A Comparative Effectiveness Research Tool Kit for Managed Care and the Treatment of Rheumatoid Arthritis
TARGET AUDIENCE

This activity is designed to meet the educational needs of pharmacists, physicians, and other healthcare professionals involved in the management of patients with rheumatoid arthritis.

STATEMENT OF NEED/PROGRAM OVERVIEW

The number of new biologic and possible combinations has magnified the importance of Comparative Effectiveness Research (CER) in Rheumatoid Arthritis (RA). Making coverage decisions is challenging due to the lack of data, specifically as it relates to direct cost comparisons. The use of CER will increase as more results are accessible and education on CER improves. Health plans need processes to conduct, analyze, and use CER data to understand the results in their own populations, enabling effective benefit designs and better treatment decisions. By reviewing the most current data and utilizing the resources and references provided in this CER/RA Tool Kit, this activity will guide the audience to implement evolving CER strategies for RA.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Explain the unique role and utility of CER to improve outcomes for the treatment of RA within a managed care setting.
- Identify currently available CER data and interpret the results for enhanced managed care decision-making for the treatment of RA.
- Apply the use of CER for the treatment of RA within a managed care setting.
- Provide accurate and appropriate counsel as part of the treatment team.
ACCREDITION

PHYSICIAN ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Annenberg Center for Health Sciences at Eisenhower and Impact Education, LLC. The Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation
The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Credit Designation
This program has been developed according to the ACPE Criteria for Quality and is assigned ACPE Universal Activity # 0797-9999-13-135-H04-P. This program is designated for up to 1.0 contact hours (0.10 CEUs) of continuing pharmacy education credit.

Upon receipt of the completed activity evaluation form, transcript information will be available at www.mycpemonitor.net immediately.

TYPE OF ACTIVITY
Knowledge

FEE INFORMATION
There is no fee for this educational activity.

CE information continued on page 5
The purpose of this Comparative Effectiveness Research (CER)/Rheumatoid Arthritis (RA) Tool Kit is to provide examples of resources that have been used successfully by clinicians, educators, peer review organizations, managed care organizations, and others to improve care of patients with RA. This Tool Kit does not specifically endorse any of the enclosed tools and resources.

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<thead>
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<th>Reported Financial Relationship</th>
</tr>
</thead>
</table>
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<tr>
<th>Name of Planner or Manager</th>
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<tbody>
<tr>
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There are no fees for participating and receiving CME credit for this activity. During the period April 29, 2013 through November 30, 2014, participants must read the learning objectives and faculty disclosures and study the educational activity. If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on “Find Post-test/Evaluation by Course” and search by course ID 9295. Upon registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately.

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The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.
Introduction: Burden of Rheumatoid Arthritis

- **Definition:** Chronic, progressive, inflammatory, autoimmune disease of unknown etiology
- **Prevalence:** ~0.6% of the US population
- **Disability:** Many patients unable to work within 10 years of onset:
  - Pre-biologic era: 50%
  - Current (2008): 35%
- **Cardiovascular risk:** 5x higher CV event rate vs. general population
- **Excess deaths:** Mortality rate 1.5 to 1.6-fold higher in RA patients vs. general population
- **Cost:** Annual per patient direct medical cost ~$13,012 vs. $4950 for control
  - Total annual excess direct cost of RA vs. control ~$22.3 billion


Pathogenesis: Important Molecules and Signal Mediators

<table>
<thead>
<tr>
<th>Molecule or Signal Mediator</th>
<th>Disease-Relevant Function</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor inhibitor (TNF-α)</td>
<td>Induce production of cytokines chemokines, adhesion molecules, matrix enzymes; suppresses regulatory T-cell function; activates of osteoclasts; resorption of cartilage and bone</td>
<td>Approved drug</td>
</tr>
<tr>
<td>Interleukin-1α /1β</td>
<td>Induce matrix-enzyme production; activate osteoclasts</td>
<td>Approved drug</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Activates leukocytes and osteoclasts; is involved in B-lymphocyte differentiation; regulates lipid metabolism, acute-phase response, and anemia of chronic disease; and is implicated in hypothalamic-pituitary adrenal axis dysfunction and fatigue</td>
<td>Approved drug</td>
</tr>
<tr>
<td>CD20</td>
<td>Function of CD20 remains unclear; postulated that CD20 mediates Ca²⁺ influx across plasma membranes, maintaining intracellular Ca²⁺ concentration, and allowing activation of B cells</td>
<td>Approved drug</td>
</tr>
<tr>
<td><strong>B-Cell Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-Cell Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cell co-stimulation</td>
<td>T-cell activation occurs when the T-cell receives a secondary (costimulatory) signal; activated T-cells secrete cytokines involved in synovial inflammation</td>
<td>Approved drug</td>
</tr>
<tr>
<td><strong>Intracellular Signaling Molecules and Transcription Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janus Kinase inhibitor (JAK)</td>
<td>Tyrosine kinase that regulates cytokine-mediated leukocyte maturation and activation, cytokine production, and immunoglobulin production</td>
<td>Approved drug</td>
</tr>
</tbody>
</table>


