2014 American College of Rheumatology Recommendations for the for the Use of Disease-Modifying Antirheumatic Drugs, Biologic Agents, and Glucocorticoids in the Treatment of Rheumatoid Arthritis

Project Plan

PARTICIPANTS

Core Oversight Team

Jasvinder A. Singh, MD, MPH (project PI)
Timothy McAlindon, MD, MPH, MRCP
(literature review leader)
Lou Bridges, MD, PhD

Ken Saag, MD, MSc
Holger Schünemann, MD (GRADE Consultant)

Literature Review Team – Content Experts

Jeff Curtis, MD, MPH
Daniel Furst, MD
Deborah Parks, MD
Rob Simms, MD
Robert Schmerling, MD

Raveendhara Bannuru, MD
Matt Sullivan
Lisa Vayfbrot, MD

Literature Review Team – Methods Experts/Abstractors

Voting Panel

Joan Bathon, MD
David Felson, MD, MPH
Seth Ginsberg, BSc
Arthur Kavanaugh, MD
Charles King, MD
Amye Leong, MBA

Eric Matteson, MD
Eileen Moynihan, MD
Jim O’Dell, MD,
John Schousboe, MD, PhD
William St. Clair, MD
Elizabeth Tindall, MD

ACR Staff

Amy Miller, Regina Parker

Janet Joyce, Research Librarian
Tamara Rader, Research Librarian
ORGANIZATIONAL LEADERSHIP AND SUPPORT

This clinical practice guideline is being developed by the American College of Rheumatology (ACR) with funding by the ACR.

BACKGROUND

Rheumatoid arthritis (RA) is an autoimmune disease, the most common type of inflammatory arthritis that affects more than 1.3 million Americans. Of these, about 75% are women. The disease most often begins between the fourth and sixth decades of life; however, RA can start at any age. Symptoms commonly include joint tenderness, joint swelling and pain. Blood test results for RA patients typically show the presence of rheumatoid factor, antibodies to cyclic citrullinated peptides (anti-CCP), and an elevated erythrocyte sedimentation rate or C-reactive protein.

Although the cause of RA is not known, research is providing more knowledge about what makes the immune system attack the body and create inflammation in the joints, and what role genetics plays. Evidence suggests that activation of immune cells leads to an imbalance between pro-inflammatory and anti-inflammatory cytokines. The hallmarks of RA are synovitis (affecting joints and periarticular structures including tendon sheaths), extra-articular features such as nodules, interstitial lung disease, vasculitis etc. and systemic inflammation that can lead to early and/or accelerated atherosclerosis and premature heart disease.[1]

Early RA is defined as RA disease with a duration of less than 6 months, and established RA as disease with a duration greater than 6 months [2 4] or meeting the 1987 classification criteria. The distinction between early and established is important because 1) it is the expectation that the earlier the treatment, the better the outcome; 2) it is widely thought that joint damage is largely irreversible so prevention of damage is an important goal; and 3) there is data that early intensive therapy may provide the best opportunity to preserve physical function and health-related quality of life and reduce work-related [5 13]

The goals of RA treatment are to reduce symptoms, reduce functional limitations, prevent joint deformity and destruction, and decrease complications of the disease.

The mainstays of treatment have been disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine. Over the past decade, biologic therapies have greatly altered the approach to treatment of RA. In addition, within the last year, a new oral small molecule agent has become available. With the availability of more treatment options and more information about existing therapies, updated recommendations for the treatment of RA patients are needed to help clinicians optimize the care of these patients.

OBJECTIVES

The objective of this project is to develop recommendations for the medical management of patients with RA.

Specifically, we aim to:

1. Develop recommendations for the use of glucocorticoids, non-biologic traditional and biologic disease-modifying anti-rheumatic drugs (DMARDs), including the new small molecule oral agent, taking into consideration both efficacy and safety issues
2. Clarify differences in treatment recommendations for patients with early RA vs. established RA
3. Include recommendations related to high-risk patients with RA (e.g., congestive heart failure, hepatitis B or C, cancer, history of serious infections)
4. Make recommendations about immunizations for patients with RA with live vaccine (herpes zoster)

METHODS AND PROCESSES

Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used. [14] Transparency in determining recommendations is the hallmark of GRADE, from grading the quality of evidence to determining the strength of recommendations. Patient-important outcomes are evaluated, whenever possible, for example, increased functional ability, reduced pain, reduction of adverse effects, and patients’ values and preferences are taken into account. A survey among Voting Panel members, which includes patient representation, will be completed to determine ranking of critical and important outcomes. Outcomes are being voted on for 3 groups of patients - 1) patients with early RA treated with synthetic/traditional DMARDS, anti-TNF biologics, non-TNF biologics or oral tofacitinib, 2) patients with established RA treated with synthetic/traditional DMARDS, anti-TNF biologics, non-TNF biologics, oral tofacitinib, and 3) patients with early or established RA treated with glucocorticoids versus other treatments (synthetic/traditional DMARDS, anti-TNF biologics, non-TNF biologics, or oral tofacitinib. The outcomes voted on will be joint pain, function or functional ability (ability to function in society, work, etc., work productivity, employability, disability, work disability); generic quality of life (including fatigue, sleep, mood stress, anxiety, depression); preventing joint damage (structural damage, deformity); joint stiffness, death; morbidity (diabetes, osteoporosis due to corticosteroid use, prevention of cardiovascular morbidity); serious infections (including but not limited to tuberculosis, fungal and opportunistic infections, serious bacterial infections); minor or non-serious infections; cancer; major organ toxicity (including but not limited to reversible liver damage, reversible renal failure, ocular toxicity, etc.); allergic reaction; maternal toxicity (e.g. difficulties with conception, pregnancy, delivery); fetal toxicity, and cost.

PICO (Population/Patients, Intervention/Treatment, Comparator, and Outcomes) questions, that is, clinical questions that need to be answered to inform the guideline recommendations, will be developed by the Core Team, with input from the GRADE consultant.

