Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis in Adults – An Update to the 2007 Report

I. Background and Objectives for the Systematic Review

Rheumatoid arthritis (RA) is among the most disabling forms of arthritis. It is an autoimmune disease that is characterized by inflammation of the synovium (a thin layer of tissue lining a joint space) and progressive erosion of bone that lead, in most cases, to misalignment of the joint, loss of function, and disability. The disease tends to affect the small joints of the hands and feet in a symmetric pattern, but other joint patterns are often seen. The diagnosis of RA is based primarily on the clinical history and physical examination. Nearly 2 million adults (1%) in the United States have been diagnosed with the disease.[1]

Treatment of RA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability. Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs), and injectable biologic DMARDs. The oral DMARDs that are used to treat patients with RA are hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine and the biologic DMARDs are abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab, certolizumab pegol, golimumab, and tocilizumab. The biologic DMARDs are a newer category of DMARDs, which differ from conventional DMARDs in that they target specific components of the immune system.

In the treatment of RA, experts have not reached a consensus about the comparative efficacy of different types of combination therapy—that is, a mixture of oral DMARDs, oral DMARDs and corticosteroids, or oral (often methotrexate) and biologic DMARDs. In addition, there is debate about how early in the disease process combination therapy should be initiated and whether patients will respond to a biologic agent if a different biologic agent has been ineffective. Many questions remain about the risks of these agents across a spectrum of adverse events—from relatively minor side effects such as injection site reactions to severe and possibly life-threatening problems such as severe infections or infusion reactions. Finally, very little is known about the benefits or risks of these drugs AMONG different patient subgroups, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities.

This comparative effectiveness review (CER) is an update of the original one conducted in 2007 for the Agency for Healthcare Research and Quality and poses the same key questions.[2] The first review did not include certolizumab pegol, golimumab, and tocilizumab (listed above), because these drugs had not been approved by the U.S. Food and Drug Administration (FDA) for the treatment RA at the time of the first review.

*Source: **www.effectivehealthcare.ahrq.gov***
Published Online: December 6, 2010

II. The Key Questions (KQs)

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

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

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

Question 4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Changes in the wording of KQ1 and KQ2 wording from draft protocol

- As suggested by our Technical Expert Panel, the wording of KQ1 was revised to replace the words "patient-reported symptoms" with "disease activity." Concurrently, "disease activity" was removed from KQ2 and replaced with "patient-reported symptoms."

PICOTS criteria for the KQs above:

- **Population(s):**
  - Adults with RA
  - All stages of disease, prior therapy, demographics, concomitant therapies, and comorbidities
- **Interventions:**

Comparisons will be made between treatment strategies including any of the following biologic DMARDs, oral DMARDs, or corticosteroids approved by the U.S. Food and Drug Administration (FDA).

- Corticosteroids

Generic Name	Trade Name
Methylprednisolone	Medrol®, Depo-Medrol®, Solu-Medrol®
Prednisone	Deltasone®, Sterapred®, LiquiPred®
Prednisolone	Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®

- Oral DMARDS

Generic Name	Trade Name
Hydroxychloroquine	Plaquenil®

Leflunomide	Arava®
Methotrexate	Trexall®, Folex®, Rheumatrex®
Sulfasalazine	Azulfidine®, EN-tabs®, Sulfazine®

- Biologic DMARDS

Generic Name	**Trade Name**
Abatacept	Orencia®
Adalimumab	Humira®
Anakinra	Kineret®
Etanercept	Enbrel®
Infliximab	Remicade®
Rituximab	Rituxan®
Certolizumab pegol,	Cimzia®
Golimumab	Simponi®
Tocililizumab	Actemra®, RoActemrai®

- **Comparators:**

  For all KQs: all review drugs listed above; placebo (with biologic DMARDs only)

- **Outcomes for each KQ**

  - KQ 1 and KQ4:
    i. Progression of joint damage
    ii. Remission

  - KQ2 and KQ4:
    i. Physical functioning
    ii. Quality of life

  - KQ3 and KQ4:
    i. Morbidity, mortality, and other serious adverse events
    ii. Tolerability
    iii. Adherence
    iv. Other adverse effects

