



Evidence-based Practice Center Systematic Review Protocol

Project Title: Drug Therapy for Early Rheumatoid Arthritis in Adults – An Update

I. Background and Objectives for the Systematic Review

A. Background of Disease

Epidemiology

Rheumatoid arthritis (RA), an autoimmune systemic inflammatory arthritis condition, affects 1 percent of the world's population, including more than 1 million American adults.¹ RA causes inflammation of the synovial lining of joints, leads to progressive erosion of bone (in most cases to irreversible damage to the joint), loss of function, and disability. The average annual incidence of RA in the United States is approximately 70 per 100,000 annually.² Onset of RA can begin at any age but increases with age; onset is highest at 60 years.³ Incidence of RA is 2 to 3 times higher in women.

Etiology

Multiple environmental and genetic factors contribute to the development of RA. Obesity and smoking increase the risk of RA.³ Women who have not given birth may also be at greater risk of developing RA.³ Rates of RA development are increased in monozygotic twins, implicating genetics as a contributing factor.⁴ Genome-wide association studies have characterized over 100 loci associated with RA risk, most involving immune mechanisms.⁵ Epigenetics, through the integration of environmental and genetic factors, also contributes to the pathogenesis of RA.⁶ Environmental risk factors associated with RA, though not well understood, include smoking, low socioeconomic status, and viral and bacterial infections.⁷⁻⁹ Additionally, researchers using animal model studies are investigating the microbiome effect on RA disease risk.¹⁰

Burden of Disease

Disability associated with RA is significant. Over 35 percent of patients with RA have work disability after 10 years.¹¹ The life span of patients with RA is 3 to 12 years less than that of the general population.¹² Patients with high disease activity have increased risk of cardiovascular disease that contributes to higher mortality risk.

Definitions of Early RA and Challenges With the Definitions

No consensus exists on the definition of early RA. Expert group definitions range from defining early RA at the onset of when symptoms develop to when early RA is diagnosed by a clinician. The American College of Rheumatology (ACR) uses a duration of fewer than 6 months of symptoms of disease,¹³ other organizations have advocated for a later cut off of up to 2 years after diagnosis.^{14, 15} Experts guide their initial treatment

recommendations based on time from diagnosis, or more stringently, on time from initial symptoms.

From a pathophysiology perspective, synovial cytokine patterns (inflammatory mediators) differ at the 4-month mark of initial symptoms of RA,¹⁶ which are thought to be important in the response to therapy. Based on these findings, many clinicians advocate starting therapy (methotrexate [MTX] preferred) by the 3-month mark of initial symptoms of RA. However, data on disease-modifying antirheumatic drug (DMARD) use in the first 3 months are limited. Additionally, at this early stage, many patients may not meet the criteria for diagnosis but have features that predict a high risk of disease progression to RA.¹⁷ The course of RA is highly variable; some researchers have suggested defining early RA as before development of bone erosion, but some patients never develop erosions. Given this variability, a recent task force of experts in RA and clinical trial methodology recommended defining early RA as no more than 1 year of diagnosed disease duration.¹⁸

Disease activity, categorized as low, moderate, and high by validated scales, can guide choice and change of DMARD therapy.¹⁹ Disease activity, as well as structural damage observed on X-rays and functional assessments, should be measured regularly. Based on these findings, drug therapy may need to change at regular intervals until the treatment target, ideally remission, is reached.

B. Current Practice and Treatment Strategies

In patients newly diagnosed with RA (early RA), the goal is early treatment with rapid, sustained remission. Treatment of RA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability.