Identification of Studies/Management of Studies and Data

Literature search strategies, based on PICO questions, will be developed by a research librarian (JJ) in consultation with the PI (JS), the literature review leader (TM), and with input from additional members of the Core Leadership Team. The strategies will be reviewed by another medical librarian [TR] using Peer Review of Electronic Search Strategies Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960’s +) for articles not included in Medline.
The search strategies will be developed using the controlled vocabulary for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library, and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library. Terminology will be used to retrieve the population of interest (patients 13 and older with rheumatoid arthritis), and the treatments of interest. (See Appendix A, search strategy for OVID Medline). Study design filters will be used to limit retrieval to study designs of interest, that is, systematic reviews, randomized controlled trials, observational studies, and articles about harm. Retrieval will be limited to English language publications only.

Gray literature (the kind of material that is not published in easily accessible journals or databases and conference abstracts, etc.)[15] will be searched, specifically metaRegister of Controlled Trials, to identify ongoing and completed trials, and the literature will then be searched to determine if there are published results. The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases. Conference abstracts will be searched via Embase database, reviewed, and tracked to determine if the studies have subsequently been published.

References and abstracts will be imported into bibliographic management software (Reference Manager[16], duplicates removed, and exported to a web-based systematic review management software. Both title/abstract screening, and manuscript/article screening will take place in this web-based software.

Screening, Data Extraction, and Analysis Phases

Search results will be divided among screeners, and two screeners will review each title/abstract, and next each manuscript that has been screened in, with disagreements being discussed and adjudicated by the literature review leader (TM), if necessary.

Those studies that meet inclusion criteria will be quality-assessed. Systematic reviews/meta-analyses (SR/MA) will be assessed using the AMSTAR tool [17]; randomized controlled trials (RCTs) will be assessed using the Cochrane Risk of Bias tool [18] and observational studies if used, the Newcastle-Ottawa tool [19].

Data from SR/MA and RCTs will be extracted and analyzed in Review Manager (RevMan) software. [20] In accordance with GRADE methodology, the literature review will report on critical and important outcomes and harms across studies, using appropriate statistical methods, and will result in Summary of Findings (SOF) tables for each PICO question. RevMan software will be used to produce the Summary of Findings Tables.

Using GRADEPro software,[21] the quality of evidence (high, moderate, low, very low) will be assessed for each outcome. Determinants of quality include 1) study design; 2) inconsistency; 3) indirectness; 4) imprecision; and 5) publication bias. The direction and strength of recommendations (strongly or conditionally for or against) will be determined.
These Summary of Findings tables and evidence profiles for each PICO, including explanatory material, will be presented to Voting Panel members along with preliminary recommendations drafted by the Core Oversight Team that are based on this information. The Voting Panel will initially vote on each PICO question independently, using an electronic voting mechanism. Their votes will include feedback on the direction and strength of the drafted recommendations, as well as suggestions for wording edits, if needed. Subsequently, the Voting Panel, PI, literature review leader, selected literature review panel members, and the GRADE consultant, will meet face-to-face at a meeting to review areas of agreement, discuss areas of disagreement, and make final recommendations for the guidelines.

Literature searches will be updated after the Voting Panel meeting but prior to publication of the guidelines, to ensure completeness. New publications will be reviewed by the PI and lit review leader to determine whether or not they would likely change the direction or substance of the Voting Panel’s recommendations. If there is any suspicion that new publications would influence the panel to change a recommendation, then the related clinical question will be posed to the Voting Panel again with the new evidence included, either by e-mail or phone, with a request for a re-vote on that question.

**Treatment Scenarios:**

**1. Treatment of patients with early RA**
- Patients who have not failed any traditional DMARD therapy (DMARD-naïve)
- Failed traditional DMARD therapy

**2. Treatment of patients with established RA**
- Patients who have not failed any traditional DMARD therapy (DMARD-naïve)
- After traditional DMARD-FAILURE
- After Single anti-TNF biologic therapy FAILURE
- After Multiple anti-TNF biologic therapy FAILURE
- After non-TNF biologic FAILURE
- After Both anti-TNF biologic and non-TNF biologic therapy FAILURE

**3. Safety in high risk patients**
- Congestive heart failure (CHF)
- Hepatitis B
- Hepatitis C
- Cancer- Melanoma skin cancer
- Cancer- Non-melanoma skin cancer
- Cancer- Lymphoproliferative disorder (includes leukemia, lymphoma etc.)
- Solid organ cancer
- Serious infections

**4. Live Vaccine: Immunization with Herpes Zoster**
5. Glucocorticoids

- Early RA
- Established RA

Definitions
DMARD = conventional/traditional DMARDs such as Methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF).
Mono-DMARD therapy = MTX, SSZ, HCQ, LEF.
Combination DMARD therapy = therapy with more than one traditional DMARD
  - Double DMARD therapy = MTX+SSZ, MTX + HCQ, SSZ+HCQ, or combinations with LEF
  - Triple DMARD therapy = MTX+SSZ+HCQ
Anti-TNF biologic therapy = adalimumab, etanercept, golimumab, certolizumab pegol, infliximab
Non-TNF biologic therapy = abatacept, rituximab, tocilizumab
Oral agent = Tofacitinib

Low dose glucocorticoid <= 10 mg/day of prednisone or prednisolone
High dose glucocorticoid = up to 60 mg/day with a rapid taper (i.e. COBRA regimen)

Acute hepatitis B = Hepatitis Surface Antigen positive, total Hepatitis B core Antibody positive, IgM Hepatitis B core Antibody negative, hepatitis B surface antibody negative

Chronic hepatitis B = Hepatitis Surface Antigen positive, total Hepatitis B core Antibody positive, IgM Hepatitis B core Antibody positive, hepatitis B surface antibody negative

Moderate or high disease activity = moderate or high RA disease activity as defined by 2012 ACR article on disease activity measures and in table 2 of the 2012 ACR RA treatment guidelines

Low disease activity = low RA disease activity as defined by ACR article on disease activity measures, and table 2 of the ACR 2012 guidelines document

Adult RA patient = Adults, 18 years and older, meeting ACR RA classification criteria (1987 or revised criteria)

Health Benefits and Harms = Efficacy and safety outcomes

Proposed Drug categories (based on previous guidelines and the voting by two panels):
1. Methotrexate (MTX)
2. Non-MTX synthetic DMARDs (SSZ, HCQ, LEF) and Combination DMARD therapy, as defined above (MTX+SSZ, MTX + HCQ, SSZ+HCQ, or combination with LEF)
3. Triple DMARD therapy
4. Anti-TNF biologics = adalimumab, etanercept, golimumab, certolizumab pegol, infliximab
5. Non-TNF biologics = tocilizumab, abatacept, rituximab
6. Oral agent = Tofacitinib
7. Glucocorticoids

Due to the lack of new evidence and uncommon/rare use certain traditional DMARDs (cyclosporine, azathioprine, gold) and one biologic (anakinra) will not be included in literature search for the 2014 ACR RA recommendations.

