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

This activity is jointly sponsored by
Annenberg Center For Health Sciences at Eisenhower
Impact Education, LLC
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This activity is supported by educational grants from Bristol-Myers Squibb and Genentech, and an educational donation from Amgen Inc.
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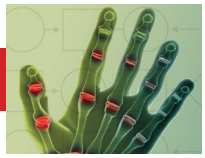


TARGET AUDIENCE

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.

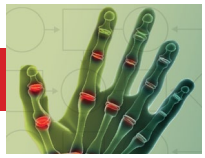
STATEMENT OF NEED/PROGRAM OVERVIEW

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.



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TYPE OF ACTIVITY

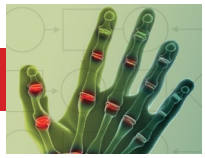
Knowledge

FEE INFORMATION

There is no fee for this educational activity.

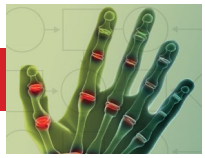
CE information continued on page 5

Comparative Effectiveness Research/Rheumatoid Arthritis Tool Kit



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.

TABLE OF CONTENTS



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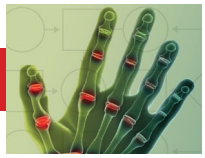

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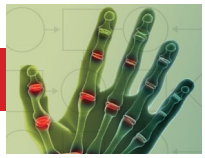


Introduction: Burden of Rheumatoid Arthritis

- **Definition:** Chronic, progressive, inflammatory, autoimmune disease of unknown etiology
- **Prevalence:** ~0.6% of the US population[1]
- **Disability:** Many patients unable to work within 10 years of onset:
  - Pre-biologic era: 50%[2]
  - Current (2008): 35%[3]
- **Cardiovascular risk:** 5x higher CV event rate vs. general population[4]
- **Excess deaths:** Mortality rate 1.5 to 1.6-fold higher in RA patients vs. general population[5]
- **Cost:** Annual per patient direct medical cost ~$13,012 vs. $4950 for control[6]
  - Total annual excess direct cost of RA vs. control ~$22.3 billion[6]

1. Helmick CG. *Arthritis Rheum*. 2008;58:15-25; 2. Yelin E, et al. *Ann Intern Med.* 1980; 93:551–556; 3. Allaire S, et al. *Arthritis Rheum.* 2008;59:474-480; 4. Maradit-Kremers H, et al. *Arthritis Rheum*. 2005;52:402-411; 5. Sokka T, et al. *Clin Exp Rheumatol.* 2008;26(5 Suppl 51):S35-61; 6. Kawatkar AA, et al. *Arthritis Care Res*. 2012;64:1649-1656.

Pathogenesis: Important Molecules and Signal Mediators

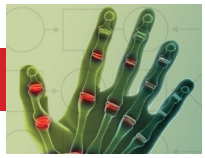
Molecule or Signal Mediator	Disease-Relevant Function	Status
	Cytokines	
Tumor necrosis factor inhibitor (TNF-α)	Induce production of cytokines chemokines, adhesion molecules, matrix enzymes; suppresses regulatory T-cell function; activates of osteoclasts; resorption of cartilage and bone	Approved drug
Interleukin-1a /1b	Induce matrix-enzyme production; activate osteoclasts	Approved drug
Interleukin-6	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	Approved drug
	B-Cell Agents	
CD20	Function of CD20 remains unclear; postulated that CD20 mediates Ca^{2+} influx across plasma membranes, maintaining intracellular Ca^{2+} concentration, and allowing activation of B cells	Approved drug
	T-Cell Agents	
T-cell co-stimulation	T-cell activation occurs when the T-cell receives a secondary (costimulatory) signal; activated T-cells secrete cytokines involved in synovial inflammation	Approved drug
	Intracellular Signaling Molecules and Transcription Factors	
Janus Kinase inhibitor (JAK)	Tyrosine kinase that regulates cytokine-mediated leukocyte maturation and activation, cytokine production, and immunoglobulin production	Approved drug

McInnes IB, Schett G. *N Engl J Med*. 2011;365:2205-2216.

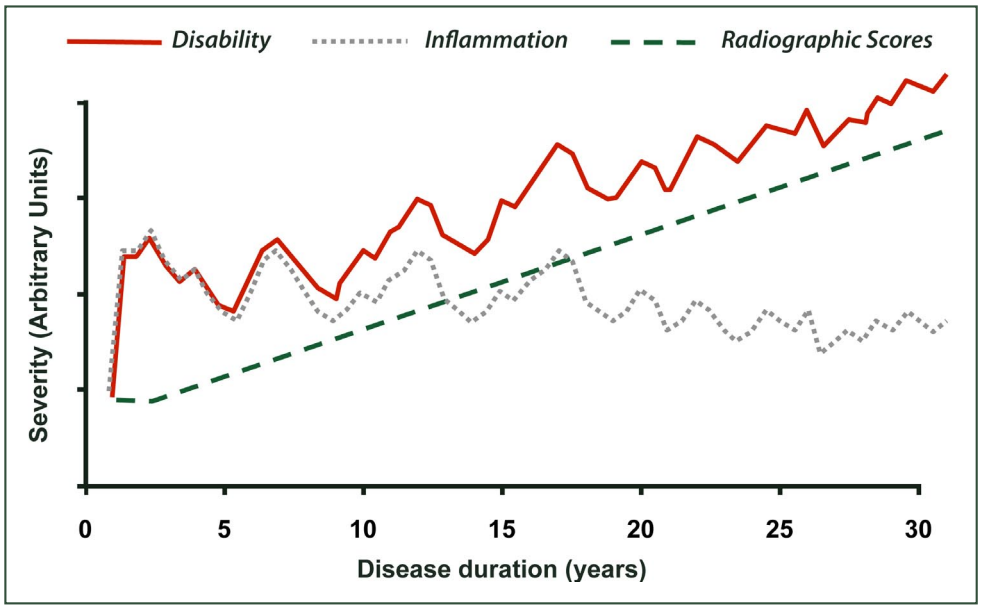
Unmet Needs: Current Treatment Patterns Practice May Be Suboptimal

- A 'start low, go slow' approach remains common in RA management[1]
- Delayed treatment or prolonged under-treatment contributes to uncontrolled inflammation and irreversible tissue damage[2]
- 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[3]
- Patients frequently receive irregular follow-up and minimal therapeutic adjustment[4]

1. Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569–2581; 2. Breedveld FC, Combe B. *Arth Res Ther*. 2011;13(suppl 1):S3; 3. Schmajuk G, et al. *Arthritis Rheum*. 2007;57:928-934; 4. Kievit W. *Ann Rheum Dis.* 2009;68:844-849.