The ACR recommends a treat-to-target approach to remission or low disease activity rather than a nontargeted approach, for symptomatic early RA, based on a low level of evidence.¹³ Treating to target includes regular monitoring of disease activity and adverse events and escalating treatment according to treatment protocols if a treatment target (ideally remission) is not achieved.¹⁹ DMARD monotherapy (MTX preferred) is recommended instead of double or triple therapy in patients who have never taken a DMARD.¹³ If disease activity remains moderate or high, double or triple combination DMARDs or a tumor necrosis factor (TNF) or non-TNF biologic DMARD is recommended (with or without MTX). Low-dose glucocorticoids (≤ 10 mg/day prednisone or equivalent) are recommended to be added if disease activity is moderate or high despite DMARD use.¹³ The European League against Rheumatism (EULAR) task force recommends starting treatment with DMARDs as soon as the RA diagnosis is made. They also recommend a treat-to-target approach to remission or low disease activity. EULAR advocates for the efficacy of conventional synthetic DMARDs (csDMARDs) (hydroxychloroquine, leflunomide, methotrexate, sulfasalazine), as monotherapy or combination therapy with leflunomide or sulfasalazine as the initial DMARD treatment strategy. If the treatment target is not achieved with the first DMARD, such as MTX, a different csDMARD (e.g., sulfasalazine or leflunomide) should be considered in the absence of poor prognostic factors (e.g., high disease activity, early joint damage, autoantibody positivity). If poor prognostic factors are present, addition of a TNF or non-TNF biologic is recommended. They also now regard all

currently approved biologic DMARDs as similarly effective (with the exception of anakinra, which has not shown strong efficacy when compared with other DMARDs) and similarly safe after csDMARD failure.²⁰ Anakinra was not included in ACR guidelines because of its infrequent use in RA and lack of new data since 2012.¹³

FDA-Approved Drugs

Available DMARD therapies for RA include corticosteroids, csDMARDs, TNF and non-TNF biologics, targeted synthetic DMARDs (tsDMARDs), and biosimilars (see Table 1).

Table 1. U.S. Food and Drug Administration (FDA)–approved drugs for RA

Group	Names
Corticosteroids	Methylprednisone, prednisone, prednisolone
csDMARDs	Hydroxychloroquine, leflunomide, methotrexate, sulfasalazine
TNF biologics	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
Non-TNF biologics	Abatacept, rituximab, tocilizumab, sarilumab, ^a sirukumab ^a
tsDMARDs	Tofacitinib ^b
Biosimilars	Adalimumab atto, infliximab-dyyb, infliximab-abda, ^b etanercept-szsz

^a FDA is currently evaluating for approval

^b New medications that have been approved since the 2012 review

cs = conventional synthetic; DMARD = disease-modifying antirheumatic drug; FDA = U.S. Food and Drug Administration; RA = rheumatoid arthritis; TNF = tumor necrosis factor; ts = targeted synthetic.

Definition of Remission and Response

The ACR/EULAR joint task force defines remission as a tender joint count, swollen joint count, C-reactive protein level, and patient global assessment of ≤ 1 each or a simplified Disease Activity Score (DAS) of ≤ 3.3 .¹³ This definition is used consistently in the report.

Response, or improvement, is defined using the DAS28 from one patient on two different time points. The EULAR response criteria are defined as shown in Table 2.

Table 2. EULAR Response Criteria

Present DAS28 ^a	DAS28 improvement >1.2	DAS28 improvement >0.6 and ≤ 1.2	DAS28 improvement ≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 and ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

^a DAS28 disease activity thresholds: High disease activity >5.1; Low disease activity <3.2; Remission <2.

DAS28 = Disease Activity Score using 28 joints

Challenges in Treating Early RA

Challenges and controversies related to RA include (1) definition of early disease, (2) the appropriate use and order or combination of different therapeutic options, (3) optimal approach to managing RA therapy in the setting of coexisting conditions (malignancy,

infections, pregnancy), and (4) the role of newly approved drugs in the treatment strategies in the context of older medications.

Given the varying definitions of early disease, defining early RA as no more than 1 year after diagnosis will be inclusive of the ACR definition of duration shorter than 6 months of symptoms of disease.¹⁸ This time period since diagnosis is also clinically consistent with early RA in practice. Going further than 1 year would not be consistent with current rheumatology practice.¹⁸

A second challenge that clinicians face is which DMARD they should start with for their patients with early RA. Traditionally, biologics are not approved as first-line treatment, but the issue remains as to whether clinicians should institute csDMARDs or biologics. The optimal initiation strategy to use is under debate; among the questions clinicians have is whether they should (1) step up treatment (progress from single therapy to combination therapy), (2) step down therapy (begin with combination therapy and back down treatment when symptoms are under control), or (3) aggressively treat to target using disease activity remission criteria (i.e., escalating treatment according to treatment protocols if a treatment target—ideally, remission—is not achieved). Unlike step up or step down therapy, clinical studies using treat to target strategies use stringent DAS measures to guide treatment.¹⁹

RA treatment tapering/stopping strategies is also debated. When patients respond (i.e., reach low disease activity) or reach remission, the main question is whether DMARDs should be tapered off or stopped. This raises questions about other issues, such as how to define remission or set the appropriate taper. Also, patients may want to taper off DMARDs when feeling better when it is probably inappropriate.