The questions are presented as:
P=patients
I=Intervention
C=Comparator
O=Outcomes
1. EARLY RA (<6 months of disease)

DMARD-naive

1.1 In patients with early RA with only low disease activity, who have not failed any traditional DMARD therapy, what is the impact of combination double DMARD therapy compared to mono-DMARD therapy on improving symptoms and causing harmful side effects?

P: Adult RA patient with early RA with mild disease activity
I: combination double DMARD therapy (MTX+SSZ, MTX + HCQ, or SSZ+HCQ; Leflunomide combinations)
C: mono-DMARD therapy (HCQ, SSZ, MTX, LEF)
O: Health Benefits and Harms

1.2 In patients with early RA with only low disease activity, who have not failed any traditional DMARD therapy, what is the impact of combination triple DMARD therapy compared to mono-DMARD therapy on improving symptoms and causing harmful side effects?

P: Adult RA patient with early RA with only low disease activity
I: combination triple DMARD therapy (MTX+SSZ+HCQ)
C: mono-DMARD therapy (HCQ, SSZ, MTX, LEF)
O: Health Benefits and Harms

1.3 In patients with early RA with moderate or high disease activity, who have not failed any traditional DMARD therapy, what is the impact of combination double DMARD therapy compared to mono-DMARD therapy on improving symptoms and causing harmful side effects?

P: Adult RA patient with early RA with moderate or high disease activity who have not failed any traditional DMARD therapy
I: combination double DMARD therapy
C: mono-DMARD therapy (HCQ, SSZ, MTX, LEF)
O: Health Benefits and Harms and safety outcomes

1.4 In patients with early RA with moderate or high disease activity, who have not failed any traditional DMARD therapy, what is the impact of combination triple traditional DMARD therapy compared to mono-DMARD therapy on improving symptoms and causing harmful side effects?

P: Adult RA patient with early RA with moderate or high disease activity who have not failed any traditional DMARD therapy
I: combination triple DMARD therapy
C: mono-DMARD therapy (HCQ, SSZ, MTX, LEF)
O: Health Benefits and Harms and safety outcomes
DMARD experienced

1.5 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of anti-TNF biologic monotherapy compared to triple DMARD therapy on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: anti-TNF biologic therapy (any of the 5 approved drugs)
C: Combination triple DMARD therapy
O: Health Benefits and Harms

1.6 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of anti-TNF biologic+MTX therapy compared to triple DMARD therapy on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: anti-TNF biologic therapy (any of the 5 approved drugs)+MTX
C: Combination triple DMARD therapy
O: Health Benefits and Harms

1.7 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of anti-TNF monotherapy compared to non-TNF biologic on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: anti-TNF biologic therapy (any of the 5 approved drugs)
C: non-TNF biologic therapy
O: Health Benefits and Harms

1.8 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of anti-TNF biologic +MTX compared to non-TNF biologic +MTX on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: anti-TNF biologic therapy (any of the 5 approved drugs)+MTX
C: non-TNF biologic therapy+MTX
O: Health Benefits and Harms
1.9 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib compared to anti-TNF biologic on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib
C: anti-TNF biologic therapy
O: Health Benefits and Harms

1.10 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib+MTX compared to anti-TNF biologic +MTX on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib+MTX
C: anti-TNF biologic therapy+MTX
O: Health Benefits and Harms

1.11 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib compared to non-TNF biologic on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib
C: non-TNF biologic therapy
O: Health Benefits and Harms

1.12 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib+MTX compared to non-TNF biologic +MTX on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib+MTX
C: non-TNF biologic therapy+MTX
O: Health Benefits and Harms

1.13 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib compared to combination triple DMARD therapy on improving symptoms and causing harmful side effects?
P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib
C: Combination triple DMARD therapy
O: Health Benefits and Harms
1.14 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD mono- or combination therapy, what is the impact of tofacitinib+MTX compared to combination triple DMARD therapy on improving symptoms and causing harmful side effects?

P: Adult RA patient with early RA with moderate or high disease activity
I: tofacitinib+MTX
C: Combination triple DMARD therapy
O: Health Benefits and Harms

2. ESTABLISHED RA (RA of 6 months or longer disease duration)

DMARD-naive

2.1 In patients with established RA with only low disease activity, who have not failed any traditional DMARD therapy, what is the impact of anti-TNF biologic therapy compared to mono-DMARD therapy in improving symptoms and causing harmful effects?

P: Adult RA patient with established RA with only low disease activity
I: anti-TNF biologic therapy
C: DMARD monotherapy
O: Health Benefits and Harms

2.2 In patients with established RA with only low disease activity, who have not failed any traditional DMARD therapy, what is the impact of anti-TNF biologic therapy compared to combination DMARD therapy in improving symptoms and causing harmful effects?

P: Adult RA patient with established RA with only low disease activity
I: anti-TNF biologic therapy
C: combination DMARD double or triple therapy
O: Health Benefits and Harms

After DMARD-FAILURE

2.3 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy on improving symptoms and causing harmful effects compared to non-TNF biologic therapy?