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

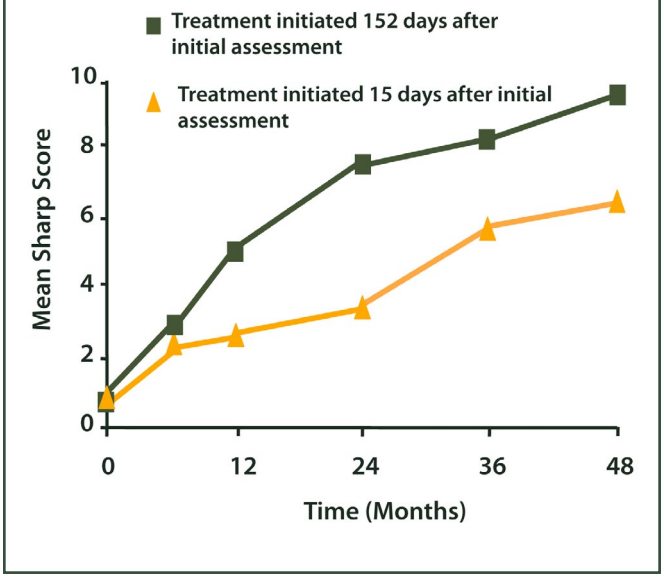


*50% rates of loss of function based on Health Assessment Questionnaire (HAQ) scores.

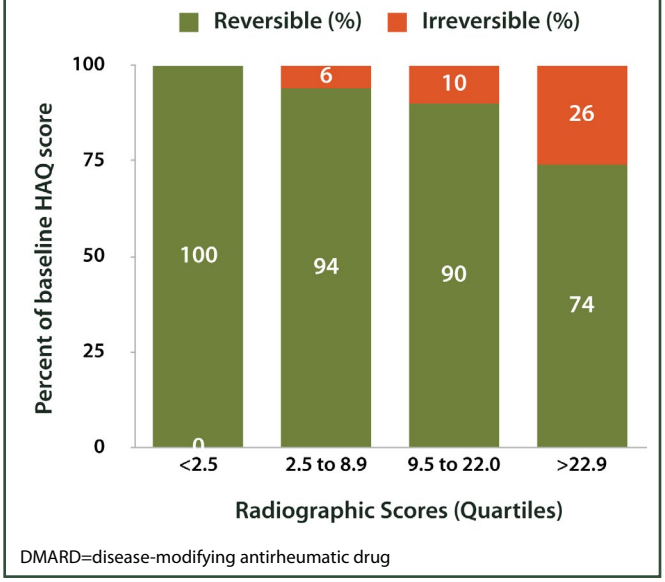
Kirwan J. *J Rheumatol*. 1999;26:720-725; Wolfe F, Cathey MA. *J Rheumatol*. 1991;18:1298-1306.

Unmet Needs: Early Treatment is Associated with Better Outcomes

Early Treatment Reduced Radiographic Evidence of Erosion[1]

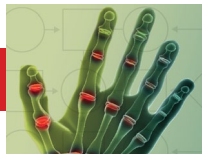


Functional Limitations Minimized by Early DMARD Therapy[2]



DMARD=disease-modifying antirheumatic drug

Reprinted with permission from 1. van Aken J, et al. *Ann Rheum Dis*. 2004;63:274-279; 2. van der Heijde DM. *Br J Rheum*. 1995;34 (suppl 2):74-78.



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

JOINT DISTRIBUTION (0-5)	Points
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
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

≥ 6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ Prospectively over time (cumulatively)

→ Retrospectively if data on all four domains have been adequately recorded in the past

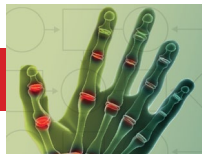
ACR=American College of Rheumatology; EULAR=European League Against Rheumatism; RF=rheumatoid factor; Anti-CCP=Anti-cyclic citrullinated peptide; CRP=c-reactive protein; ESR=erythrocyte sedimentation rate.

Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569–2581.

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

Smolen JF, et al. *Ann Rheum Dis*. 2010;69:631-637.



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:

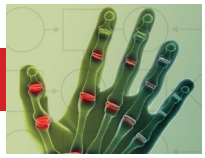
- Improvement of 20%, 50%, or 70% from baseline in the swollen joint count
  AND
- Improvement of 20%, 50%, or 70% from baseline in the tender joint count
  AND
- Improvement of 20%, 50%, or 70% from baseline in at least 3 of the following 5 measures:
  - *Patient Global Assessment (VAS 0-10)*
  - *Physician 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.

Felson DT, et al. *Arthritis Rheum*. 1998;41:1564-1570.