A third challenge for clinicians is treating RA in patients with significant coexisting conditions such as hepatitis C, congestive heart failure, diabetes, and cancer. Choosing a RA treatment drug can be difficult with these populations.

Newly approved drugs and those under review by the FDA are described in Section B (see Table 1) above. Few data are available on efficacy for these drugs; even less is known about how their effectiveness and harms compared with that of existing drugs. We will include these drugs in the literature search, including those under review in the event they are approved during our review period.

Methods challenges, moreover, remain the same as with past reviews. Studies differ considerably on multiple PICOTS (population, intervention/exposure, comparator, outcomes, time frames, country settings, study design) dimensions, for instance, so appropriately grouping studies for evidence synthesis is not simple. Also, some study methods lead to a high risk of bias. As with most clinical studies, participants may not be representative of individuals receiving treatment in usual care settings.

C. Rationale for the Review

This systematic review (SR) and meta-analysis will update the 2012 report, *Drug Therapy for Rheumatoid Arthritis in Adults: An Update*,²¹ but with a targeted scope focusing solely on patients with early RA.

Evidence Gaps From Prior Review

In the 2012 review, the existing evidence was insufficient to draw conclusions on the best treatment regimen for patients with early RA. Studies were of limited duration, which did not allow comparisons of whether early initiation of a biologic DMARD improved disease severity, radiographic findings, functional capacity, or quality of life compared with csDMARDs (hydroxychloroquine, leflunomide, methotrexate, sulfasalazine).²¹ There were also no studies comparing efficacy, effectiveness, and harms among subgroup populations.

What has Changed

New drugs: Additional clinical trials of three biosimilar drugs and a tsDMARD (an oral synthetic Janus kinase inhibitor) have become available.

Populations: Studies have become more multinational, which may affect applicability.

What This Review Aims to Do

This review will focus on patients with early RA and update the 2012 review on the comparative effectiveness of drug therapies on disease activity, joint damage, patient-reported symptoms, functional capacity, and quality of life. We will also examine comparative harms of drug therapies in terms of tolerability, adherence, and adverse effects. Finally, we will examine comparative effectiveness and harms of drug therapies in patient subgroups.

II. The Key Questions

Key Question (KQ) 1: For patients with early RA, do drug therapies differ in their ability to reduce disease activity, slow or limit the progression of radiographic joint damage, or induce remission?

KQ 2: For patients with early RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

KQ 3: For patients with early RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

KQ 4: What are the comparative benefits and harms of drug therapies for early RA in subgroups of patients based on disease activity, prior therapy, demographics (e.g., women in their childbearing years), concomitant therapies, and presence of other serious conditions?

Contextual Questions (CQs)

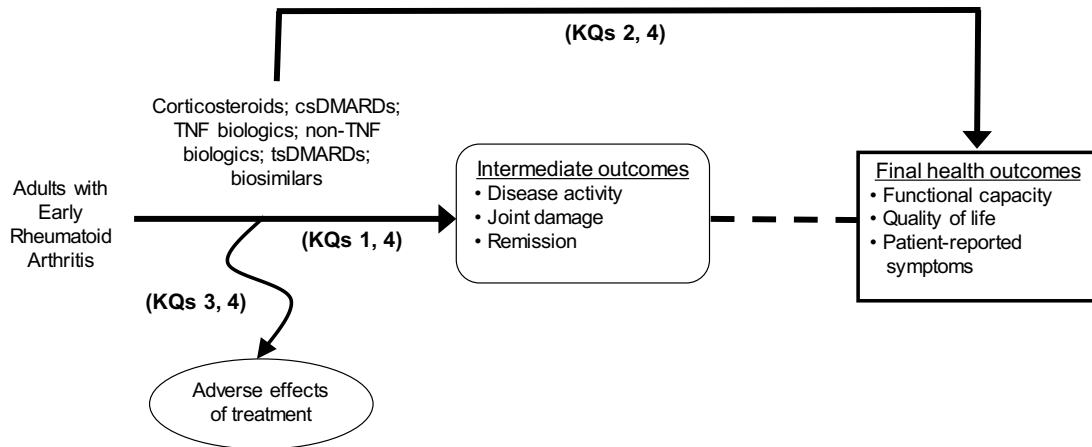
Contextual questions are not systematically reviewed and use a “best evidence” approach. Information about the contextual questions may be included as part of the introduction or discussion section and related as appropriate to the SR.²²

