Considerations for optimal trial design for RA 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 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 subject 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. RA prevention studies provide an important experimental framework for generating deeper insights into risk stratification and 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.
Introduction

What might be the realistic goals for 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 hyperlipidaemia 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 prior to detection of RA-associated autoantibodies [3-5]. Here, risk would be attributable to genetic, demographic and lifestyle factors, as well as family history. Defining an optimal duration for intervention, including changes to lifestyle behaviours [4], becomes 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 ACPA, or high titre ACPA [6], and to sub-clinical evidence of synovitis or osteitis defined by imaging modalities [7-10]. Targeting a higher risk population might justify more robust therapeutic interventions. While tertiary prevention is less relevant to the current discussion, concepts of quaternary prevention that address issues around risk and benefit of intervention remain relevant. Thus, based on our current knowledge and understanding of RA risk [11], and the lack of reliable immune biomarkers that describe a susceptible immune state, a realistic goal for treating individuals during the pre-clinical phase of RA most closely aligns with concepts of secondary prevention. The current landscape of prevention trials puts this into context (Figure 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 subject look like?_

The contributions of specific factors that confer risk of developing RA has been described in a previous chapter in this series [6], and so 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 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 ACR/EULAR 2010 criteria for the diagnosis [12] are not met, 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, 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 1 and informed by recent published guidelines [13]. This assessment can be seen as the most basic framework, upon which other parameters 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

These are covered in detail in the Chapter by van Boheemen and van Schaardenburg [6]. In brief, additional assessments can be included, depending on local resources, that may focus on imaging (ultrasonography – US [9], and magnetic resonance imaging - MRI [10]), serology (maturation of the immune response through epitope spreading an isotype usage [14]) and tissue biopsies (lymph node and synovium [15-17]). Algorithms and risk scores, and how they may impact 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, and that more precise, personalized risk predictions 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 subjects.

*Which subjects might be considered less suitable for RA prevention studies?*

Experienced physicians recognise new onset RA when they see it. Using 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 be in a position to recognise 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. Randomisation of extremely high risk subjects to the placebo arm of a clinical trial would be a potential concern from the perspective of the at risk subject. It could also confound evaluation of the therapeutic under investigation under circumstances where the IMP does not affect rapid clinical responses. This would as relevant to slow acting DMARDs 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 this imminent RA group, there are other groups who may be less suitable for prevention studies. For example, risk scores take duration of symptoms into account, and data suggest that subjects with arthralgia for > 12 months may be at lower risk than those 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. There are also subjects presenting with more chronic widespread pain, in whom joint assessments could be challenging, especially in the case of symptoms are clearly unrelated to an inflammatory process. A history suggestive of palindromic symptoms can be more tricky to evaluate, given the wide variation in duration and frequency of symptomatic episodes, but we 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 co-morbidities. Historically this has had as much to do with safety than anything else, but in the context of a prevention trial consideration needs to be given to avoiding treatment of co-morbid 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 APIPPRA trial we also have been uncompromising about the inclusion of ACPA+ arthralgia subjects who have a history of crystal arthropathies, acknowledging that swollen joints attributed to a gout flare could trigger a per protocol primary endpoint assessment, albeit inadvertently.

Strategies for recruitment of the at risk patient?

A growing appreciation of the “at risk” phenotype prompts two questions. Firstly, has the rheumatology community reached a stage at which active screening to identify at
risk subjects in the community should be encouraged? Secondly, 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 subject defined simply as an ACPA positive individual with inflammatory joint pain, since these individuals form the core target population from which a more refined cohort of study subjects might be recruited.

In addressing the first question one is minded of the World Health Organisation’s guidelines for screening or “Wilson’s Criteria”, where strategies focus on identifying the possible presence of an as yet undefined disease [20]. While a screening approach may be “universal” (targeting all subjects 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 WHO in 1968, remain the same. These principles were revised in 2008 with advanced molecular and genomic technologies in mind (Table 2) [21].

These guidelines highlight some of the challenges faced by establishing such a screening programme. Perhaps the most important, highlighted in Table 2, 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 to consider population-based screening policies. Nonetheless, there remains
enthusiasm for exploiting the existence of cohorts of subjects enriched for risk, such as family-based studies.

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 subjects 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 in most centres. Experience suggests that the flow of at risk subjects 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 subjects with inflammatory joint pain. Some will have tested positive for rheumatoid factor (RF), some for anti-CCP 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 RF and/or anti-CCP testing in the community.