Strengths and Limitations of the ACR Criteria

Strengths	Limitations
Includes objective measures as well as patient and physician evaluation, including functional assessment	Limited application to clinical practice
Requires an initial assessment	Relative response, not an absolute assessment of disease activity
Useful in clinical trials	Patients with significant clinical response may still have very active disease

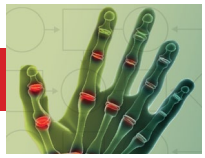


Composite Clinical Tools Used to Assess Disease Activity

Measure	Research Tool	Clinical Instruments			Patient-reported Instruments	
	ACR20	DAS28	SDAI	CDAI	MHAQ	RAPID3
Patient Function	✓				✓	✓
Patient Pain	✓		✓	✓		✓
Patient Global	✓	✓	✓	✓		✓
MD Global	✓		✓	✓		
Number of Tender Joints	✓	✓	✓	✓		
Number of Swollen Joints	✓	✓	✓	✓		
ESR or CRP	✓	✓	✓			

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.

Singh JA, et al. *Arthritis Care Res*. 2012;64:625-639; Landewe R. *Eur Musculoskel Rev.* 2011;6:88-93.

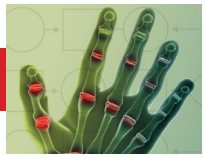


Description of the Composite Clinical Tools Used to Assess Disease Activity in RA

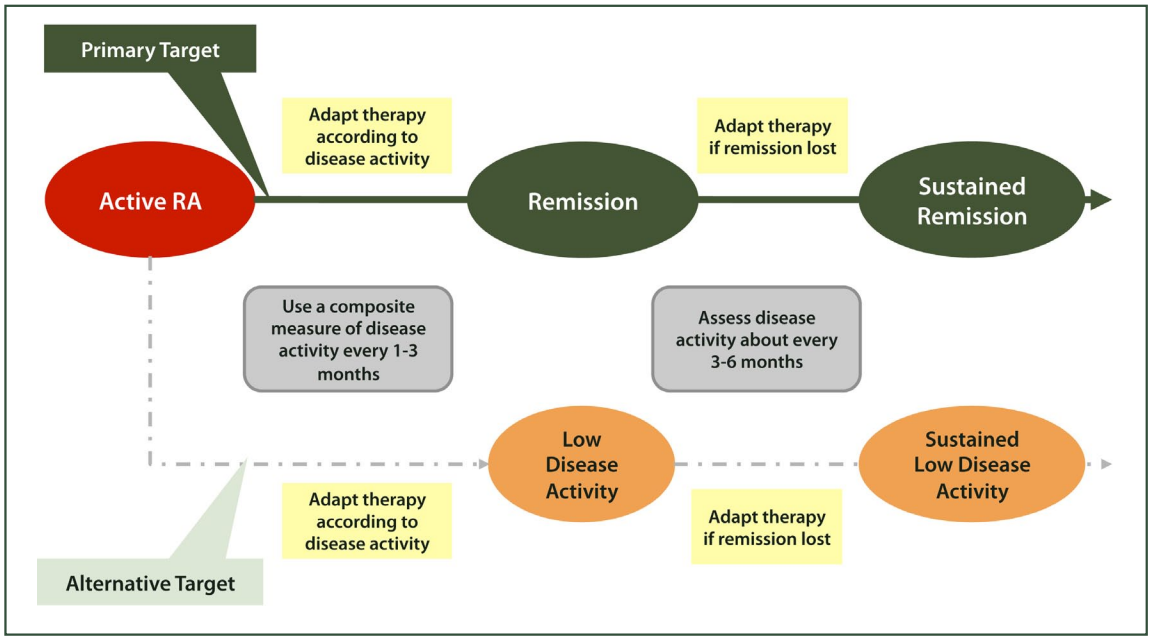
Measure	Formula	Disease Activity			Comment
		Low	Moderate	High	
DAS28	$(0.56 \times \sqrt{TJC}) = 90.28 \times \sqrt{SJC}) + (0.70 \times \log_n ESR) + (0.014 \times PGA)$	< 2.6	< 3.2	< 5.1	Can quantify disease activity at the first clinic visit and be used in subsequent visits for comparison; requires ESR or CRP on day one
SDAI	SJC + TJC + PGA + PhGA + CRP	≤ 11	11 - 26	> 26	Less cumbersome than the DAS28, yet the performance is similar to the DAS28
CDAI	SJC + TJC + PGA + PhGA	≤ 10	10 - 22	> 22	Does not require ESR or CRP; to determine the disease activity score; treatment decisions can be made immediately
MHAQ	Patient rating of ability to perform 8 ADLs using a score from 0 ("without difficulty") to 3 ("unable to do")	0	1-2	3	Requires less time to calculate than the HAQ; strong correlation with other disease activity measures
RAPID3	Composite index of physical function, pain, and patient global estimate, each scored 0-10, for a total of 30	3.1 – 6.0	6.1 – 12.0	> 12.0	RAPID3 is considered he most time-efficient index for usual clinical care

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.

Pincus T, et al. *Bull NYU Hosp Joint Dis.* 2009;67:211-225.



Treat-to-Target Algorithm



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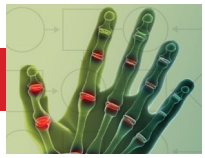
Commonly Used Non-Biologic Disease Modifying Drugs

Drug	Mechanism of Action	Route of Administration	Adverse Effects
Methotrexate	Dihydrofolate reductase inhibitor	Oral	Hepatotoxicity; teratogenesis; alopecia
Leflunomide (Arava)[1]	Pyrimidine synthesis inhibitor	Oral	Alopecia; hepatoxicity; GI effects; teratogenesis; opportunistic infections
Hydroxychloroquine (Plaquenil)[2]	Not well defined	Oral	Ocular toxicity (rare); alopecia; GI effects
Sulfasalazine (Azulfidine)[3]	Not well defined	Oral	Anemia; renal and hepato-toxicities; GI effects; skin reactions

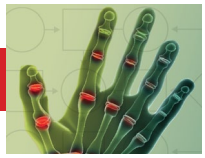
1. Arava [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2012; 2. Plaquenil [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2012; 3. Azulfidine [package insert]. New York, NY: Pfizer, Inc.; 2012.