Unmet Needs: Current Treatment Patterns Practice May Be Suboptimal

- A ‘start low, go slow’ approach remains common in RA management
- Delayed treatment or prolonged under-treatment contributes to uncontrolled inflammation and irreversible tissue damage
- Patients not referred to a rheumatologist are less likely to receive disease-modifying anti-rheumatic drug (DMARD)-based therapy within 12 months of symptom onset
- Patients frequently receive irregular follow-up and minimal therapeutic adjustment

Unmet Needs: Functional Decline Begins Early in the Course of the Disease

Unmet Needs: Early Treatment is Associated with Better Outcomes


RA Management: American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria

**JOINT DISTRIBUTION (0-5)**

<table>
<thead>
<tr>
<th>Joint Distribution</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

- ≥ 6 = definite RA

**SEROLOGY (0-3)**

- Negative RF AND negative Anti-CCP: 0
- Low positive RF OR low positive Anti-CCP: 2
- High positive RF OR high positive Anti-CCP: 3

**SYMPTOM DURATION (0-1)**

- <6 weeks: 0
- ≥6 weeks: 1

**ACUTE PHASE REACTANTS (0-1)**

- Normal CRP AND normal ESR: 0
- Abnormal CRP OR abnormal ESR: 1

ACR=American College of Rheumatology; EULAR=European League Against Rheumatism; RF=rheumatoid factor; Anti-CCP=Anti-cyclic citrullinated peptide; CRP=c-reactive protein; ESR=erythrocyte sedimentation rate.


**Treating-to-Target**

- Primary target for treatment is clinical remission
  - Defined as the absence of signs and symptoms of significant inflammatory disease activity
- Low disease activity may be an acceptable alternative therapeutic goal
- Drug therapy should be adjusted at least every 3 months
- Measures of disease activity must be obtained and documented regularly
- Validated composite measures of disease activity are needed in routine clinical practice to guide treatment decisions
- Structural changes and functional impairment should be considered when making clinical decisions
- Treatment target should be maintained throughout the course of the disease
- Choice of the disease activity measure and level of the target value may be influenced by presence of morbidities, patient factors, and drug-related risks
- Patient has to be appropriately informed about the treatment target

Assessing Disease Activity: ACR Criteria

The ACR criteria are the gold standard criteria used in clinical trials to determine the effectiveness of new agents. Improvement is denoted as ACR 20, ACR 50 or ACR 70 reflecting an improvement of 20%, 50%, or 70% in the laboratory, clinical, physician, and patient disease activity parameters utilized in the assessment tool.

Disease parameters included in the ACR criteria include:

- Improvement of 20%, 50%, or 70% from baseline in the swollen joint count

- Improvement of 20%, 50%, or 70% from baseline in the tender joint count

- Improvement of 20%, 50%, or 70% from baseline in at least 3 of the following 5 measures:
  - Patient Global Assessment (VAS 0-10)
  - Physician Global Assessment (VAS 0-10)
  - Patient Assessment of Pain (VAS 0-10)
  - Acute Phase Reactant (ESR or CRP)
  - Functional Disability (HAQ)

VAS=visual analogue score; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; HAQ=Health Assessment Questionnaire.


Strengths and Limitations of the ACR Criteria

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Includes objective measures as well as patient and physician evaluation, including functional assessment</td>
<td>Limited application to clinical practice</td>
</tr>
<tr>
<td>Requires an initial assessment</td>
<td>Relative response, not an absolute assessment of disease activity</td>
</tr>
<tr>
<td>Useful in clinical trials</td>
<td>Patients with significant clinical response may still have very active disease</td>
</tr>
</tbody>
</table>
## Composite Clinical Tools Used to Assess Disease Activity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Research Tool</th>
<th>Clinical Instruments</th>
<th>Patient-reported Instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR20</td>
<td>DAS28</td>
<td>SDAI</td>
</tr>
<tr>
<td>Patient Function</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Patient Pain</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Patient Global</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MD Global</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Number of Tender Joints</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Number of Swollen Joints</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ESR or CRP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

ACR20=American College of Rheumatology 20% improvement criteria; CDAI=Clinical Disease Activity Index; DAS28=Disease activity score in 28 joints; MHAQ=Modified Health Assessment Questionnaire; RAPID3=Routine Assessment of Patient Index Data 3; SDAI=Simplified Disease Activity Index.