P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms
2.4 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to non-TNF biologic therapy+MTX?
P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy+MTX
C: non-TNF biologic therapy+MTX
O: Health Benefits and Harms

2.5 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy on improving symptoms and causing harmful effects compared to oral agent tofacitinib therapy?
P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy
C: oral agent tofacitinib therapy
O: Health Benefits and Harms

2.6 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to oral agent tofacitinib therapy+MTX?
P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy+MTX
C: oral agent tofacitinib therapy+MTX
O: Health Benefits and Harms

2.7 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy on improving symptoms and causing harmful effects compared to combination triple DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy
C: Combination triple DMARD therapy
O: Health Benefits and Harms
2.8 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD mono- or double therapy, what is the impact of anti-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to combination triple DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity
I: anti-TNF biologic therapy
C: Combination triple DMARD therapy
O: Health Benefits and Harms

After Single anti-TNF biologic therapy FAILURE

2.9 In patients with established RA with moderate or high disease activity, who have failed a single anti-TNF biologic therapy, what is the impact of non-TNF biologic therapy on improving symptoms and causing harmful effects compared to another anti-TNF biologic?
P: Adult RA patient with established RA with moderate or high disease activity
I: non-TNF biologic therapy
C: another anti-TNF biologic therapy
O: Health Benefits and Harms

2.10 In patients with established RA with moderate or high disease activity, who have failed a single anti-TNF biologic therapy, what is the impact of non-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to another anti-TNF biologic +MTX?
P: Adult RA patient with established RA with moderate or high disease activity
I: non-TNF biologic therapy+MTX
C: another anti-TNF biologic therapy+MTX
O: Health Benefits and Harms

2.11 In patients with established RA with moderate or high disease activity, who have failed a single anti-TNF biologic therapy, what is the impact of non-TNF biologic therapy on improving symptoms and causing harmful effects compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity
I: non-TNF biologic therapy
C: oral agent tofacitinib therapy
O: Health Benefits and Harms
2.12 In patients with established RA with moderate or high disease activity, who have failed a single anti-TNF biologic therapy, what is the impact of non-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to oral agent tofacitinib+MTX?  
**P**: Adult RA patient with established RA with moderate or high disease activity  
**I**: non-TNF biologic therapy+MTX  
**C**: oral agent tofacitinib therapy+MTX  
**O**: Health Benefits and Harms

**After Multiple anti-TNF biologic therapy FAILURE**

2.13 In patients with established RA with moderate or high disease activity, who have failed multiple anti-TNF biologic therapies, what is the impact of non-TNF biologic therapy on improving symptoms and causing harmful effects compared to another anti-TNF?  
**P**: Adult RA patient with established RA with moderate or high disease activity  
**I**: non-TNF biologic therapy  
**C**: another anti-TNF biologic therapy  
**O**: Health Benefits and Harms

2.14 In patients with established RA with moderate or high disease activity, who have failed multiple anti-TNF biologic therapies, what is the impact of non-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to another anti-TNF biologic +MTX?  
**P**: Adult RA patient with established RA with moderate or high disease activity  
**I**: non-TNF biologic therapy+MTX  
**C**: another anti-TNF biologic therapy+MTX  
**O**: Health Benefits and Harms

2.15 In patients with established RA with moderate or high disease activity, who have failed multiple anti-TNF biologic therapies, what is the impact of non-TNF biologic therapy on improving symptoms and causing harmful effects compared to oral agent tofacitinib?  
**P**: Adult RA patient with established RA with moderate or high disease activity  
**I**: non-TNF biologic therapy  
**C**: oral agent tofacitinib therapy  
**O**: Health Benefits and Harms
2.16 In patients with established RA with moderate or high disease activity, who have failed multiple anti-TNF therapies, what is the impact of non-TNF biologic therapy+MTX on improving symptoms and causing harmful effects compared to oral agent tofacitinib+MTX?
P: Adult RA patient with established RA with moderate or high disease activity
I: non-TNF biologic therapy+MTX
C: oral agent tofacitinib therapy+MTX
O: Health Benefits and Harms

2.17 In patients with established RA with moderate or high disease activity, who have failed anti-TNF biologic therapy, what is the impact of tofacitinib therapy on improving symptoms and causing harmful effects compared to another anti-TNF biologic?
P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib
C: another anti-TNF biologic therapy
O: Health Benefits and Harms

2.18 In patients with established RA with moderate or high disease activity, who have failed anti-TNF biologic therapy, what is the impact of tofacitinib therapy+MTX on improving symptoms and causing harmful effects compared to another anti-TNF biologic +MTX?
P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib+MTX
C: another anti-TNF biologic therapy+MTX
O: Health Benefits and Harms

After non-TNF biologic therapy FAILURE

2.19 In patients with established RA with moderate or high disease activity, who have failed non-TNF biologic therapy, what is the impact of tofacitinib therapy on improving symptoms and causing harmful effects compared to another non-TNF biologic?
P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib
C: another non-TNF biologic therapy
O: Health Benefits and Harms
2.20 In patients with established RA with moderate or high disease activity, who have failed non-TNF biologic therapy, what is the impact of tofacitinib therapy + MTX on improving symptoms and causing harmful effects compared to another non-TNF biologic + MTX?

P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib + MTX
C: another non-TNF biologic therapy + MTX
O: Health Benefits and Harms

After Both anti-TNF biologic and non-TNF biologic therapy FAILURE

2.21 In patients with established RA with moderate or high disease activity, who have failed both anti-TNF and non-TNF biologic therapy, what is the impact of tofacitinib therapy on improving symptoms and causing harmful effects compared to another anti-TNF biologic?

P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib
C: another anti-TNF biologic therapy
O: Health Benefits and Harms

2.22 In patients with established RA with moderate or high disease activity, who have failed both anti-TNF and non-TNF biologic therapy, what is the impact of tofacitinib + MTX therapy on improving symptoms and causing harmful effects compared to another anti-TNF biologic + MTX?

P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib
C: another anti-TNF biologic therapy
O: Health Benefits and Harms

2.23 In patients with established RA with moderate or high disease activity, who have failed both anti-TNF and non-TNF biologic therapy, what is the impact of tofacitinib therapy on improving symptoms and causing harmful effects compared to another non-TNF biologic?

P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib
C: another non-TNF biologic therapy
O: Health Benefits and Harms
2.24 In patients with established RA with moderate or high disease activity, who have failed both anti-TNF biologic and non-TNF biologic therapy, what is the impact of tofacitinib therapy+MTX on improving symptoms and causing harmful effects compared to another non-TNF biologic +MTX?

P: Adult RA patient with established RA with moderate or high disease activity
I: tofacitinib+MTX
C: another non-TNF biologic therapy+MTX
O: Health Benefits and Harms

3. SAFETY in HIGH-RISK patients

Congestive Heart Failure (CHF)

3.1 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of CHF NYHA class III or IV, compared to combination DMARD therapy?

P: Adult RA patient with established RA with moderate or high disease activity and CHF, class III or IV
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including Worsening CHF)

3.2 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of CHF NYHA class III or IV compared to non-TNF biologic therapy?