- **Timing:**
  Minimum of 3 months of follow-up

- **Settings:**
  Primary care and rheumatology specialty settings

III. Analytic Framework

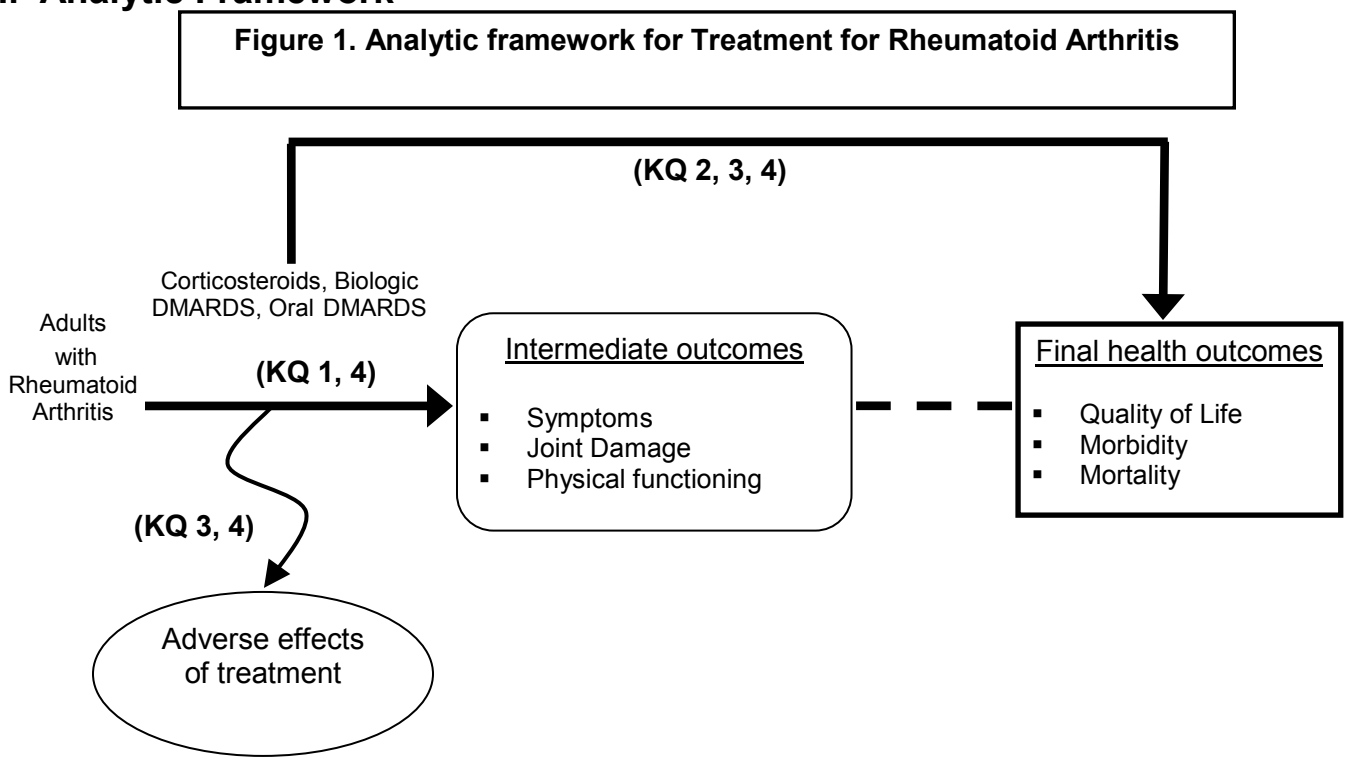

Figure 1: This figure depicts the key questions (KQs) within the context of the PICOTS described in the previous section. In general, the figure illustrates how treatment with corticosteroids, biologic DMARDs, or oral DMARDs vs. any of these same treatments may result in intermediate outcomes such as symptoms, joint damage, physical functioning, and/or long-term outcomes such as quality of life, morbidity, or mortality. Also, adverse events may occur at any point after the treatment is received.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Exhibit 4-1 presents the inclusion/exclusion criteria we will use during the abstract and full-text reviews.