Description of the Composite Clinical Tools Used to Assess Disease Activity in RA

<table>
<thead>
<tr>
<th>Measure</th>
<th>Formula</th>
<th>Disease Activity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>$(0.56 \times \sqrt{TJC}) = 90.28 \times \sqrt{SJJC} + (0.70 \times \log_{10} (ESR)) + (0.014 \times PGA)$</td>
<td>&lt; 2.6</td>
<td>&lt; 3.2</td>
</tr>
<tr>
<td>SDAI</td>
<td>SJC + TJC + PGA + PhGA + CRP</td>
<td>≤ 11</td>
<td>11 - 26</td>
</tr>
<tr>
<td>CDAI</td>
<td>SJC + TJC + PGA + PhGA</td>
<td>≤ 10</td>
<td>10 - 22</td>
</tr>
<tr>
<td>MHAQ</td>
<td>Patient rating of ability to perform 8 ADLs using a score from 0 (&quot;without difficulty&quot;) to 3 (&quot;unable to do&quot;)</td>
<td>0</td>
<td>1-2</td>
</tr>
<tr>
<td>RAPID3</td>
<td>Composite index of physical function, pain, and patient global estimate, each scored 0-10, for a total of 30</td>
<td>3.1 – 6.0</td>
<td>6.1 – 12.0</td>
</tr>
</tbody>
</table>

DAS28=Disease Activity Score using 28 joint counts; SDAI=Simplified Disease Activity Index; CDAI=Clinical Disease Activity Index; MHAQ=Modified Health Assessment Questionnaire; RAPID3=Routine Assessment Patient Data Index; TJC=Tender Joint Count; SJC=Swollen Joint Count; ESR=Erythrocyte Sedimentation Rate; PGA=Patient Global Assessment; CRP=C-Reactive Protein; PhGA=Physician Global Assessment.

Treat-to-Target Algorithm


Commonly Used Non-Biologic Disease Modifying Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Route of Administration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Dihydrofolate reductase inhibitor</td>
<td>Oral</td>
<td>Hepatotoxicity; teratogenesis; alopecia</td>
</tr>
<tr>
<td>Leflunomide (Arava)¹</td>
<td>Pyrimidine synthesis inhibitor</td>
<td>Oral</td>
<td>Alopecia; hepatotoxicity; GI effects; teratogenesis; opportunistic infections</td>
</tr>
<tr>
<td>Hydroxychloroquine (Plaquinil)²</td>
<td>Not well defined</td>
<td>Oral</td>
<td>Ocular toxicity (rare); alopecia; GI effects</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine)³</td>
<td>Not well defined</td>
<td>Oral</td>
<td>Anemia; renal and hepatotoxicities; GI effects; skin reactions</td>
</tr>
</tbody>
</table>

## Biologic Disease Modifying Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Route of Administration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Anti-TNFα</td>
<td>SQ</td>
<td>Tuberculosis (TB); opportunistic infections; Injection reactions</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>Anti-TNFα</td>
<td>SQ</td>
<td>TB; opportunistic infections; Injection reactions</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Anti-TNFα</td>
<td>SQ</td>
<td>TB; opportunistic infections; Injection reactions</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Anti-TNFα</td>
<td>SQ</td>
<td>TB; opportunistic infections; Injection reactions</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Anti-TNFα</td>
<td>IV</td>
<td>TB; Opportunistic infections; Infusion reactions</td>
</tr>
<tr>
<td>Abatacept (Oencia)</td>
<td>Costimulator blocker; cytotoxic T-lymphocyte antigen</td>
<td>IV or SQ</td>
<td>TB; Opportunistic infections; Infusion/injection reactions</td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>IL-1 antagonist</td>
<td>SQ</td>
<td>TB; Opportunistic infections; Injection reactions</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Anti-CD20</td>
<td>IV</td>
<td>TB; Opportunistic infections; Infusion reactions; Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>IL-6 antagonist</td>
<td>IV</td>
<td>TB; Opportunistic infections; Infusion reactions</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>JAK inhibitor</td>
<td>Oral</td>
<td>TB; Opportunistic infections; hepatotoxicity; lipid disorders</td>
</tr>
</tbody>
</table>