Biologic Disease Modifying Drugs

Drug	Mechanism of Action	Route of Administration	Adverse Effects
Adalimumab (Humira)[1]	Anti-TNFa	SQ	Tuberculosis (TB); opportunistic infections; Injection reactions
Certolizumab pegol (Cimzia)[2]	Anti-TNFa	SQ	TB; opportunistic infections; Injection reactions
Etanercept (Enbrel)[3]	Anti-TNFa	SQ	TB; opportunistic infections; Injection reactions
Golimumab (Simponi)[4]	Anti-TNFa	SQ	TB; opportunistic infections; Injection reactions
Infliximab (Remicade)[5]	Anti-TNFa	IV	TB; Opportunistic infections; Infusion reactions
Abatacept (Orencia)[6]	Costimulator blocker; cytoxic T-lymphocyte antigen	IV or SQ	TB; Opportunistic infections; Infusion/injection reactions
Anakinra (Kineret)[7]	IL-1 antagonist	SQ	TB; Opportunistic infections; Injection reactions
Rituximab (Rituxan)[8]	Anti-CD20	IV	TB; Opportunistic infections; Infusion reactions; Progressive multifocal leukoencephalopathy (PML)
Tocilizumab (Actemra)[9]	IL-6 antagonist	IV	TB; Opportunistic infections; Infusion reactions
Tofacitinib (Xeljanz)[10]	JAK inhibitor	Oral	TB; Opportunistic infections; hepatotoxicity; lipid disorders

1. Humira [package insert]. North Chicago, IL: Abbott Laboratories; 2012; 2. Cimzia [package insert]. Smyrna, GA: UCB, Inc.; 2012; 3. Enbrel [package insert]. Thousand Oaks, CA: Amgen; 2012; 4. Simponi [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2012; 5. Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2011; 6. Orencia [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2011; 7. Kineret [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2012; 8. Rituxan [package insert]. S. San Francisco, CA: Genentech, Inc.; 2012; 9. Actemra [package insert]. S. San Francisco, CA: Genentech, Inc.; 2012; 10. Xeljanz [package insert]. New York, NY: Pfizer, Inc.; 2012.



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

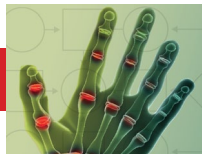
Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: The National Academies Press; 2009.

CER: What is Being Compared?

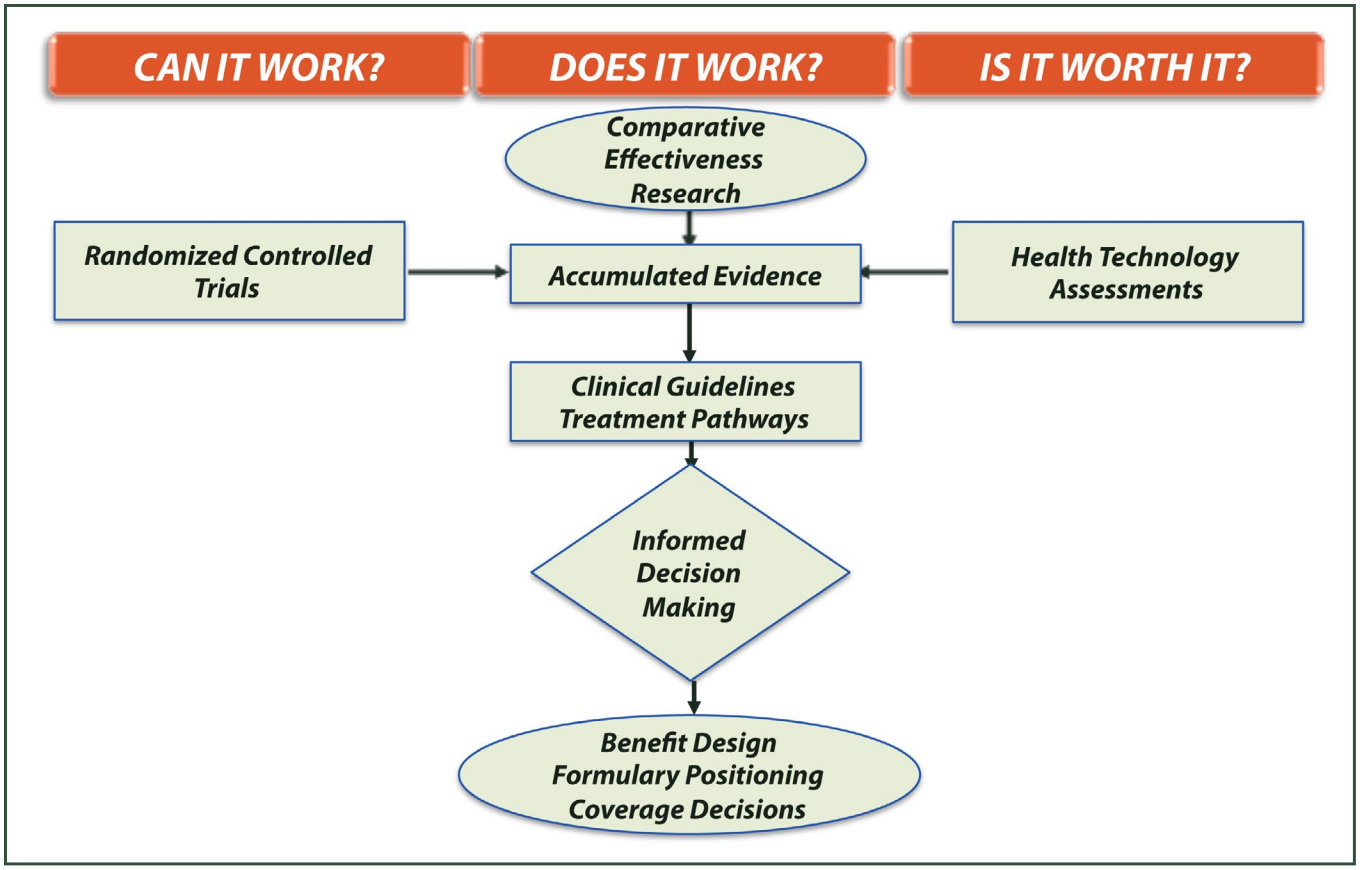
- Competing treatment alternatives
  - Novel vs. current standard of care
  - Competing vs. novel interventions
- Health or economic outcomes resulting from an intervention
  - Overall Survival
  - Cost-effectiveness
- Harms resulting from an intervention
  - Occurrence of adverse events among competing interventions
- Patient preferences for competing interventions