Exhibit 4-1. Inclusion/Exclusion Criteria for the Systematic Review

Category	Criteria	
	Inclusion	Exclusion
Study population	Adults (age 19 and older for PubMed) with rheumatoid arthritis, all races, ethnicities, cultural groups	Children

Category	Criteria	
	Inclusion	**Exclusion**
Study outcomes	• KQ1 and KQ4: joint damage, maintenance of remission (as measured by ACR, DAS, radiographic measures, total joint count, etc) • KQ2: physical functioning (as measured by HAQ, SF36 Health Survey, etc), quality of life • KQ3: harms, tolerability, adherence, adverse effects (including patient reported symptoms, morbidity and mortality)	
Study geography	No limits	
Time period	June 1, 2006, through June 30, 2009, to be updated after draft CER goes out for peer review	Prior to June 1, 2006
Settings	All other settings	
Interventions	Corticosteroids • Methylprednisolone • Prednisone • Prednisolone Oral DMARDs • Hydroxychloroquine • Leflunomide • Methotrexate • Sulfasalazine Biologic DMARDs • Abatacept • Adalimumab • Anakinra • Etanercept • Infliximab • Rituximab • Certolizumab pegol • Golimumab • Tocilizumab	
Publication language	English	All other languages
Admissible evidence (study design and other criteria)	Original research; eligible study designs include: • Randomized controlled trials with a sample size ≥100 • Nonrandomized controlled trials • Observational studies with a sample size ≥100: prospective and retrospective cohort studies, case-control studies, and cross-sectional studies • Meta-analyses or systematic reviews Study duration must be 3 months or longer	• Case series • Case report • Review articles • Editorials • Letters to the editor • Studies with insufficient sample sizes

*Source: **www.effectivehealthcare.ahrq.gov***
Published Online: December 6, 2010

Abbreviations: ACC = American College of Radiology; DAS = Disability Assessment Scale; HAQ = Health Assessment Questionnaire.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will systematically search, review, and analyze the scientific evidence for each key question and any subsidiary questions. The steps that we will take to accomplish the literature review are described below.

To identify articles relevant to each key question, we began with a focused MEDLINE search on pharmacological treatments for RA and psoriatic arthritis by using a variety of terms (MeSH and major subject headings) and limiting the studies to English language and human subjects only. We also searched other databases (The Cochrane Library and the Cochrane Central Trials Registry). Results from initial database searches are presented in Exhibit 4-2.

Exhibit 4-2. Results of a Literature Search Combining Rheumatoid and Psoriatic Arthritis

Search Strategy 1

#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	85528
#2	Search "Adrenal Cortex Hormones"[MeSH] OR corticosteroid*	239378
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	31900
#4	Search "TNFR-Fc fusion protein"[Substance Name] OR etanercept OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin"[Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR "interleukin 1 receptor antagonist protein"[Substance Name] OR anakinra	15567
#5	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1127
#6	Search "golimumab "[Substance Name]	12
#7	Search #2 OR #3 OR #4 OR #5 OR #6	283303
#8	Search #7 AND #1	11283
#9	Search #7 AND #1 Limits: Editorial, Letter, Practice Guideline	1368
#10	Search #8 NOT #9	9915
#11	Search #8 NOT #9 Limits: Humans, English, All Adult: 19+ years	4079
#12	Search Limits: Entrez Date from 2006/06/01, Humans, English, All Adult: 19+ years	498212
#13	Search #11 AND #12	1027

Analogous search terms were used to search other literature databases and yielded the following results:

EMBASE: 288 (duplicates 67)
Cochrane: 15 (duplicates 0)
IPA: 142 (duplicates 10)

A total of 1395 references were imported into an EndNote® bibliographic database (Thomson Reuters, New York, NY) specifically designed for this CER.

Search Strategy 2

With FDA approval of tocilizumab imminent, an additional search was conducted by using the strategy given below.

#1	Search "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH]	85692
#2	Search actemra	4
#4	Search "tocilizumab "[Substance Name]	103
#5	Search #2 OR #4	104
#6	Search #5 AND #1	75
#7	Search #5 AND #1 Limits: Editorial, Letter, Practice Guideline	8
#8	Search #6 NOT #7	67
#9	Search #6 NOT #7 Limits: Humans, English, All Adult: 19+ years	14
#10	Search #9 Limits: Entrez Date from 2006/06/01	14

Of the 14 new references retrieved from PubMed, 6 were duplicates and 8 were new.

Analogous terms were used to search other databases and yielded the following results:

EMBASE: 8 (6 duplicates; 2 new studies)
Cochrane: 0 reviews; 8 clinical trials (7 duplicates; 1 new study)
IPA: 15 (6 duplicates; 9 new studies)

Altogether, an additional 20 new references imported into the bibliographic database.