CQ 1: Does treatment of early RA improve disease trajectory and disease outcomes compared with the trajectory or outcomes of treatment of established RA?

CQ 2: What barriers prevent individuals with early RA from obtaining access to indicated drug therapies?

III. Analytic Framework

Figure 1. Analytic Framework for Drug Therapy for Early RA



cs = conventional synthetic; DMARD = disease-modifying antirheumatic drug; KQ = Key Question; RA = rheumatoid arthritis; TNF = tumor necrosis factor; ts = targeted synthetic.

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies are designed to identify studies that can answer the above KQs and are based on the PICOTS shown below (Table 3).

Table 3. Eligibility Criteria

PICOTS	Inclusion	Exclusion
Population	All KQs: Adult outpatients ages 19 or older with an early RA diagnosis, defined as 1 year or less from disease diagnosis; we will include studies with mixed populations if >50% of study populations had an early RA diagnosis. KQ 4 only: Subpopulations by age, sex/gender, race/ethnicity, disease activity, prior therapies, concomitant therapies, and other serious conditions	Adolescents and adult patients with disease greater than 1 year from diagnosis
Intervention/ exposure	FDA approved <u>Corticosteroids</u> : methylprednisolone, prednisone, prednisolone <u>csDMARDs</u> : hydroxychloroquine, leflunomide, methotrexate, sulfasalazine <u>TNF biologics</u> : adalimumab, certolizumab pegol, etanercept, golimumab, infliximab <u>Non-TNF biologics</u> : abatacept, rituximab, tocilizumab <u>tsDMARDs</u> : tofacitinib <u>Biosimilars</u> : adalimumab-atto, infliximab-dyyb, infliximab-abda, etanercept-szss Under review by FDA <u>Non-TNF biologics</u> : sarilumab, sirukumab	Anakinra is excluded because, although it is approved for RA, clinically it is not used anymore for this population ²³
Comparator	<u>For head-to-head RCTs, head-to-head nRCTs, and prospective, controlled cohort studies (all KQs)</u> : any active intervention listed above <u>For additional observational studies of harms (i.e., overall [KQ 3] and among subgroups [KQ 4])</u> : any active intervention listed above or no comparator (e.g., postmarketing surveillance study of an active intervention with no comparison group) <u>For double-blinded, placebo-controlled trials for network meta-analysis (all KQs)</u> : placebo	All other comparisons, including active interventions not listed above
Outcomes	KQs 1, 4: Disease activity, radiographic joint damage, remission KQs 2, 4: Functional capacity, quality of life, patient-reported symptoms KQs 3, 4: Overall risk of harms, overall discontinuation, discontinuation because of adverse effects, risk of serious adverse effects, specific adverse effects, patient adherence	All other outcomes not listed
Timing	All KQs: At least 3 months of treatment	<3 months treatment
Settings	All KQs: Outpatients	Inpatients
Country setting	All KQs: Any geographic area	None
Study designs	For all KQs (i.e., benefits and harms overall [KQs 1, 2, 3] and among subgroups [KQ 4]), we will include head-to head RCTs and nRCTs; prospective, controlled cohort studies (N ≥100); double-blinded, placebo-controlled trials for network meta-analysis; and SRs for identification of additional references only. For studies of harms (i.e., overall [KQ 3] and among subgroups [KQ 4]), we will also include any other observational study (e.g., cohort, case-control, large case series, post marketing surveillance) (N ≥100).	All other designs not listed
Publication language	All KQs: English	Languages other than English

cs = conventional synthetic; DMARDs = disease-modifying anti-rheumatic drugs; FDA = U.S. Food and Drug Administration; KQ = Key Question; N = number; nRCT = non-randomized controlled trial; PICOTS = population, intervention/exposure, comparator, outcomes, time frames, country settings, study design; RA = rheumatoid arthritis; RCT = randomized controlled trial; SR = systematic review; TNF = tumor necrosis factor; ts = targeted synthetic.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the KQs