CER as a Decision Support Tool

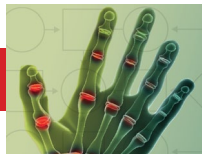
- Informs development of treatment pathways to support guideline-concordant care
  - Reduces variability in outcomes
  - Reduces variability in costs
  - Invests in patients' health and improves health outcomes
  - Reduces wasteful spending by reducing toxicities
- CER can be used to address clinical and cost endpoints
  - Identify subgroups of responders
  - Include patient-centered outcomes
  - Examine the impact of patient cost-sharing on clinical outcomes



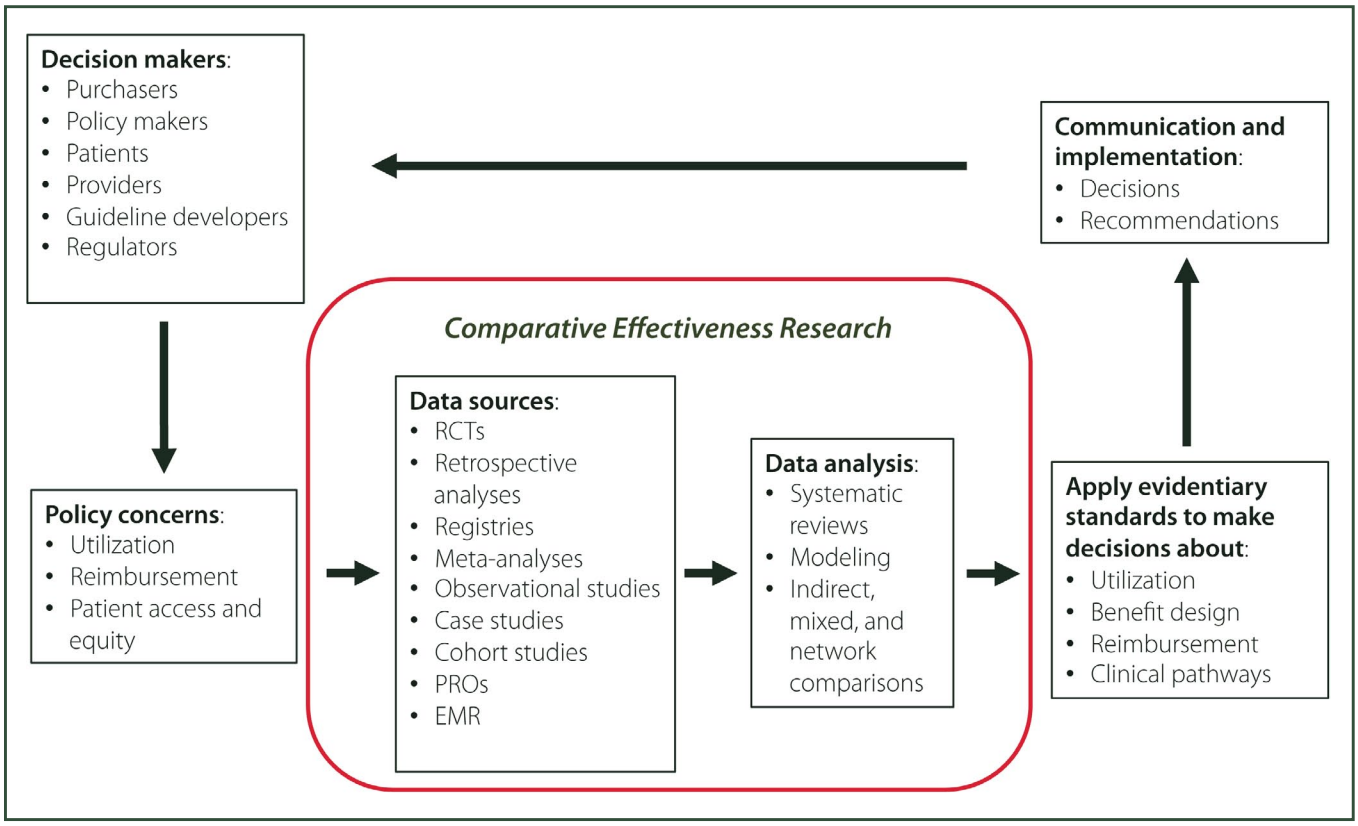
CER: Utilized to Differentiate the Effectiveness vs. Efficiency of Treatment Alternatives

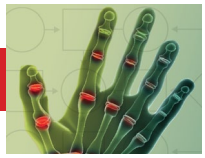


Drummond MF, et al. *Int J Technol Assess Health Care*. 2008;24:244-258.



CER: Processes, Stakeholders, and Data Sources





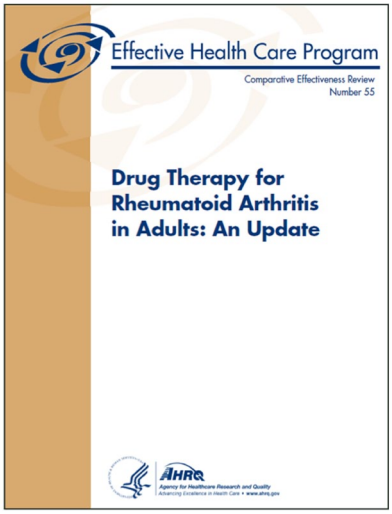
CER: Modeling to Generate and Synthesize Comparative Data

Model Type	Description	Best Suited For
Decision tree	Diagrams the risk of events and states of nature over a fixed time horizon	Interventions for which the relevant time horizon is short and fixed
Markov	Simulates a hypothetical cohort of individuals through a set of health states over time	Modeling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events
Microsimulation	Tracks the past health states of individual and models risk of future events	Modeling complex disease processes, when Markov models are too limiting
Discrete event simulation	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	Evaluating alternative health care systems

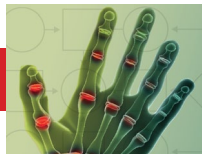
Sainfort F, et al. *Value Health*. 2013;16:133-139; Beresniak A, et al. *Clin Exp Rheumatol*. 2012;30(Suppl. 73):S96-S101.