Decision Support Tools: Comparative Effectiveness Research (CER) Enables Better Informed Decision Making

- **Definition**
  - “Generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care”
  - Compares the relative merits of one intervention vs. competing interventions

- **Purpose**
  - “Synthesize existing evidence in order to address knowledge gaps and drive patient-focused clinical decisions and outcomes”

- **Perspective**
  - Considers the needs of patients, clinicians, purchasers, and policy makers
  - Addresses a broad range of topics including tests, treatments, prevention strategies, care delivery and monitoring
  - Includes study populations that are commonly seen in clinical practice
  - Focuses on patient-centered decision-making in order to tailor tests/treatments to specific patients


**CER: What is Being Compared?**

- Competing treatment alternatives
  - Novel vs. current standard of care
  - Competing vs. novel interventions

- Health or economic outcomes resulting from an intervention
  - Overall Survival
  - Cost-effectiveness

- Harms resulting from an intervention
  - Occurrence of adverse events among competing interventions

- Patient preferences for competing interventions

**CER as a Decision Support Tool**

- Informs development of treatment pathways to support guideline-concordant care
  - Reduces variability in outcomes
  - Reduces variability in costs
  - Invests in patients’ health and improves health outcomes
  - Reduces wasteful spending by reducing toxicities

- CER can be used to address clinical and cost endpoints
  - Identify subgroups of responders
  - Include patient-centered outcomes
  - Examine the impact of patient cost-sharing on clinical outcomes
CER: Utilized to Differentiate the Effectiveness vs. Efficiency of Treatment Alternatives

CER: Processes, Stakeholders, and Data Sources

**Decision makers:**
- Purchasers
- Policy makers
- Patients
- Providers
- Guideline developers
- Regulators

**Policy concerns:**
- Utilization
- Reimbursement
- Patient access and equity

**Comparative Effectiveness Research**

**Data sources:**
- RCTs
- Retrospective analyses
- Registries
- Meta-analyses
- Observational studies
- Case studies
- Cohort studies
- PROs
- EMR

**Data analysis:**
- Systematic reviews
- Modeling
- Indirect, mixed, and network comparisons

**Communication and implementation:**
- Decisions
- Recommendations

**Apply evidentiary standards to make decisions about:**
- Utilization
- Benefit design
- Reimbursement
- Clinical pathways
CER: Modeling to Generate and Synthesize Comparative Data

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Description</th>
<th>Best Suited For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision tree</td>
<td>Diagrams the risk of events and states of nature over a fixed time horizon</td>
<td>Interventions for which the relevant time horizon is short and fixed</td>
</tr>
<tr>
<td>Markov</td>
<td>Simulates a hypothetical cohort of individuals through a set of health states over time</td>
<td>Modeling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events</td>
</tr>
<tr>
<td>Microsimulation</td>
<td>Tracks the past health states of individual and models risk of future events</td>
<td>Modeling complex disease processes, when Markov models are too limiting</td>
</tr>
<tr>
<td>Discrete event simulation</td>
<td>Simulates time to an event and subsequent events, one individual at a time as well as interactions among individuals or within a health care system</td>
<td>Evaluating alternative health care systems</td>
</tr>
</tbody>
</table>


CER: Agency for Healthcare Research and Quality (AHRQ) Review of RA Drug Therapy

- In 2011, AHRQ published an update of the 2007 systematic review on the comparative effectiveness of corticosteroids, and oral and biologic DMARDs in the treatment of adults with RA
- The 2011 analysis included 258 published articles reporting on 211 studies:
  - 31 head-to-head randomized controlled trials
  - 1 head-to-head nonrandomized controlled trial
  - 44 placebo-controlled trials
  - 28 meta-analyses or systematic reviews
  - 107 observational studies
  - 30 studies for quantitative synthesis for analysis of effects on disease activity and joint damage
  - 42 studies for quantitative syntheses for analysis of adverse effects
- AHRQ compiled this report to summarize and integrate the available data to support evidence-based practice decision making