P: Adult RA patient with established RA with moderate or high disease activity and CHF, class III or IV
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including Worsening CHF)

3.3 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of CHF NYHA class III or IV compared to oral agent tofacitinib?

P: Adult RA patient with established RA with moderate or high disease activity and CHF, class III or IV
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including Worsening CHF)
3.4 In patients with established RA with moderate or high disease activity, if the CHF worsened while on anti-TNF biologic therapy, is it safe to use a different anti-TNF biologic compared to non-TNF biologic therapy?

P: Adult RA patient with established RA with moderate or high disease activity and history of CHF that worsened on anti-TNF biologic therapy.
I: a different anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including Worsening CHF)

3.5 In patients with established RA with moderate or high disease activity, if the CHF worsened while on anti-TNF biologic therapy, is it safe to use a different anti-TNF biologic compared to combination DMARD therapy?

P: Adult RA patient with established RA with moderate or high disease activity and history of CHF that worsened on anti-TNF biologic therapy.
I: a different anti-TNF biologic therapy
C: combination double or triple DMARD therapy
O: Health Benefits and Harms (including Worsening CHF)

3.6 In patients with established RA with moderate or high disease activity, if the CHF worsened while on anti-TNF biologic therapy, is it safe to use a different anti-TNF biologic compared to tofacitinib?

P: Adult RA patient with established RA with moderate or high disease activity and history of CHF that worsened on anti-TNF biologic therapy.
I: a different anti-TNF biologic therapy
C: tofacitinib
O: Health Benefits and Harms (including Worsening CHF)
**Hepatitis B**

3.7 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of acute hepatitis B infection compared to combination DMARD therapy?

- **P:** Adult RA patient with established RA with moderate or high disease activity and evidence of acute hepatitis B infection
- **I:** Anti-TNF biologic therapy
- **C:** combination DMARD therapy
- **O:** Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.8 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of acute hepatitis B infection compared to non-TNF?

- **P:** Adult RA patient with established RA with moderate or high disease activity and evidence of acute hepatitis B infection
- **I:** Anti-TNF biologic therapy
- **C:** non-TNF biologic therapy
- **O:** Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.9 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of acute hepatitis B infection compared to oral agent tofacitinib?

- **P:** Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis B
- **I:** Anti-TNF biologic therapy
- **C:** oral agent tofacitinib
- **O:** Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.10 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of chronic hepatitis B infection compared to combination DMARD therapy?

- **P:** Adult RA patient with established RA with moderate or high disease activity and evidence of chronic hepatitis B infection
- **I:** Anti-TNF biologic therapy
- **C:** combination DMARD therapy
- **O:** Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)
3.11 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of chronic hepatitis B infection compared to non-TNF? 
P: Adult RA patient with established RA with moderate or high disease activity and evidence of chronic hepatitis B infection 
I: Anti-TNF biologic therapy 
C: non-TNF biologic therapy 
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.12 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of chronic hepatitis B infection compared to oral agent tofacitinib? 
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis B 
I: Anti-TNF biologic therapy 
C: oral agent tofacitinib 
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

Hepatitis C

3.13 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with high viral load compared to combination DMARD therapy? 
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with high viral load 
I: Anti-TNF biologic therapy 
C: combination DMARD therapy 
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.14 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with high viral load compared to non-TNF? 
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with high viral load 
I: Anti-TNF biologic therapy 
C: non-TNF biologic therapy 
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)
3.15 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with high viral load compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with high viral load
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.16 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with low or undetectable viral load compared to combination DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with low or undetectable viral load
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.17 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with low or undetectable viral load compared to non-TNF biologic?
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with low or undetectable viral load
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)

3.18 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of hepatitis C with low or undetectable viral load compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity and evidence of hepatitis C with low or undetectable viral load
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including worsening hepatitis or liver failure or liver toxicity)
Cancer- Melanoma skin cancer

3.19 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated melanoma skin cancer compared to combination DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity and previously treated or untreated melanoma skin cancer
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.20 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated melanoma skin cancer compared to non-TNF biologic therapy?
P: Adult RA patient with established RA with moderate or high disease activity and previously treated or untreated melanoma skin cancer
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.21 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated melanoma skin cancer compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity and previously treated or untreated melanoma skin cancer
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including recurrence of cancer)
Cancer- Non-melanoma skin cancer

3.22 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated non-melanoma skin cancer compared to combination DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated or untreated non-melanoma skin cancer
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.23 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated non-melanoma skin cancer compared to non-TNF biologic therapy?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated or untreated non-melanoma skin cancer
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.24 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated or untreated non-melanoma skin cancer compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated or untreated non-melanoma skin cancer
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including recurrence of cancer)
Cancer- Lymphoproliferative disorder (includes leukemia, lymphoma etc.)

3.25 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated lymphoproliferative disorder compared to combination DMARD therapy?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated lymphoproliferative disorder
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.26 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated lymphoproliferative disorder compared to non-TNF biologic therapy?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated lymphoproliferative disorder
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.27 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated lymphoproliferative disorder compared to oral agent tofacitinib?
P: Adult RA patient with established RA with moderate or high disease activity and history of previously treated lymphoproliferative disorder
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including recurrence of cancer)
Cancer - Solid organ cancer

3.28 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated solid organ cancer compared to combination DMARD therapy?

P: Adult RA patient with established RA with moderate or high disease activity and previously treated solid organ cancer
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.29 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated solid organ cancer compared to non-TNF biologic therapy?

P: Adult RA patient with established RA with moderate or high disease activity and previously treated solid organ cancer
I: Anti-TNF biologic therapy
C: non-TNF biologic therapy
O: Health Benefits and Harms (including recurrence of cancer)

3.30 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previously treated solid organ cancer compared to oral agent tofacitinib?

P: Adult RA patient with established RA with moderate or high disease activity and previously treated solid organ cancer
I: Anti-TNF biologic therapy
C: oral agent tofacitinib
O: Health Benefits and Harms (including recurrence of cancer)

Serious Infections

3.31 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previous serious infections compared to combination DMARD therapy?

P: Adult RA patient with established RA with moderate or high disease activity and previous serious infections
I: Anti-TNF biologic therapy
C: combination DMARD therapy
O: Health Benefits and Harms
3.32 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previous serious infections compared to non-TNF biologic therapy?