We will systematically search, review, and analyze the scientific evidence for each KQ. The steps that we will take to accomplish the literature review are described below. We will include any population that authors of a study define as early RA, provided that it includes a disease diagnosis no more than 1 year in the past. We will include studies with mixed populations if more than 50 percent of the study populations had an early RA diagnosis. Because no consensus on the definition of early RA exists, we will also internally track studies with RA between 1 to 2 years of diagnosis to describe the number of studies using this time frame. If a study article meeting our other PICOTS criteria gives no clear definition, we will attempt to contact authors to request clarification of the definition with one standard email request to the corresponding author. We will give the author 2 weeks to respond. If we do not receive a response, we will not include the study in question.

To identify relevant published literature, we will search the following databases: PubMed/MEDLINE®, the Cochrane Library, Embase, and International Pharmaceutical Abstracts. The preliminary search strategies formatted for MEDLINE are shown in the Appendix A and comprise medical subject heading (MeSH) terms and natural language terms reflective of RA drug interventions and outcomes of interest. The search strategy will be adapted for the other databases as needed. An experienced librarian familiar with SRs will design and conduct all searches in consultation with the review team.

The 2012 review, searched from June 2006 to January 2011. For the present update, our literature searches will include articles published from July 2010 (to allow 1 year's indexing time from the 2012 update) to April 2017. The literature search will be updated concurrently during the draft report peer/public review. We will manually search the reference lists of SR articles to supplement searches for the report. At the outset, we will ensure that our update adequately builds on the body of evidence of the previous 2012 update, including new drugs. Because the scope of this update is limited to patients with early RA, we will carefully examine included studies in the prior review to identify those that focused exclusively on patients with early RA or mixed populations of patients with early diagnosis of RA.

We will also search the gray literature for unpublished studies relevant to this review and include studies that meet all the inclusion criteria and contain enough methodological information to assess risk of bias. Gray literature sources will include ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, the New York Academy of Medicine's Grey Literature Index, and Scientific Evidence and Data (SEAD) information received from targeted requests and from a *Federal Register* Notice (FRN). When we update our published literature search concurrently with the peer review process (mentioned previously), we will also update the gray literature searches.

Data Abstraction and Data Management

To ensure accuracy, two reviewers will independently review all titles and abstracts. We will use Abstrackr, an online citation screening tool, to review title and abstract records and manage the results.²⁴ We will then retrieve the full text for all citations deemed potentially appropriate for inclusion by at least one of the reviewers. Two team members will independently review each full-text article, including any articles that peer reviewers suggest or that may arise from the public posting process, for eligibility. Any disagreements will be resolved by a third team member or consensus. We will maintain a record of studies excluded at the full-text level with reasons for exclusion and will include this list in our final report.

After we select studies for inclusion, we will abstract data into categories that include (but are not limited to) the following: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, attrition (overall and due to adverse effects [AEs]), results, and AE incidence. A second team member will verify abstracted study data for accuracy and completeness.

Assessment of Methodological Risk of Bias of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we will use the ROBINS-I²⁵ for observational studies. We will adapt the Cochrane ROB tool²⁶ for RCT trials by adding items about the statistical analyses of RCTs. We will use predefined criteria based on the Agency for Healthcare Quality and Research (AHRQ) *Methods Guide for Comparative Effectiveness Reviews*. These include questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias; concepts covered include adequacy of randomization, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.²⁷

Two independent reviewers will assess risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

In general terms, results from a study assessed as having low risk of bias are considered valid. A study with medium risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as having high risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) is affected by substantial issues that may invalidate its results.