(3) Primary care database searches: databases in primary care provide ideal platforms to screen for subjects with joint pains. Search strategies can be stratified by gender, age and, if already available, positive testing for RA associated autoantibodies. At the same time concurrent medications will identify those 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 the majority of NHS Trusts in the UK. Some of the larger and more specialised 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 room or from 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 subjects with inflammatory sounding joint pains “on the high street” [22].

Thus, pathways for identifying subjects at risk of developing RA depend not only on awareness of primary and secondary care physicians, but on at risk individuals themselves.
Communicating risk

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, we are much less familiar with communicating concepts of risk before the disease has started, since, 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, which included patient experts, were invited to suggest suitable examples of prevention strategies for discussion with the at-risk subject. 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 hypercholesterolaemia to prevent future cardiovascular events, the use of daily injections of insulin for glycaemic control, and the self-administration of low molecular weight heparin for prophylaxis against venous thromboembolism. While 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 subjects 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 recognise concepts of “harm”, and so a discussion about how disease associated immune reactions (e.g. 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 I 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 post marketing surveillance and biologics registries in communicating safety profiles cannot be under-estimated [26], since they give reassurance to the at risk subject 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 we face in prevention trials is to limit exposure to 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 study drug, without unnecessary exposure and its associated risks. The second challenge depends on the specific question the clinical trial is seeking to address. If the study is more exploratory, and investigating symptom control or modification of pathogenic immune responses in an
at risk population, then the period of exposure might be considerably shorter (e.g. 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 towards a healthy state, then after an appropriate period of study IMP, a defined period off 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 3). When endpoints 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 traditional cancer remission inducing protocols or whether they morph into chronic therapy, rather like anti-hypertensives. The potential for reversibility of harmful autoimmune reactions by inducing immune tolerance at different stages of pre-RA will undoubtedly influence the approaches used. Ultimately, the type of therapy, the mode, frequency and duration of administration must be acceptable to patients [27].

*What do at risk subjects stand to gain from participating in RA prevention trials?*

Patients increasingly recognise the concept that research can be good for your health. 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 subject was randomised 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

Figure 1 illustrates some of the trial design options, with randomised, placebo controlled parallel group studies being the most commonly adopted to date. The control group may receive no intervention, as in the case of lifestyle modifications, placebo alone (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 (Figure 1; ref 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 prior to the onset of clinical arthritis.
Here, the aim would be to prevent progression using serial or combinations of interventions, an approach similar to that used for optimising treatment of patients with established RA.

**Trial endpoints**

Prevention studies are similar to drug tapering or withdrawal studies [28,29], where the endpoint 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 endpoints 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 endpoint as it achieves two goals. Firstly, in the trial setting it signals in a rather unambiguous way that the disease has progressed. Secondly, 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 very straightforward. Given that joint swelling can be a rather subjective assessment, especially in the very earliest stages of undifferentiated inflammatory arthritis, documenting with confidence that a joint is swollen raises some challenges.
There are several pragmatic approaches that can be adopted to provide confidence in documenting swollen joints for the first time, including confirmation by independent 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 we have adopted in APIPPRA, illustrated in Figure 2, and undertaken by the same ultrasonographers who completed the routine US study assessments up until the time of the primary endpoint 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 endpoint 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 subjects in the trial setting. Understanding and documenting the very 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, nor appropriate for evaluating subjects with pre-RA, especially where symptoms are modest or even absent. The Modified Illness Perception Questionnaire (Modified IPQ) and the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire are examples of just two at risk focused patient
reported outcomes that are currently being evaluated in the setting of RA prevention trials. A set of sample assessments currently in use in prevention trials is summarised in Table 4.

**Operational challenges and solutions**

RA prevention trials present challenges. Some are generic to RA, while 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 5).

**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 capitalise 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. Figure 3 summarises the relationship between risk, intervention, follow up, sample size and endpoints, and how study subjects 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:

- In depth understanding of symptom complexes from the outset of the preclinical phase and how they evolve over time
- 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 cell and B cell receptor clonal diversity
• Development of guidelines for imaging assessments in subjects with clinically suspicious arthralgia using conventional modalities
• Evaluation of novel, sensitive imaging tools, e.g. using radio-isotope based methods, for quantifying sub-clinical inflammation at a whole body level, and to identify those at highest risk, while excluding those with features suggestive of other rheumatic diseases
• Generation and validation of relevant outcome measures for prevention trials, including primary endpoints and a core set of outcomes to be used in all trials
• Development of a portfolio of at risk focused reported questionnaires
• Expanding the repertoire of seropositive RA subjects in those deemed seronegative by conventional clinical laboratory testing (i.e. negative for rheumatoid factor and ACPA), thereby increasing the target population for prevention studies

In the longer term this “tool box” could be used as an experimental framework to facilitate recruitment of more homogeneous sub-groups of study subjects to prevention trials, aligned to the intervention under investigation.