Overall, we identified a total of 1,415 citations. We will review our search strategy with the Technical Expert Panel (TEP) and supplement it as needed according to their recommendations. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that might have been missed by electronic searches. We will also conduct an updated literature search (in MEDLINE, the Cochrane Library, and the Cochrane Central Trials Registry) before completing the final draft of the report. We will be reviewing the results of a gray literature search conducted by the Scientific Resource Center as a means of confirming that we have captured all of the relevant studies.

C. Data Abstraction and Data Management

All titles and abstracts identified through searches against our inclusion/exclusion criteria will be independently reviewed by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. A senior member of the team will review all the studies marked for exclusion by both reviewers. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in the EndNote database.

For the next step, we will retrieve and review the full text of all titles included during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third, independent party, who is usually the principal investigator. As described above, all results will be tracked in an EndNote database. Where applicable, we will record the reason why each excluded study did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

We will design data-collection forms to include questions that will help the reviewer identify pertinent information for each article, including study design, methods, and results. These questions will be focused specifically on answering the KQs. Trained abstractors will extract the relevant data from each included article into the abstraction system. All abstractions will be reviewed for completeness and accuracy by a second senior member of the team, most often the lead author of the KQ to which the study pertains.

D. Assessment of Methodological Quality of Individual Studies

To assess the quality (internal validity) of studies, we will use predefined criteria based on those developed by the US Preventive Services Task Force[3] (ratings: good, fair, or poor) and the National Health Service Centre for Reviews and Dissemination.[4] In general terms, a “good” study has the least bias and its results are considered to be valid. A “fair” study is susceptible to some bias but probably not sufficient enough to invalidate its results. A “poor” study has significant bias (e.g., stemming from serious errors in design or analysis) that may invalidate its results. To assess the quality of observational studies, we will use criteria outlined by Deeks and colleagues.[5]

Two independent reviewers will assign quality ratings to each study. The abstractor is the first to rate the quality of the studies after the abstraction is complete. The senior reviewer is the second to rate the quality of the studies. As described above, this reviewer completes a second full review of the study and is well positioned to perform an independent quality rating. Disagreements between the abstractor and the senior reviewer will be resolved by discussion and consensus or by consulting a third, independent party.

E. Data Synthesis

We anticipate that the data found in the literature review will be synthesized qualitatively. However, if we find a sufficient number (three or more) of similar studies of factors that influence the treatments we are analyzing, we will consider performing quantitative analyses (indirect comparisons, or meta-analysis) of the data from those studies.

F. Grading the Evidence for Each Key Question

We will rate the strength of evidence based on the standard methods of the Evidence-based Practice Centers, which use a revised version of the approach devised by the GRADE Working Group.[6] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates the following elements: study design, study quality, consistency, directness, presence of imprecise or sparse data, high probability of publication bias, and magnitude of the effect. In this approach, we use four grades: high, moderate, low, and insufficient.

V. References

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008/01/01 ed 2008:15-25

2. Donahue KE, Gartlehner G, Jonas DE, et al. *Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults*, Comparative Effectiveness Review No. 11 (Prepared by RTI–University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016). Rockville, MD: Agency for Healthcare Research and Quality; November 2007. AHRQ Publication No. 08-ENC004-EF.

3. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.

4. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001

5. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating nonrandomised intervention studies. *Health Technol Assess* 2003;7(27):1-173, iii-x.

6. Atkins D, Eccles M, Flottorp S, et al, for the GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches: the GRADE Working Group. *BMC Health Serv Res* 2004;4:38.

VI. Definition of Terms

Definitions of terms are provided within the text.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

For comparative effectiveness reviews (CERs), the Key Questions were posted for public comment and finalized after the comments are reviewed. For other systematic reviews, Key Questions submitted by partners are reviewed and refined as needed by the Evidence-based Practice Center (EPC) and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is to be reviewed.

IX. Technical Expert Panel (TEP)

The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived to be healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, study designs, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not perform analyses of any kind nor does it contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewers may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. For some specific reports, such as reports requested by the Office of Medical Applications of Research at the National Institutes of Health, there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published e months after the publication of the evidence report.

It is our policy not to release the names of the peer reviewers or TEP members until the final report is published so that they can maintain their objectivity during the review process.