Principles for Conducting the AHRQ CER Review

- Conduct a timely, relevant, objective, and scientifically rigorous systematic review of all relevant clinical studies (funded by AHRQ) to synthesize the evidence in a report summarizing what is known and not known about the select clinical issue
- Approach the evidence from a clinical, patient-centered perspective
- Fully explore the clinical logic underlying the rationale for a service
- Casting a broad net with respect to types of evidence, which includes placing a high value on effectiveness and applicability, in addition to internal validity
- Present benefits and harms for different treatments and tests in a consistent manner

Clinical Questions Addressed by the CER Review of RA Therapies

- Clinical questions addressed by the comparative effectiveness review include:
  - Do drug therapies for RA differ in their ability to reduce disease activity, to slow or limit the progression of joint damage, or to maintain remission?
  - Do drug therapies for RA differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
  - Do drug therapies for RA differ in harms, tolerability, patient adherence, or adverse effects?
  - 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?


Outcomes Assessed by the CER Review of RA Therapies

- Clinically significant outcomes of interest included:
  - Disease activity and symptoms
    - ACR 20/50/70: American College of Rheumatology response scores
    - DAS and DAS28: disease activity score
  - Radiographic changes
    - Sharp/van der Heijde Method (SHS) for scoring radiographs
  - Functional capacity
    - HAQ: Health Assessment Questionnaire
    - HAQ-DI: disability index of the Health Assessment Questionnaire
    - Quality of life
    - SF-36
    - EQ-5D
  - Adverse effects of interest included:
    - Withdrawal due to adverse events
    - Time to withdrawal
    - Infusion and injection-site reactions
    - Infections
    - Malignancy
    - Mortality
    - Cardiovascular and cerebrovascular events
    - Rare but serious adverse events: demyelination, autoimmunity, pancytopenia, and hepatotoxicity

CER Review of RA Therapies: Search Strategy Used to Identify Data for the Analysis

- Relevant published randomized controlled trials (RCTs), reviews, and meta-analyses were included and were identified by searching databases such as MEDLINE, Embase, the Cochrane Library, Scopus, and the International Pharmaceutical Abstracts
- Additional searches were conducted on the database from the Center for Drug Evaluation and Research (CDER) to locate unpublished research
- Study selection criteria were based on application to the 4 key clinical questions
- Studies were selected for the review based on the following criteria:
  - Research in humans and published in the English language
  - Studies with sample sizes of at least 100 and duration of at least 3 months
  - Studies that used doses within the recommended dosing range or doses that would be considered equivalent to the recommended range
  - Head-to-head trials and prospective cohort trials comparing one drug to another for efficacy and effectiveness
  - Placebo-controlled, double-blind RCTs for biologic DMARDs
  - Head-to-head trials, high-quality systematic reviews and observational studies to compare harms and tolerability, and efficacy and effectiveness in different subgroups


Disease Activity Measurement Included in the AHRQ CER Review

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Range of Scores</th>
<th>How Improvement is Reflected</th>
<th>Clinically Significant Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR Improvement from baseline</td>
<td>0 – 100%</td>
<td>Increase</td>
<td>—</td>
</tr>
<tr>
<td>ACR 30, 50, or 70% criteria for improvement</td>
<td>0 – 100%</td>
<td>Increase</td>
<td>ACR 20 is 20% minimal improvement; ACR 50/70 considered more clinically significant</td>
</tr>
<tr>
<td>Arthritis-specific Health Index (ASHI)</td>
<td>0 – 100</td>
<td>Increase</td>
<td>—</td>
</tr>
<tr>
<td>Disease Activity Score (DAS)</td>
<td>0 – 10</td>
<td>Decrease</td>
<td>DAS &lt;1.6 correlates with remission</td>
</tr>
<tr>
<td>DAS Short Form (DAS28)</td>
<td>0 – 10</td>
<td>Decrease</td>
<td>DAS28 &lt;2.6 correlates with remission</td>
</tr>
<tr>
<td>Dermatology Life Quality Index (DLQI)</td>
<td>0 – 30</td>
<td>Decrease</td>
<td>—</td>
</tr>
<tr>
<td>EuroQol Quality of Life Questionnaire (EQ-5D)</td>
<td>0 – 1</td>
<td>Increase</td>
<td>—</td>
</tr>
<tr>
<td>EULAR Response</td>
<td>N/A</td>
<td>N/A</td>
<td>—</td>
</tr>
<tr>
<td>Health Assessment Questionnaire Disability Index (HAQ-DI)</td>
<td>0 – 3</td>
<td>Decrease</td>
<td>—</td>
</tr>
<tr>
<td>Short Form 36 Health Survey (SF-36)</td>
<td>0 – 100</td>
<td>Increase</td>
<td>SF-36 physical or mental component—2 standard errors of the mean</td>
</tr>
<tr>
<td>Sharp/van der Heijde Scores (SHS)</td>
<td>0 – 148</td>
<td>Decrease</td>
<td>Change in joint damage of 5 units of the SHS score is minimally clinically important</td>
</tr>
</tbody>
</table>

