could be viewed as an attractive option. For example, access to an expert team offers the prospect of prompt therapy in the event that the disease progresses to clinically apparent arthritis. In the context of a prevention trial, the latter scenario might justifiably be deemed the "worst case scenario," regardless of whether the study patient was randomly assigned to IMP or placebo. Complete resolution of symptoms, at the other extreme, might be considered a much better outcome and if sustained could be considered the "best case scenario." In our experience, patients appreciate open discussion about the spectrum of possible outcomes.

Study Design

Some of the trial design options, with randomized, placebo-controlled parallel group studies being the most commonly adopted to date, are described in Fig. 1. The control group may receive no intervention, as in the case of lifestyle modifications, placebo alone

Table III. Rheumatoid arthritis prevention trial design, intervention, and follow-up.

Study/Drug	Sample Size	Intervention	Primary Outcome	Period of Follow-up, mo
Steroids	83	Dexamethasone	50% reduction of antibodies	26
PRAIRI	82	Rituximab	Clinical arthritis	29
APIPPRA	206	Abatacept	Clinical arthritis or rheumatoid arthritis	24
ARIAA	95	Abatacept	Change in inflammation	18
Treat Earlier	200	Depo/methotrexate	Clinical arthritis	24
STAPRA	220	Atorvastatin	Clinical arthritis	48
StopRA	200	Hydroxychloroquine	Clinical arthritis	36

APIPPRA = Arthritis Prevention in the Pre-clinical Phase of Rheumatoid Arthritis with Abatacept; ARIAA = Abatacept Reversing Subclinical Inflammation as Measured by MRI [magnetic resonance imaging] in ACPA [anti-citrullinated protein antibody] Positive Arthralgia; PRAIRI = Prevention of RA by Rituximab; STAPRA = Statins to Prevent Rheumatoid Arthritis; StopRA = Strategy for the Prevention of Onset of Clinically-Apparent RA [rheumatoid arthritis].

(as in the case of APIPPRA, Stop RA, and Treat Earlier studies), or the administration of corticosteroids (as in the case of the PRAIRI study, to blind for the administration of concomitant steroids given with rituximab).[28] Given the range of therapeutic interventions available (Fig. 1)[3] and the current uncertainties as to how each therapeutic target contributes to the distinct phases of pre-RA, a more innovative adaptive trial design would permit switching of interventions according to outcomes associated with symptoms control but before the onset of clinical arthritis. Here, the aim would be to prevent progression with the use of serial or combinations of interventions, an approach similar to that used for optimizing treatment of patients with established RA.

Trial end points

Prevention studies are similar to drug tapering or withdrawal studies,[28,29] in which the end point is progression or flare defined by worsening of signs and/or symptoms. This contrasts to the more traditional efficacy study in established active disease in which trial readouts focus on suppression of disease. For primary prevention studies end points should focus on the progression from a disease or symptom-free state to the onset of symptoms. In this context, progression could manifest as onset of symptoms, onset of symptoms and signs (such as joint swelling), or fulfilling disease classification criteria. In secondary RA prevention studies, the prodrome manifests as joint pain and the presence of disease-associated autoantibodies, and so a logical progression event would be the development of joint swelling.[28]

Joint swelling is a pragmatic end point because it achieves two goals. First, in the trial setting it signals in an unambiguous way that the disease has progressed. Second, progression to this state triggers a therapy decision, because trial IMP under these circumstances would be withdrawn and replaced by standard treatment for new-onset RA, for example. At first sight this seems straightforward. Given that joint swelling can be a rather subjective assessment, especially in the earliest stages of undifferentiated inflammatory arthritis, documenting with confidence that a joint is swollen raises some challenges.