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



Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



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

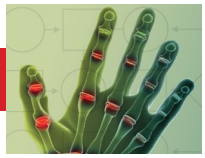
- Clinical questions addressed by the comparative effectiveness review include:
  - Do drug therapies for RA differ in their ability to reduce disease activity, to slow or limit the progression of joint damage, or to maintain remission?
  - Do drug therapies for RA differ in their ability to improve 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?

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.

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

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



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

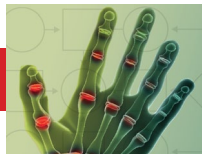
- Relevant published randomized controlled trials (RCTs), reviews, and meta-analyses were included and were identified by searching databases such as MEDLINE, Embase, the Cochrane Library, Scopus, and the International Pharmaceutical Abstracts
- Additional searches were conducted on the database from 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

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.

Disease Activity Measurement Included in the AHRQ CER Review

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

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.

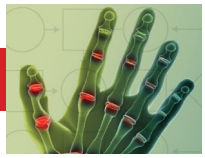


AHRQ CER Review Summary of Findings: Oral DMARDs

Key Comparison	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	• No differences in ACR 20 or radiographic responses (**Low**) • No clinically significant difference for functional capacity (**Low**) • Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide (**Low**)	• No consistent differences in tolerability and discontinuation rates (**Low**) • Mixed results for specific adverse events (**Insufficient**)
Leflunomide vs. sulfasalazine	• Mixed ACR response rates (**Insufficient**) • No differences in radiographic changes (**Low**) • Greater improvement in functional capacity for leflunomide (**Low**)	• No differences in tolerability and discontinuation rates (**Low**) • Mixed results for specific adverse events (**Insufficient**)
Sulfasalazine vs. MTX	• No differences in ACR 20 response, disease activity scores and radiographic changes† (**Moderate**) • No differences for functional capacity† (**Moderate**)	• No differences in tolerability; more patients stayed on MTX long term (**Low**) • Mixed results for specific adverse events (**Insufficient**)
Oral DMARD Combination vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	• In patients with early RA, no differences in ACR 20 response rates or radiographic changes (**Moderate**) • No differences in functional capacity (**Moderate**)	• Withdrawal rates attributable to adverse events higher with combination (**Low**) • Insufficient evidence for specific adverse events (**Insufficient**)
Oral DMARD plus prednisone vs. oral DMARD	• Mixed results for disease activity (**Insufficient**) • Less radiographic progression in patients on DMARD plus prednisone (**Low**) • In patients with early RA, significantly lower radiographic progression and fewer eroded joints (**Low**) • Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy (**Moderate**) • No difference in quality of life (**Low**)	• No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment (**Moderate**) • No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications (**Low**)

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

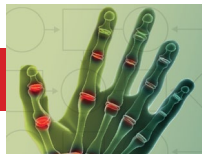
Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



AHRQ CER Review Summary of Findings: Biologic DMARDs

Key Comparison	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biologic DMARD vs. Biologic DMARD		
Abatacept vs. Infliximab	• 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**)	• Discontinuation rates and severe adverse events higher with infliximab (**Low**)
Biologic vs. biologic (Mixed treatment comparisons)	• 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**)	• 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**)
Biologic DMARD vs. Oral DMARD		
Anti-tumor necrosis factor drugs vs. MTX	• 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**)	• No differences in adverse events in efficacy studies (**Low**) • Insufficient evidence on differences in the risk for rare but severe adverse events (**Insufficient**)

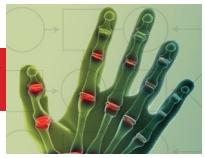
Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



AHRQ CER Review Summary of Findings: Biologic DMARD Combinations

Key Comparison	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biologic DMARD Combinations		
Biologic DMARD + biologic DMARD vs. biologic DMARD	• 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**)	• Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy (**Moderate**)
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-naïve 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**)

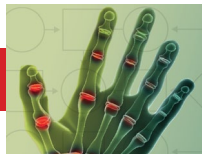
Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