## AHRQ CER Review Summary of Findings: Oral DMARDs

<table>
<thead>
<tr>
<th>Key Comparison</th>
<th>Efficacy (Strength of Evidence)</th>
<th>Harms (Strength of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral DMARD vs. Oral DMARD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide vs. MTX</td>
<td>• No differences in ACR 20 or radiographic responses (Low)</td>
<td>• No consistent differences in tolerability and discontinuation rates (Low)</td>
</tr>
<tr>
<td></td>
<td>• No clinically significant difference for functional capacity (Low)</td>
<td>• Mixed results for specific adverse events (Insufficient)</td>
</tr>
<tr>
<td></td>
<td>• Greater improvement in health-related quality of life (SF-38 physical component) for leflunomide (Low)</td>
<td></td>
</tr>
<tr>
<td>Leflunomide vs. sulfasalazine</td>
<td>• Mixed ACR response rates (Insufficient)</td>
<td>• No differences in tolerability and discontinuation rates (Low)</td>
</tr>
<tr>
<td></td>
<td>• No differences in radiographic changes (Low)</td>
<td>• Mixed results for specific adverse events (Insufficient)</td>
</tr>
<tr>
<td></td>
<td>• Greater improvement in functional capacity for leflunomide (Low)</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine vs. MTX</td>
<td>• No differences in ACR 20 response, disease activity scores and radiographic changes† (Moderate)</td>
<td>• No differences in tolerability; more patients stayed on MTX long term (Low)</td>
</tr>
<tr>
<td></td>
<td>• No differences for functional capacity† (Moderate)</td>
<td>• Mixed results for specific adverse events (Insufficient)</td>
</tr>
<tr>
<td><strong>Oral DMARD Combination vs. Oral DMARD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy</td>
<td>• In patients with early RA, no differences in ACR 20 response rates or radiographic changes (Moderate)</td>
<td>• Withdrawal rates attributable to adverse events higher with combination (Low)</td>
</tr>
<tr>
<td></td>
<td>• No differences in functional capacity (Moderate)</td>
<td>• Insufficient evidence for specific adverse events (Insufficient)</td>
</tr>
<tr>
<td>Oral DMARD plus prednisone vs. oral DMARD</td>
<td>• Mixed results for disease activity (Insufficient)</td>
<td>• No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment (Moderate)</td>
</tr>
<tr>
<td></td>
<td>• Less radiographic progression in patients on DMARD plus prednisone (Low)</td>
<td>• No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications (Low)</td>
</tr>
<tr>
<td></td>
<td>• In patients with early RA, significantly lower radiographic progression and fewer eroded joints (Low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy (Moderate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No difference in quality of life (Low)</td>
<td></td>
</tr>
</tbody>
</table>

† at MTX doses ranging from 7.5 to 25 mg per week.