- **P:** Adult RA patient with established RA with moderate or high disease activity and previous serious infections
- **I:** Anti-TNF biologic therapy
- **C:** non-TNF biologic therapy
- **O:** Health Benefits and Harms

3.33 In patients with established RA with moderate or high disease activity, is it safe to use anti-TNF biologic therapy in presence of previous serious infections compared to oral agent tofacitinib?

- **P:** Adult RA patient with established RA with moderate or high disease activity and previous serious infections
- **I:** Anti-TNF biologic therapy
- **C:** oral agent tofacitinib
- **O:** Health Benefits and Harms

4. **Live vaccine- Immunization with Herpes Zoster**

4.1 In patients with early RA currently on biologics, is it safe to give live attenuated vaccines such as herpes zoster (shingles) vaccine?

- **P:** Adult RA patient currently on biologics
- **I:** live attenuated vaccines such as herpes zoster (shingles) vaccine
- **C:** no vaccine
- **O:** Health Benefits (including seroconversion or “adequate protection against disease”) and Harms

4.2 In patients with established RA currently on biologics, is it safe to give live attenuated vaccines such as herpes zoster (shingles) vaccine?

- **P:** Adult RA patient currently on biologics
- **I:** live attenuated vaccines such as herpes zoster (shingles) vaccine
- **C:** no vaccine
- **O:** Health Benefits (including seroconversion or “adequate protection against disease”) and Harms
5. **GLUCOCORTICOIDS**

**Early RA**

4.3 In patients with early RA with only low disease activity, what is the impact of short-term high-dose glucocorticoid therapy on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?

P: Adult RA patient with early RA with low activity
I: short-term high-dose glucocorticoid therapy
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms

4.4 In patients with early RA with moderate or high disease activity, what is the impact of short-term high-dose glucocorticoid therapy on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?

P: Adult RA patient with early RA with moderate or high disease activity
I: short-term high-dose glucocorticoid therapy
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms

4.5 In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to traditional DMARDs on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?

P: Adult RA patient with early RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + traditional DMARDs
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms

4.6 In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to anti-TNF biologic therapy on improving symptoms and causing harmful effects, compared to anti-TNF biologic without glucocorticoids?

P: Adult RA patient with early RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + anti-TNF biologic therapy
C: anti-TNF biologic therapy without glucocorticoids
O: Health Benefits and Harms
4.7 In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to non-TNF biologic therapy on improving symptoms and causing harmful effects, compared to non-TNF biologic without glucocorticoids?
P: Adult RA patient with early RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + non-TNF biologic therapy
C: non-TNF biologic therapy without glucocorticoids
O: Health Benefits and Harms

4.8 In patients with early RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term high-dose glucocorticoid therapy to traditional DMARDs on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?
P: Adult with early RA with moderate or high disease activity and an acute flare
I: short-term high-dose glucocorticoid taper therapy + traditional DMARDs
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms

Established RA

4.9 In patients with established RA with only low disease activity, what is the impact of adding short-term high-dose glucocorticoid therapy on improving symptoms and causing harmful effects, compared to traditional DMARDs?
P: Adult RA patient with established RA with low activity
I: short-term high-dose glucocorticoid therapy
C: traditional DMARDs
O: Health Benefits and Harms

4.10 In patients with established RA with moderate or high disease activity, what is the impact of short-term high-dose glucocorticoid therapy on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?
P: Adult RA patient with established RA with moderate or high disease activity
I: short-term high-dose glucocorticoid therapy
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms
4.11 In patients with established RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to traditional DMARDs on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?
P: Adult RA patient with established RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + traditional DMARDs
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms

4.12 In patients with established RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to anti-TNF biologic therapy on improving symptoms and causing harmful effects, compared to anti-TNF biologic without glucocorticoids?
P: Adult RA patient with established RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + anti-TNF biologic therapy
C: anti-TNF biologic therapy without glucocorticoids
O: Health Benefits and Harms

4.13 In patients with established RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to non-TNF biologic therapy on improving symptoms and causing harmful effects, compared to non-TNF biologic without glucocorticoids?
P: Adult RA patient with established RA with moderate or high disease activity
I: long-term low-dose glucocorticoid therapy + non-TNF biologic therapy
C: non-TNF biologic therapy without glucocorticoids
O: Health Benefits and Harms

4.14 In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term high-dose glucocorticoid therapy to traditional DMARDs on improving symptoms and causing harmful effects, compared to traditional DMARDs without glucocorticoids?
P: Adult with established RA with moderate or high disease activity and an acute flare
I: short-term high-dose glucocorticoid taper therapy + traditional DMARDs
C: traditional DMARDs without glucocorticoids
O: Health Benefits and Harms
AUTHORSHIP

Authorship of the guidelines will include Dr. Jasvinder Singh, PI, as the lead author; Dr. Timothy McAlindon, literature review leader; Drs. Lou Bridges and Kenneth Saag, core leadership group members; and Dr. Holger Schünemann, GRADE consultant. Members of the systematic review team will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using ICMJE Uniform Requirements for Manuscripts as guidance.

Voting panel members will receive special acknowledgement for their participation in the development of the guidelines and will also be listed as collaborators in the PubMed reference for the guidelines.

DISCLOSURES / CONFLICTS OF INTEREST

The ACR’s disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on the ACR web site under Policies & Procedures. See Appendix B for participant disclosures.
APPENDIX A

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

--------------------------------------------------------------------------------
1. Arthritis, Rheumatoid/ (83608)
2. (rheumatoid adj2 arthriti$).tw. (80487)
3. 1 or 2 (107432)
4. limit 3 to "all adult (19 plus years)" (47211)
5. limit 3 to "adolescent (13 to 18 years)" (8332)
6. 4 or 5 (48980)
7. disease modifying antirheumatic drug$.tw. (2423)
8. (disease modifying anti-rheumatic drug$ or DMARD$).tw. (2898)
9. hydroxychloroquine/ or methotrexate/ or sulfasalazine/ (37618)
10. (hydroxychloroquine$ or methotrexate$ or sulfasalazine$ or sulphasalazine$ or leflunomide$).tw. (37641)
11. Minocycline/ or minocycline$.tw. (6697)
12. Azathioprine/ or azathioprine$.tw. (20490)
13. Cyclosporine/ or cyclosporine$.tw. (42200)
14. antirheumatic agents/ (16481)
15. (adalimumab or etanercept or golimumab or certolizumab pegol or infliximab).tw. (12832)
16. exp Receptors, Tumor Necrosis Factor/tu [Therapeutic Use] (3744)
17. Tumor Necrosis Factor-alpha/tu [Therapeutic Use] (1486)
18. ((tumor or tumour) adj necrosis factor adj (block$ or inhibitor$)).tw. (921)
19. (TNF inhibitor$ or TNFi).tw. (1261)
TNFR-Fc fusion protein.tw. (8)