**Concluding remarks and future perspectives**

The last decade has seen major advances in the field of RA prevention. At risk populations are now increasingly recognised, 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 where 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 safe 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 we will be in a better position to offer preventative strategies to a broader group of at risk individuals. There exists a fine line between primary and secondary prevention. If primary prevention is the ultimate goal then these discussions will be invaluable.
Considerations for optimal trial design for RA prevention studies

References


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### Tables

**Table 1: Key assessments for screening at risk subjects**

<table>
<thead>
<tr>
<th>Screening assessment for RA prevention trial participants</th>
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#### History taking:
- Joint symptoms of recent onset (< 12 months)
- Symptoms localised to MCP joints
- Duration of morning stiffness ≥ 60 mins
- More severe symptoms present in the early morning
- First degree relative with RA
- Demographic factors (smoker, BMI)
- 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 grey 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

adapted from van Steenbergen et al 2017 [10]
Table 2: WHO guidelines for screening 2008 (adapted from ref XXX)

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.
Table 3: RA prevention trial design, intervention and follow up

<table>
<thead>
<tr>
<th>Study/Drug</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Period of follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>83</td>
<td>dexamethosone</td>
<td>50% reduction Ab</td>
<td>26 months</td>
</tr>
<tr>
<td>PRAIRI</td>
<td>82</td>
<td>rituximab</td>
<td>clinical arthritis</td>
<td>29 months</td>
</tr>
<tr>
<td>APIPPRA</td>
<td>206</td>
<td>abatacept</td>
<td>clinical arthritis or RA</td>
<td>24 months</td>
</tr>
<tr>
<td>ARIA A</td>
<td>95</td>
<td>abatacept</td>
<td>change in inflammation</td>
<td>18 months</td>
</tr>
<tr>
<td>TREAT EARLIER</td>
<td>200</td>
<td>depo/MTX</td>
<td>clinical arthritis</td>
<td>24 months</td>
</tr>
<tr>
<td>STAPRA</td>
<td>220</td>
<td>atorvastatin</td>
<td>clinical arthritis</td>
<td>48 months</td>
</tr>
<tr>
<td>STOPRA</td>
<td>200</td>
<td>hydroxychloroquine</td>
<td>clinical arthritis</td>
<td>36 months</td>
</tr>
</tbody>
</table>
Table 4: Sample outcome measures for RA prevention trials

- 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 5: Challenges and solutions

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
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<tbody>
<tr>
<td>Impractical study design</td>
<td>Patient focus groups</td>
</tr>
<tr>
<td>Poor or slow recruitment</td>
<td>Optimise recruitment pathway options in primary and secondary care from the outset</td>
</tr>
<tr>
<td>Inappropriate study population</td>
<td>Adopt robust inclusion and exclusion criteria; continuous monitoring of study sites</td>
</tr>
<tr>
<td>Baseline and primary endpoint assessments</td>
<td>Inclusion of independent assessors and use of imaging modalities</td>
</tr>
<tr>
<td>Higher risk of participant withdrawals</td>
<td>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</td>
</tr>
<tr>
<td>Managing participant withdrawals</td>
<td>Continue to capture outcomes for those who do not continue on IMP; apply conservative estimates to account for dropout rates</td>
</tr>
<tr>
<td>IMP adherence</td>
<td>Adopt IMP diary; frequent contact for first 3-6 months; serum assays to measure study drug over duration of dosing period</td>
</tr>
<tr>
<td>Logistics of biological sampling</td>
<td>Establish laboratory hubs for sample processing, strategically spread across recruiting centres aiming for sampling to lab time &lt; 4hrs</td>
</tr>
</tbody>
</table>
Figures

**Figure 1: Overview of strategies for 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.

**Figure 2: The primary endpoint roadmap.** A pragmatic approach for assessing the key milestone of clinically apparent arthritis.

**Figure 3: An RA prevention trial roadmap.** The relationship between risk, intervention, follow up, sample size and endpoints, and how study subjects might be managed beyond the lifetime of the study.
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