Data Synthesis

We will summarize all included studies in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, setting (including geographic location), and results. All new qualitative and quantitative analyses will synthesize relevant studies included in the 2012 SR and this update as a single body of evidence. Unlike the prior update, this review will not synthesize relevant SRs or meta-analyses with findings from individual studies, but rather will use SRs or meta-analyses solely as sources of additional, potentially eligible references.

We expect definitions of early RA to vary between 3 months and 1 year of diagnosis. In synthesizing all evidence, we will take variations in how early RA is defined into consideration and explore the impact of different definitions on various outcomes of interest. Depending on the available data, we will employ meta-regression or subgroup analyses to assess quantitatively whether the duration of disease in early RA modifies benefits or harms of treatments. If data do not allow quantitative analyses, we will qualitatively explore such potential differences in treatment effects.

Because we are aware of the dearth of studies directly comparing interventions of interest, we plan to use prespecified criteria to conduct network meta-analyses (e.g., length of followup, high risk of bias studies). Network meta-analyses agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients in different trials.²⁸ To conduct network meta-analyses, we will include all placebo- and active-controlled RCTs that are homogenous in study populations and outcome assessments and are part of a connected network (i.e., we will ensure transitivity). We will build on the database for network meta-analyses that we used for the 2012 SR.²¹ To evaluate the presence of inconsistency between direct and indirect estimates in closed loops, we will use network sidesplitting.²⁹ Network meta-analyses will help us provide a more in-depth answer about which DMARDs should be started in patients with early RA and whether csDMARDs should be used before biologics, tsDMARDs, or biosimilar DMARDs.

If data permit, we will use pairwise or network meta-analyses to address uncertainties about different treatment strategies in early RA. Some examples of these uncertainties include the optimum order of therapeutics in early RA, and in patients who respond to treatment, whether biologic DMARDs can be tapered or stopped. In case data do not allow a quantitative approach, we will assess these questions qualitatively.

We will also carefully explore whether strategies used in average patients with early RA can be used effectively or safely for patients with significant coexisting ailments such as hepatitis C, congestive heart failure, cancer, diabetes, and others. Because we lack access to individual patient data, we will most likely use a qualitative approach to address this question. If data allow, we will employ quantitative methods such as subgroup analyses, being fully aware of ecological fallacy issues. We will interpret results of such analyses cautiously.

We will consider performing meta-analyses where we have at least three unique studies of low or medium risk of bias that we deem to be sufficiently similar (in population, interventions, comparators, and outcomes). We are aware of the potential biases of meta-analyses that include a small number of studies;³⁰ before routinely calculating a pooled summary estimate in a meta-analysis, we will carefully consider the heterogeneity across studies. Therefore, bodies of evidence containing fewer than three low or medium risk of bias studies or with heterogeneous or noncomparable study populations will only be used in qualitative syntheses.

If meta-analysis seems appropriate in these circumstances, we will perform random-effects model meta-analyses. We will present forest plots for all meta-analyses performed, either in the main report or in appendices. We plan to exclude studies deemed

high risk of bias from our main data synthesis and main analyses; we will include them only in sensitivity analyses.

To assess statistical heterogeneity in effects between studies, we will calculate the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity rather than due to chance).^{31, 32} An I^2 from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.²⁶ For the chi-squared statistic, we will adopt a p-value of 0.1 as a threshold for clinical significance. In cases of high heterogeneity, we will explore potential reasons for heterogeneity. If we encounter high unexplained heterogeneity, we will abstain from any quantitative syntheses.

To assess publication bias, we will use funnel plots and Kendall’s tests, knowing that these tests have low sensitivity to detect publication bias, particularly with a small number of studies.

Grading the SOE for Major Comparisons and Outcomes

We will grade SOE based on the guidance established for the Evidence-based Practice Center (EPC) Program.³³ Developed to grade the overall strength of a body of evidence, this approach now incorporates five key domains: risk of bias (including study design and aggregate risk of bias), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as plausible confounding that would decrease the observed effect and strength of association (i.e., magnitude of effect) or factors that would increase the strength of association (i.e., dose-response effect).

Table 4 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus.