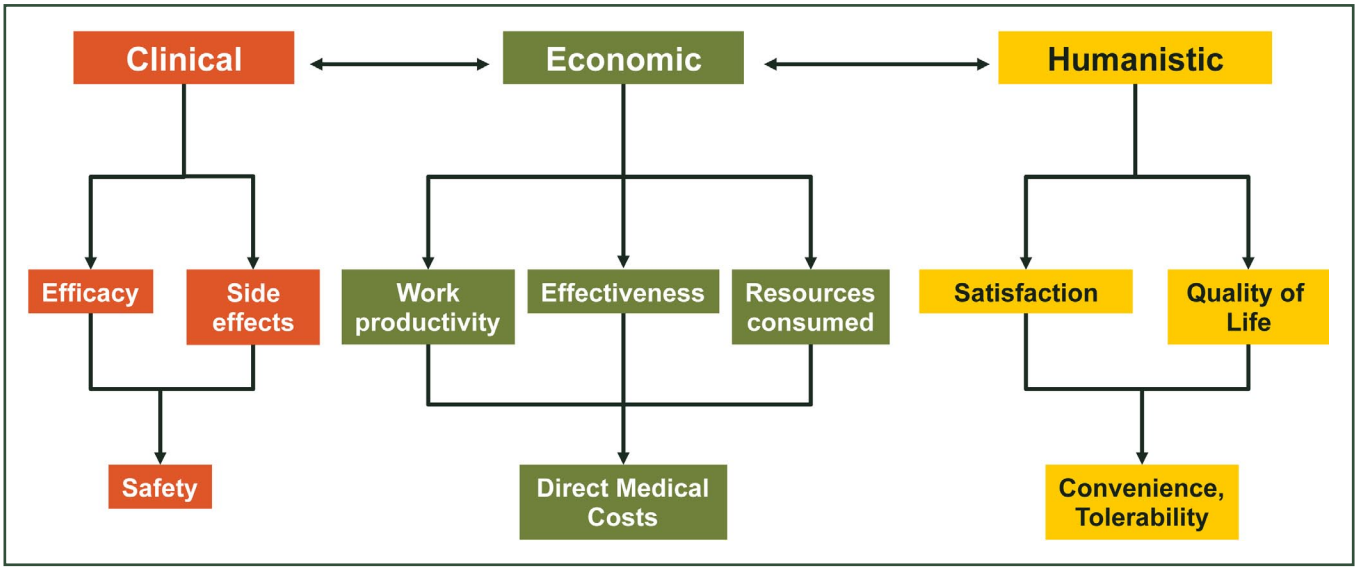
AHRQ CER Review Summary of Findings: Strategies in Early RA

Key Comparison	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Strategies in Early RA		
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**)

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.



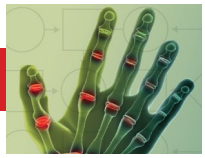
Modeling to Compare the Cost-Effectiveness of RA Treatments



Types of Comparative Cost Analyses

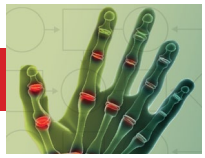
Analysis	Units of Cost Measurement	Outcome Unit
Cost-minimization	Monetary units*	Natural units†
Cost-effectiveness	Monetary units*	Natural units†
Cost-utility	Monetary units*	Quality-adjusted life years (QALYs)
Cost-benefit	Monetary units*	Monetary units*
Cost-consequence	Monetary units*	All the above*†

* monetary units such as $, €, £, etc.
† life years, mg/dL, etc.