### AHRQ CER Review Summary of Findings: Biologic DMARDs

<table>
<thead>
<tr>
<th>Key Comparison</th>
<th>Efficacy (Strength of Evidence)</th>
<th>Harms (Strength of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biologic DMARD vs. Biologic DMARD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abatacept vs. Infliximab</td>
<td>• Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference (Low)</td>
<td>• Discontinuation rates and severe adverse events higher with infliximab (Low)</td>
</tr>
<tr>
<td>Biologic vs. biologic (Mixed treatment comparisons)</td>
<td>• No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX (Low) • Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance (Low) • Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab (Low)</td>
<td>• Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab (Low) • Risk for injection site reactions apparently highest with anakinra (Low) • Mixed results for specific adverse events (Insufficient)</td>
</tr>
<tr>
<td><strong>Biologic DMARD vs. Oral DMARD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-tumor necrosis factor drugs vs. MTX</td>
<td>• In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs (Moderate) • No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX (Low; Insufficient) • Faster improvement in quality of life with etanercept than MTX (Low)</td>
<td>• No differences in adverse events in efficacy studies (Low) • Insufficient evidence on differences in the risk for rare but severe adverse events (Insufficient)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Comparison</th>
<th>Efficacy (Strength of Evidence)</th>
<th>Harms (Strength of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic DMARD Combinations</td>
<td>No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept (Low)</td>
<td>Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy (Moderate)</td>
</tr>
</tbody>
</table>
| Biologic DMARDs + MTX vs. biologic DMARDs | Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics (Moderate)  
- In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group (Low)  
- In MTX-naive subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life (Low) with combination therapy  
- In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life (Low) | No differences in adverse events in efficacy studies (Low)  
Insufficient evidence on differences in the risk for rare but severe adverse events (Insufficient) |
| Biologic DMARDs + oral DMARD other than MTX vs. biologic DMARDs | No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy (Low) | No differences in adverse events in efficacy studies (Low)  
Insufficient evidence on differences in the risk for rare but severe adverse events (Insufficient) |
| Biologic DMARD + MTX vs. MTX | Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. High for clinical response and functional capacity, Moderate for quality of life | Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis (Low)  
Mixed evidence on differences in the risk for rare but severe adverse events (Insufficient) |

### AHRQ CER Review Summary of Findings: Strategies in Early RA

<table>
<thead>
<tr>
<th>Key Comparison</th>
<th>Efficacy (Strength of Evidence)</th>
<th>Harms (Strength of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategies in Early RA</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Two oral DMARDs + prednisone vs. oral DMARD | • In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks (Low)  
• In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks (Low)  
• More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks (Low) | • No differences in discontinuation rates (Moderate) |
| Three oral DMARDs + prednisone vs. one oral DMARD | • In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability (Low)  
• In patients with early RA, significantly lower radiographic progression and fewer eroded joints (Low) | • No differences in discontinuation rates (Moderate) |
| Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab | • Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years (Low) | • No differences in serious adverse events between groups (Low) |

Modeling to Compare the Cost-Effectiveness of RA Treatments

Types of Comparative Cost Analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Units of Cost Measurement</th>
<th>Outcome Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-minimization</td>
<td>Monetary units*</td>
<td>Natural units†</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Monetary units*</td>
<td>Natural units†</td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Monetary units*</td>
<td>Quality-adjusted life years (QALYs)</td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Monetary units*</td>
<td>Monetary units*</td>
</tr>
<tr>
<td>Cost-consequence</td>
<td>Monetary units*</td>
<td>All the above*†</td>
</tr>
</tbody>
</table>

* monetary units such as $, €, £, etc.
† life years, mg/dL, etc.
## Examples of Recently Published Cost Analyses of RA Treatments

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Year</th>
<th>Journal</th>
</tr>
</thead>
</table>
Role of CER in Benefit Design and Re-evaluation

![Diagram showing CER Analysis with pathways for demonstrated superior, demonstrated similar, and insufficient evidence to judge comparative clinical effectiveness with corresponding benefit options such as preferred formulary position, formulary tier 2, and non-preferred formulary status.]

Patient-Centered Outcomes Research (PCOR) and CER

- The main objective of much of health care is improving how a patient feels and functions
- Capturing patient perspective is vital to obtain a complete picture of the impact of a treatment
- CER can be used to accelerate development of useful patient-focused evidence
  - Apply research-grade standardized questionnaires to obtain patient perspective
  - More uniform inclusion of patient-reported outcomes in clinical trials and registries
  - Integrate patient-reported outcomes into electronic medical records (EMRs)


Using Health Information Technology to Support CER: Electronic Medical Records (EMR)

• Definition
  – Longitudinal collection of health information with real-time access to person- and population-level data
  – Provides knowledge and decision-support systems that enhance the quality, safety, and efficiency of patient care
  – Improves the accuracy and efficiency of health care delivery

• Benefits
  – Timely access to accurate and complete patient information
  – Improved patient care and safety
  – Enhanced outcomes
  – Minimize/avoid adverse drug events
  – Improved quality measures
  – Increased operational efficiencies

• Core functions
  – Health information and data
  – Results management
  – Order management
  – Decision support
  – Electronic communication and connectivity
  – Patient support
  – Administrative processes and reporting
  – Reporting and population health management

• Features
  – Internal messaging and flags for coordination, collaboration, referral, and reminders
  – Personalized results for patient discussion/education
  – Lab interface for results reporting
  – Scheduling tool for follow up
  – Queries to identify patients needing specific care
  – Patient chart templates with built in guideline prompts
    • Flow sheets, tables, summaries, etc., as decision aids