Several pragmatic approaches can be adopted to provide confidence in documenting swollen joints for the first time. This includes confirmation by independent

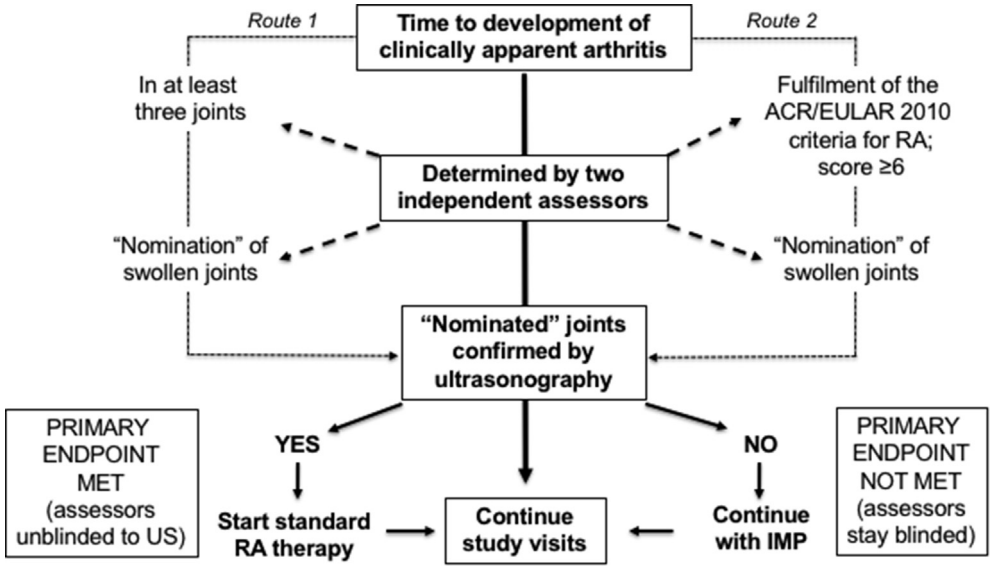

Fig. 2. The primary end point roadmap. A pragmatic approach for assessing the key milestone of clinically apparent arthritis. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; IMP = investigational medicinal product; RA = rheumatoid arthritis; US = ultrasonography.

blinded assessors[28] and/or follow-up assessment at an appropriate interval to reproduce an assessors' initial findings and to confirm the persistence of clinical arthritis. The number and distribution of joints will provide additional confidence and rule out joint swelling from causes other than imminent RA. An alternative or complimentary approach is to apply imaging modalities to confirm evidence of synovitis in nominated joints in a more objective way. This is the approach rheumatologists have adopted in APIPPRA, illustrated in Fig. 2, and undertaken by the same ultrasonographers who completed the routine ultrasonographic study assessments up until the time of the primary end point assessment. This, together with clinical assessments of extended joint counts, has provided a robust platform for studying how joint symptoms and signs progress throughout the pre-RA state and for defining the primary end point with confidence.

Secondary and Exploratory Outcome Measures

Generic questionnaires that interrogate aspects of health status, such as pain, fatigue, and function, will be of value in assessing progression to disease in at-risk patients in the trial setting. Understanding and documenting the earliest symptom complexes should give us more insights into this phase of RA's natural history. In contrast, tried and tested assessments of disease activity applied to established disease may not be sensitive enough or appropriate for evaluating patients with pre-RA, especially when symptoms are modest or even absent. The Modified Illness Perception Questionnaire and the Symptoms in Persons At Risk of Rheumatoid Arthritis questionnaire are examples of just two at-risk–focused patient-reported outcomes that are currently being evaluated

Table IV. Sample outcome measures for rheumatoid arthritis prevention trials.

Outcome Measure
Perceptions of trials questionnaire
Lifestyle factors questionnaire
Health assessment questionnaire
Illness perception questionnaire
EuroQol instruments
Hospital anxiety and depression scale
Functional assessment of chronic illness therapy
Work instability scale

Table V. Challenges and solutions.