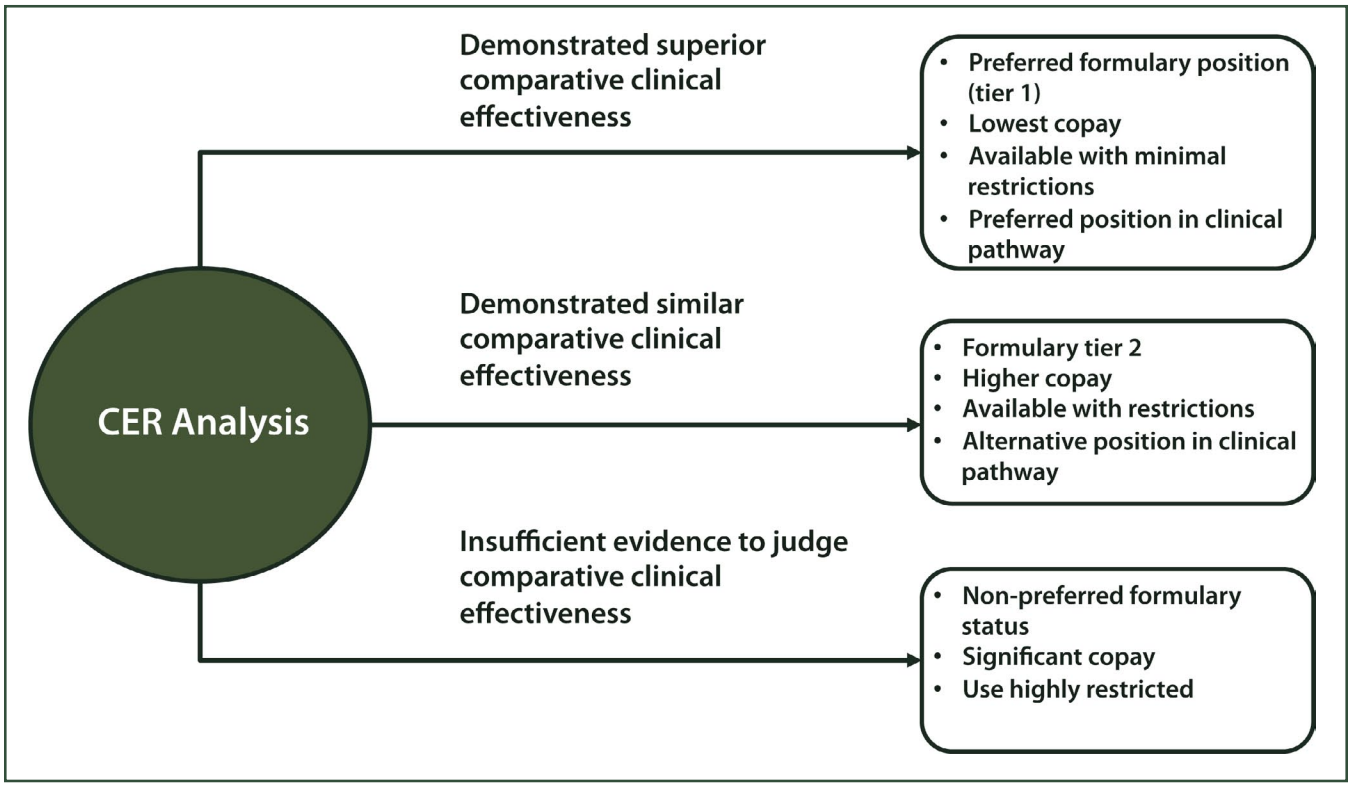


Examples of Recently Published Cost Analyses of RA Treatments

Author	Title	Year	Journal
Sullivan SD, et al.	Economic consequences of sequencing biologics in rheumatoid arthritis: a systematic review.	2013	*J Med Econ*. 16:391-396.
Beresniak A, et al.	Interest of modelling in rheumatoid arthritis.	2012	*Clin Exp Rheumatol*. 30(4 Suppl 73):S96-101.
Cardarelli WJ.	Implications for managed care and specialty pharmacy in rheumatoid arthritis.	2012	*Am J Manag Care. 18(13 Suppl):s315-324.*
Her M, Kavanaugh A.	Critical analysis of economic tools and economic measurement applied to rheumatoid arthritis.	2012	*Clin Exp Rheumatol. 30(4 Suppl 73):S107-111.*
Liu Y, et al.	Cost per responder associated with biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis.	2012	*Adv Ther*. 29:620-624.
Modena V, et al.	Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: An achievable target?	2012	*Autoimmun Rev*. Dec 3. [Epub ahead of print].
Soini EJ, et al.	Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis.	2012	*J Med Econ*. 15:340-351.
Tsao NW, et al.	The issue of comparators in economic evaluations of biologic response modifiers in rheumatoid arthritis.	2012	*Best Pract Res Clin Rheumatol*. 26:659-676.



Role of CER in Benefit Design and Re-evaluation

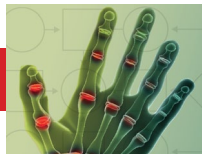


Biskupiak JE, et al. *J Manag Care Pharm*. 2012;18(5):S19-S28.

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)

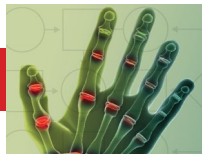
Patient-Centered Outcomes Research Institute. http://www.pcori.org/research-we-support/pcor/establishing-a-definition/.



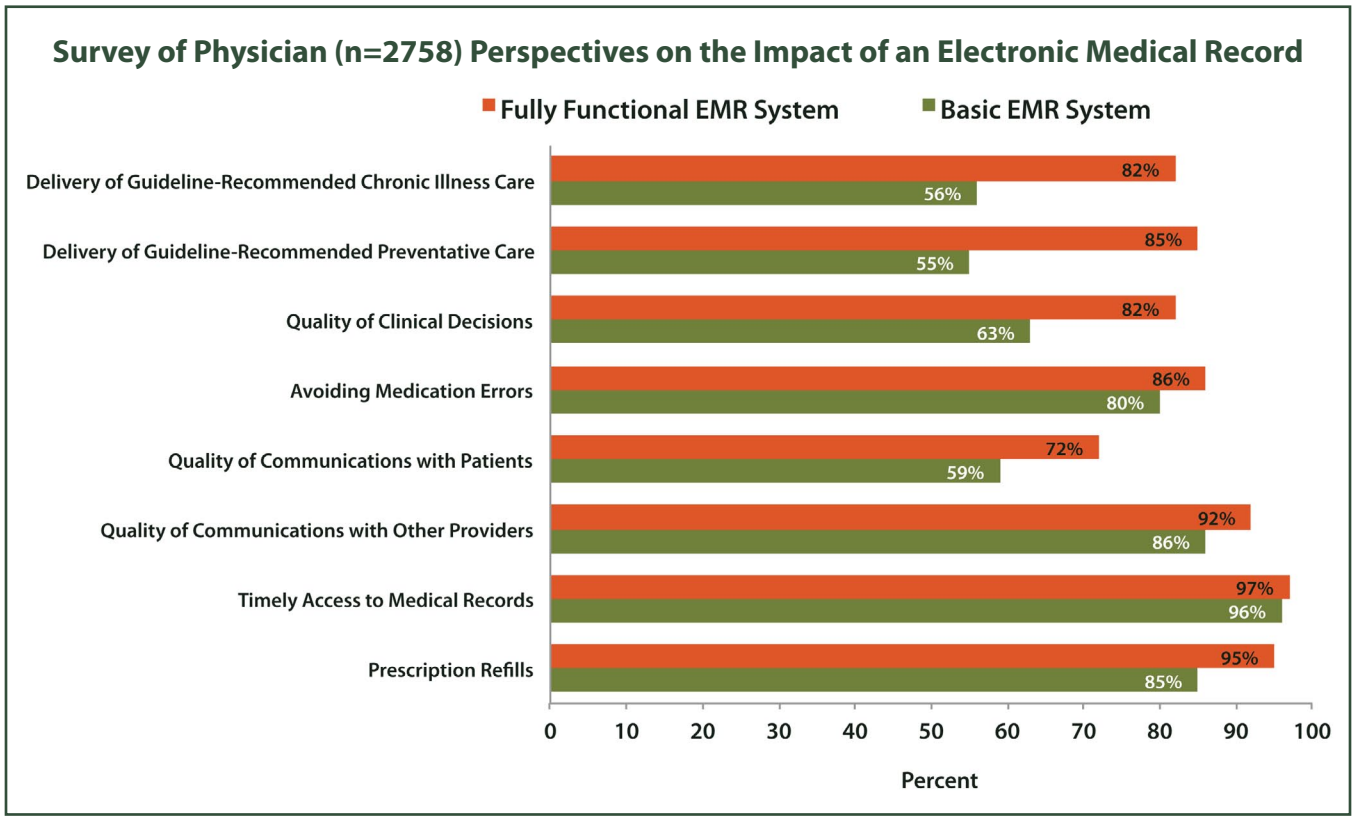
Using Health Information Technology to Support CER: Electronic Medical Records (EMR)

- 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.



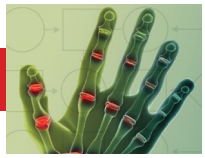
Coordination of RA Care: Adoption of EMR Improves Delivery of Guideline-Recommended Care and Improves Communication with Patients and Other Providers



DesRoches CM, et al. *N Engl J Med.* 2008;359:50-60.

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