(mab ca2 or monoclonal antibody ca2).tw. (26)

(anakinra or tocilizumab or abatacept or rituximab).tw. (12906)

tofacitinib.tw. (137)

glucocorticoids/ or dexamethasone/ or dexamethasone isonicotinate/ or prednisolone/ or prednisone/.tw. (140392)

cortisone/. (15135)

(glucocorticoid$ or dexamethasone$ or prednisolone$ or prednisone$ or cortisone$).tw. (134827)

or/7-26 (330434)

6 and 27 (11209)

meta-analysis/ or review literature/ or meta-analy$.tw. or metaanal$.tw. or (systematic$ adj4 (review$ or overview$)).tw. or meta-analysis.pt. or review.pt. or review.ti. (2079540)

case report/ or letter.pt. or historical articles.pt. (2351751)

29 not 30 [Centre for Reviews and Dissemination Strategy 2.2 IN Lee for retrieving potential systematic reviews or meta-analyses ] (1953003)

28 and 31 (476)

(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format] (940482)

28 and 33 (1930)

epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or case control.tw. or (cohort adj (study or studies)).tw. or cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or longitudinal.tw. or retrospective.tw. or cross sectional.tw. or Cross-sectional studies/ [SIGN observational studies filter available on Intertasc website] (1929289)

28 and 35 (3382)

32 or 34 or 36 (5064)

exp animals/ not humans.sh. (4066614)
39  37 not 38 (5064)
40  limit 39 to english language (4616)
41  limit 37 to in process (0)
42  40 or 41 (4616)
43  (ae or to or co).fs. or (adverse adj (effect$ or reaction$ or event$ or incident$)).tw. or toxic$.tw. or
((injurious or undesirable) adj (effect$ or reaction$ or event$ or incident$)).tw. or safety.tw. or ((drug or
chemical$) adj induced).tw. or extension.tw. or continuation.tw. or follow-on.tw. or (follow-up adj5
trial).tw. or long-term data.ti,ab. [ Filter for retrieving harms used in Singh JA, Wells GA, Christensen R,
Tanjong Ghogomu E, Maxwell L, MacDonald JK, Filippini G, Skoetz N, Francis DK, Lopes LC, Guyatt GH,
Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Cameron C, Lunn MPT, Tugwell P,
Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane
Database of Systematic Reviews 2011, Issue 2. Art. No.: CD008794] (3754741)
44  28 and 43 (6631)
45  44 not 38 (6631)
46  limit 45 to english language (5607)
47  limit 44 to in process (0)
48  46 or 47 (5607)
49  42 or 48 (7709)

References
1. Ruderman ETS, for the American College of Rheumatology. Rheumatoid Arthritis [Patient resources]. 2012.


### DISCLOSURES OF RELATIONSHIPS

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College’s integrity be maintained. The cornerstone of the ACR’s Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts.