Table 4. Definitions of the Grades of Overall Strength of Evidence

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Source: Berkman et al.³³

We will grade the SOE for the following outcomes, consistent with the prior report: disease activity, radiographic joint damage, functional capacity, quality of life and serious adverse effects.²¹

Assessing Applicability

We will assess the applicability of individual studies, as well as the applicability of the larger body of evidence, following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.²⁷ We will examine whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings. For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Some factors identified a priori that may limit the applicability of evidence include the following: race or ethnicity of enrolled populations, setting of enrolled populations, geographic setting, and availability of health insurance and other health-related employment benefits. Age and comorbidity burden have increased at first RA presentation prior to DMARD treatment over the past 25 years.³⁴ Additionally, progression rates of radiographic joint damage have slowed over time, likely related to lower baseline damage at diagnosis and earlier institution of DMARD therapy.³⁵ These trends will be taken into account when examining studies published over a decade ago.

V. References

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VI. Definition of Terms

We will define important terms in the full report.

Early RA: for the purposes of this review, RA that is identified 1 year or less from disease diagnosis.

Treat-to-target approach: regular monitoring of disease activity and adverse events and escalating treatment according to treatment protocols if a treatment target (ideally remission) is not achieved.¹⁹

VII. Summary of Protocol Amendments

No protocol amendments to date.

If we need to amend this protocol, we will give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Table 1. Example table

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

VIII. Key Informants/Technical Experts and Review of Key Questions

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions.

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, and outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development.

Key Informants and Technical Experts were included in a multi-stakeholder virtual workshop by PCORI in December 2016. The workshop reviewed scoping for the updated review, prioritization of key questions, a discussion of where the evidence base has accumulated since the prior review and emerging issues in RA. This RA protocol was developed based upon findings from the multi-stakeholder virtual workshop. Key Informants and Technical Experts do not do analysis of any kind nor do they contribute

to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

IX. Peer Reviewers

Peer Reviewers, representing the diversity of perspectives included in the definition of “Key Informants” and “Technical Experts” above, are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer Reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

Dr. Jonas discloses financial conflicts of interest (COIs), including consultancy fees and grants or contracts. Additionally, as a practicing rheumatologist, she prescribes all the medications included in this review. If her published studies on RA medications are potentially eligible for this review, Dr. Jonas will not be a reviewer of any of her own studies or any studies in the drug class for which she has a financial COI. As the lead for the project, Dr. Donahue will have the final say in the assessment of studies and the body of evidence.

XI. Role of the Funder

This project was completed under Contract No. HHS290201500011I_HHS29032010T from AHRQ, U.S. Department of Health and Human Services, through funds provided by a partnership with PCORI. The AHRQ TOO reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by PCORI, AHRQ or the U.S. Department of Health and Human Services.

XII. Registration

This protocol will be registered in the international prospective register of SRs (PROSPERO).

APPENDIX A

KQs 1 through 4 PubMed Search Strategy

Search	Query
#1	Search "arthritis, rheumatoid"[MeSH Terms] OR "rheumatoid arthritis"[All Fields]
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*
#3	Search (Methylprednisolone OR prednisone OR prednisolone)
#4	Search (Hydroxychloroquine OR Leflunomide OR Methotrexate OR Sulfasalazine)
#5	Search (Adalimumab OR "certolizumab pegol" OR etanercept OR golimumab OR infliximab OR Abatacept OR tocilizumab OR rituximab OR Tofacitinib OR Sarilumab OR Sirukumab)
#6	Search (amjevita OR Inflectra OR Erelzi)
#7	Search (#2 OR #3 OR #4 OR #5 OR #6)
#8	Search (#1 AND #7)
#9	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])
#10	Search (#8 NOT #9)
#11	Search (#8 NOT #9) Filters: English
#12	Search (#8 NOT #9) Filters: Humans; English
#13	Search (#8 NOT #9) Filters: Humans; English; Adult: 19+ years
#14	Search (("Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]))
#15	Search (((("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]))
#16	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "observational study" OR "observational studies")
#17	Search (#13 AND #14)
#18	Search (#13 AND #15)
#19	Search (#13 AND #16)
#20	Search (#13 AND #14) Filters: Publication date from 2010/07/01
#21	Search (#13 AND #15) Filters: Publication date from 2010/07/01
#22	Search (#13 AND #16) Filters: Publication date from 2010/07/01
#23	Search (#20 OR #21 OR #22) Filters: Publication date from 2010/07/01