Challenge	Solution
Impractical study design	Patient focus groups
Poor or slow recruitment	Optimize recruitment pathway options in primary and secondary care from the outset
Inappropriate study population	Adopt robust inclusion and exclusion criteria; continuous monitoring of study sites
Baseline and primary end point assessments	Inclusion of independent assessors and use of imaging modalities
Higher risk of participant withdrawals	Participant education; informative consenting process with attention to detail in participant information brochures; frequent contact with study team for at least the first 3–6 months
Managing participant withdrawals	Continue to capture outcomes for those who do not continue on IMP; apply conservative estimates to account for dropout rates
IMP adherence	Adopt IMP diary; frequent contact for first 3–6 months; serum assays to measure study drug over duration of dosing period
Logistics of biological sampling	Establish laboratory hubs for sample processing, strategically spread across recruiting centers aiming for sampling to laboratory time <4 h

IMP = investigational medicinal product.

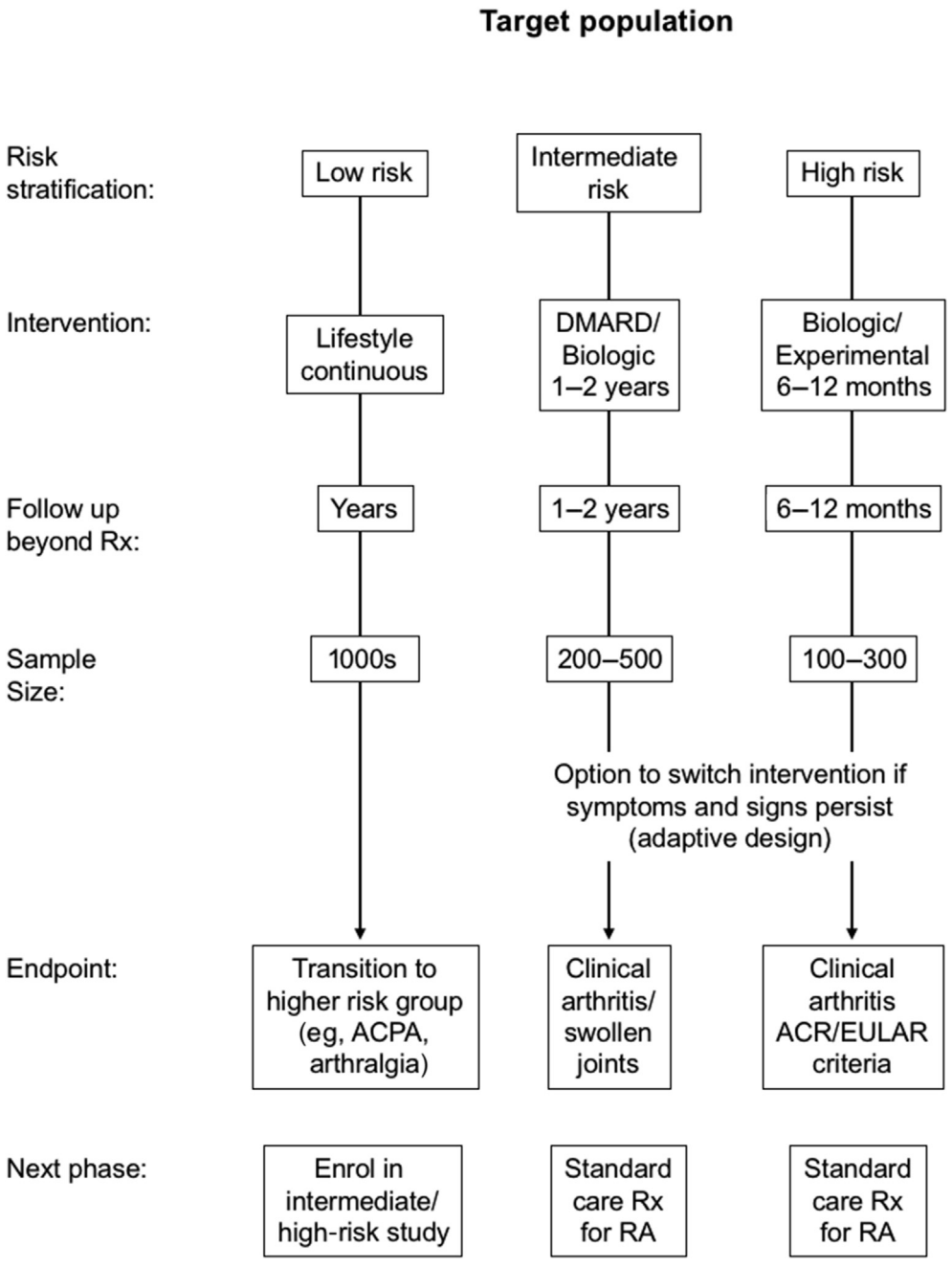

Fig. 3. A rheumatoid arthritis (RA) prevention trial roadmap. The relationship between risk, intervention, follow-up, sample size, and end points and how study patients might be managed beyond the lifetime of the study. ACPA = anti–citrullinated protein antibody; ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; Rx = medical prescription.

in the setting of RA prevention trials. A set of sample assessments currently in use in prevention trials is summarized in Table IV.

Operational Challenges and Solutions

RA prevention trials present challenges. Some are generic to RA, whereas others are more unique to the at-risk phase of the disease. It is appropriate to share some of these here and to offer some solutions that may inform and enrich the design of future studies (Table V).

THE RESEARCH AGENDA

RA prevention studies are still in their infancy, and so the learning curve remains steep. Accordingly, collective efforts should be made to capitalize on experiences to date and to design studies in ways that will generate new knowledge to inform better study design in the future. Above all, these trials are about risk. Fig. 3 summarizes the relationship between risk, intervention, follow-up, sample size, and end points, and how study patients may be managed beyond the life of the study. With these in mind, there are a number of strategic research goals that could be considered to be included in the design of future prevention trials. These include, but should not be confined to, (1) in-depth understanding of symptom complexes from the outset of the preclinical phase and how they evolve over time; (2) immune phenotyping and mapping the evolution of immune reactivities, most