Institute of Medicine Key Capabilities of an Electronic Health Record System. Available at: http://www.nap.edu/catalog/10781.html.
Comparative Effectiveness Research/Rheumatoid Arthritis Tool Kit

Coordination of RA Care: Adoption of EMR Improves Delivery of Guideline-Recommended Care and Improves Communication with Patients and Other Providers

Survey of Physician (n=2758) Perspectives on the Impact of an Electronic Medical Record

<table>
<thead>
<tr>
<th>Feature</th>
<th>Fully Functional EMR System</th>
<th>Basic EMR System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery of Guideline-Recommended Chronic Illness Care</td>
<td>56%</td>
<td>82%</td>
</tr>
<tr>
<td>Delivery of Guideline-Recommended Preventative Care</td>
<td>55%</td>
<td>85%</td>
</tr>
<tr>
<td>Quality of Clinical Decisions</td>
<td>63%</td>
<td>82%</td>
</tr>
<tr>
<td>Avoiding Medication Errors</td>
<td>80%</td>
<td>86%</td>
</tr>
<tr>
<td>Quality of Communications with Patients</td>
<td>59%</td>
<td>72%</td>
</tr>
<tr>
<td>Quality of Communications with Other Providers</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>Timely Access to Medical Records</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>Prescription Refills</td>
<td>85%</td>
<td>95%</td>
</tr>
</tbody>
</table>


Summary

- Rheumatoid arthritis is a chronic, progressive, inflammatory, autoimmune disease of unknown etiology in which functional declines begin early in the disease process
  - Early treatment with the appropriate therapy is associated with better outcomes
  - A treat-to-target approach is recommended to reduce disease activity and elicit remission
- Current treatment patterns may be suboptimal due in part to a lack of data comparing treatment options
- Comparative effectiveness research (CER) is used to compare the relative merits of one intervention vs. competing interventions
  - CER results can be used to inform clinical and economic health care decisions
- The Agency for Healthcare Research and Quality recently published an updated CER review of RA treatments comparing
  - Oral DMARDs
  - Biologic DMARDs
  - Combinations of biologic DMARDs
  - Early RA treatment strategies
- Modeling is an effective tool to compare the costs of RA treatment regimens
- CER is an effective tool to support patient-centered outcomes research
POST-TEST

If you wish to receive acknowledgment for completing this activity, please complete the post-test and evaluation on www.cmeuniversity.com. On the navigation menu, click on “Find Post-test/Evaluation by Course” and search by course ID 9295. Upon registering and successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately.

1. The research process involving generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care is referred to as ________.
   A. Patient-centered outcomes research
   B. Health economics research
   C. Clinical trial research
   D. Comparative effectiveness research

2. Comparative effectiveness research (CER) is necessary because clinical trial data comparing treatment outcomes elicited by two or more competing therapies is often not available.
   A. True
   B. False

3. Which of the following research methods is best used to determine if a novel treatment is safe and effective?
   A. Health technology assessment
   B. Randomized clinical trial
   C. Comparative effectiveness research
   D. Population registry analysis

4. CER can be used to support decision making in all the following areas EXCEPT
   A. Developing of practice guidelines
   B. Determining formulary positioning of competing products
   C. Developing of treatment pathways
   D. Establishing the specific out-of-pocket cost of a drug

5. Simulation of hypothetical cohort of patients through a set of health states over time best describes______.
   A. Microsimulation
   B. Markov modeling
   C. Discrete event simulation
   D. Decision tree analysis

6. Which of the following is NOT a data analysis technique used in comparative effectiveness research?
   A. Indirect treatment comparisons
   B. Mixed treatment comparisons
   C. Randomized comparisons
   D. Network comparisons

7. Which of the following was NOT a data source used to conduct the 2011 Agency for Healthcare Research and Quality (AHRQ) CER analysis of rheumatoid arthritis therapies?
   A. Randomized controlled clinical trials
   B. Results of meta-analyses
   C. Observational studies
   D. Data from electronic medical records

8. Capturing the patient experience with their treatment is a goal of patient-centered outcomes research. All of the following are methods used to capture the patient experience EXCEPT
   A. Utilize research-grade questionnaires to capture patient feedback
   B. Capture patient-reported outcomes in the electronic medical record during each treatment encounter
   C. Survey physician recall of patient feedback
   D. Collect patient-reported outcomes during clinical trials