easily achieved through an analysis of ACPA (fine specificities, epitope spreading, isotype usage) and analysis of T- and B-cell receptor clonal diversity; (3) development of guidelines for imaging assessments in patients with clinically suspicious arthralgia with the use of conventional modalities; (4) evaluation of new, sensitive imaging tools (eg, using radio-isotope–based methods) for quantifying subclinical inflammation at a whole-body level and to identify patients at highest risk, while excluding patients with features suggestive of other rheumatic diseases; (5) generation and validation of relevant outcome measures for prevention trials, including primary end points and a core set of outcomes to be used in all trials; (6) development of a portfolio of at risk-focused reported questionnaires; (7) expanding the repertoire of seropositive RA patients in those deemed seronegative by conventional clinical laboratory testing (ie, negative for rheumatoid factor and ACPA), thereby increasing the target population for prevention studies; and (8) understanding the pathophysiology of disease to identify new targets for prevention.

In the longer term this tool box could be used as an experimental framework to facilitate recruitment of more homogeneous subgroups of study patients to prevention trials, aligned to the intervention under investigation.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The past decade has seen major advances in the field of RA prevention. At-risk populations are now increasingly recognized, many cohorts have been established, and interventional trials are under way. In the future it should be feasible to define the different stages of the at-risk phenotype with more precision, including molecular and cellular signatures. The target population is likely to shift to earlier and earlier stages, at which point therapies with anti-inflammatory activity may be less effective, requiring consideration of more experimental therapies in populations in whom the progression rates may be low and slow. Regardless of the trial setting, capturing data to compute health economic costs as well as adverse and serious adverse events will help to determine whether interventions are cost-effective and at least as tolerable in prevention studies as they are in established disease. For these and many other reasons, the community should be encouraged to engage with their national regulatory authorities to discuss the regulatory roadmap and requirements to licensing.[30] By doing this rheumatologists will be in a better position to offer preventative strategies to a broader group of at-risk individuals. A fine line exists between primary and secondary prevention. If primary prevention is the ultimate goal, then these discussions will be invaluable.

CONFLICT OF INTEREST

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