The purpose of the ACR’s Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Role</th>
<th>Primary employer</th>
<th>Sources of personal income to include speakers bureau, honoraria, royalties, expert witness fees, advisory boards, or any other sources of income (excludes salary from primary employer)</th>
<th>Research Grants/Contracts</th>
<th>Investments to include medical industry and non-medical industry</th>
<th>Organizational Benefit</th>
<th>Activities with other organizations</th>
<th>Family or other relations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jasvinder Singh</td>
<td>Core Oversight Team</td>
<td>Birmingham VA Med Ctr; University of Alabama at Birmingham</td>
<td>Savient Pharm; Regeneron Pharm; Takeda Pharma; SAVIENT; REGENERON; TAKEDA; SAVIENT; REGENERON; TAKEDA</td>
<td>NA</td>
<td>NA</td>
<td>OMERACT; JCR; BMC MSD; VA Field Advisory Committee</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Timothy McAlindon</td>
<td>Core Oversight Team</td>
<td>Tufts Medical Center</td>
<td>Flexion Therapeutics; EMD Serono; Novartis; Biolebra; Complete Medical Group; URL Pharma; Wintherin &amp; Epithera, LLC</td>
<td>NIH/NIAMS; AHRQ; DHHS: Human Genome Sciences; NIH/NCCAM; Osteoarthritis Research Society International; NIH/NHLBI</td>
<td>NA</td>
<td>NA</td>
<td>DARSS; Arthritis &amp; Rheumatism</td>
<td>NA</td>
</tr>
<tr>
<td>Kenneth Saag</td>
<td>Core Oversight Team</td>
<td>University of Alabama at Birmingham</td>
<td>Abbott; Amgen; Ardea; Biocryst; BMS; Crescendo; Eli Lilly; Horizon; Iroko; Merck; Regeneron; Roche; AHRQ; NIH; Takeda</td>
<td>AHRQ; NIH/NIAMS</td>
<td>NA</td>
<td>NIH/NIAMS [5]</td>
<td>NA</td>
<td>National Osteoporosis Foundation; ASBMR</td>
</tr>
<tr>
<td>Stanley Louis Bridges, Jr.</td>
<td>Core Oversight Team</td>
<td>University of Alabama at Birmingham</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NIH/NIAMS [5]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Holger Schunemann</td>
<td>GRADE Consultant</td>
<td>McMaster University</td>
<td>NA</td>
<td>ACR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>ACPC</td>
</tr>
<tr>
<td>Jeffrey Curtis</td>
<td>Lit Review Team - Content Expert</td>
<td>University of Alabama at Birmingham</td>
<td>Pfizer; BMS; Crescendo; Abbott; Roche/Genentech; UCB; Janssen; CORRONA; Amgen</td>
<td>AHRQ; NIH; RRF; Amgen</td>
<td>NA</td>
<td>NIH/NIAMS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Daniel Furst</td>
<td>Lit Review Team - Content Expert</td>
<td>UCLA</td>
<td>Abbott; Actelion; Amgen; BMS; Gilead; GSK; NIH; Novartis; Pfizer; Roche Genentech; Actelion; Roche; NIH; UCB; Amgen; Colgeno; Duke Univ/NIH; NIH</td>
<td>NA</td>
<td>NIH</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Deborah Parks</td>
<td>Lit Review Team - Content Expert</td>
<td>Washington University School of Medicine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NIH/NIAMS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Robert Simms</td>
<td>Lit Review Team - Content Expert</td>
<td>Boston University School of Medicine</td>
<td>Gilead; Actelion</td>
<td>NIH; Actelion</td>
<td>NA</td>
<td>NIH/NIAMS [5]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Robert Shmerling</td>
<td>Lit Review Team - Content Expert</td>
<td>Harvard Medical Faculty Physician/Beth Israel Deaconess Medical Center</td>
<td>Advance Medical; Boston Clinical Research Institute; University Massachusetts; Harvard Health Publications; Uptodate; American College of Physicians; Marshall, Dennehey, Warner; Coleman &amp; Gsiggin, Joslin Diabetes Center; Murphy &amp; Riley, PC; Rheingold, Valtel, Rheingold, McCartyer &amp; Giffura LLP; Ballard &amp; Simmons, LLP; Martin, Magnuson, McCarthy &amp; Kenney; Bennett Law Firm; Berman &amp; Simmons; Risk Management Foundation</td>
<td>NA</td>
<td>NA</td>
<td>NIH/NIAMS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Participants</td>
<td>Role</td>
<td>Primary employer</td>
<td>Sources of personal income to include speakers bureau, honoraria, royalties, expert witness fees, advisory boards, or any other sources of income (excludes salary from primary employer)</td>
<td>Research Grants/Contracts</td>
<td>Investments to include medical industry and non-medical industry</td>
<td>Organizational Benefit</td>
<td>Activities with other organizations</td>
<td>Family or other relations</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Raveendhara Bannuru</td>
<td>Lit Review Team - Methods Experts/Abstractors</td>
<td>Tufts Medical Center</td>
<td>Genzyme Biosurgery</td>
<td>AHRQ; DePuy; Croma</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Matt Sullivan</td>
<td>Lit Review Team - Methods Experts/Abstractors</td>
<td>Tufts Medical Center</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lisa Vaysbrot</td>
<td>Lit Review Team - Methods Experts/Abstractors</td>
<td>Tufts Medical Center</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Joan Bathon</td>
<td>Voting Panel</td>
<td>Columbia University</td>
<td>NIH; ACR RRF</td>
<td>NA</td>
<td>ACR RRF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>David Felson</td>
<td>Voting Panel</td>
<td>Boston University; University of Manchester</td>
<td>Knee Creations, Ltd.</td>
<td>NIH (3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Seth D. Ginsberg</td>
<td>Voting Panel</td>
<td>GHFL; IGT Healthcare</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Arthur Kavanaugh</td>
<td>Voting Panel</td>
<td>UCSD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Charles King</td>
<td>Voting Panel</td>
<td>North Mississippi Health System</td>
<td>North Mississippi Medical Clinics; Janssen; Novartis; UCB; Genentech; Genentech/Roche; Pfizer; Consortium of Rheumatology Researchers of North America, Inc.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Amye Leong</td>
<td>Voting Panel</td>
<td>Healthy Motivation</td>
<td>GSK; Iroko; Anschote Foundation; Kaiser Family Foundation; NIH; Centers for Education &amp; Research on Therapeutics; Zimmer; Sandoz</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Bone &amp; Joint Decade; NIH; AHRQ; International Journal of Self-Help &amp; Self Care; Arthritis Foundation</td>
<td>NA</td>
</tr>
<tr>
<td>Eric Matteson</td>
<td>Voting Panel</td>
<td>Mayo Clinic College of Medicine</td>
<td>Healthcare Ed</td>
<td>NIH; Roche/Genentech/Mesoblast/Ardea; Novartis; Sanofi/Centocor-Janssen/Celgene/UCB Pharm; ACR Exact Sciences</td>
<td>NA</td>
<td>NA</td>
<td>Vasculitis Foundation</td>
<td>NA</td>
</tr>
<tr>
<td>Eileen Moynihan</td>
<td>Voting Panel</td>
<td>Self Employed; Novartis Solutions, Inc</td>
<td>MD Advantage Malpractice Insurer</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Novartis Solutions</td>
<td>NA</td>
</tr>
<tr>
<td>James O'Dell</td>
<td>Voting Panel</td>
<td>UNMC; Omaha VA</td>
<td>NA</td>
<td>VA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>John T. Schousboe</td>
<td>Voting Panel</td>
<td>Park Nicolle Health Services; University of Minnesota</td>
<td>NA</td>
<td>National Institute of Aging</td>
<td>NA</td>
<td>NA</td>
<td>International Society for Clinical Rheumatology</td>
<td>NA</td>
</tr>
<tr>
<td>E. William St.Clair</td>
<td>Voting Panel</td>
<td>Duke University</td>
<td>UpToDate</td>
<td>NIH/NAID</td>
<td>BMIS; Merck; Proctor &amp; Gamble</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Elizabeth Tindall</td>
<td>Voting Panel</td>
<td>NA</td>
<td>NA</td>
<td>Johnson &amp; Johnson; Proctor &amp; Gamble</td>
<td>NA</td>
<td>NA</td>
<td>Husband &amp; Children</td>
<td>NA</td>
</tr>
<tr>
<td>Company</td>
<td>Why listed as an affected company?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott</td>
<td>Adalimumab, <em>Humira</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amgen</td>
<td>Etanercept, <em>Enbrel</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Fostamatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>Abatacept, <em>Orencia</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAVA Pharmaceuticals, Inc.</td>
<td>Methotrexate, <em>Rheumatrex</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duramed Pharmaceuticals, Inc.</td>
<td>Methotrexate, <em>Trexall</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eli Lilly (Investigational)</td>
<td>LY3009104 (Janus Kinase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genentech</td>
<td>Rituximab, <em>Rituxan</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idex Pharmaceuticals Corp</td>
<td>Rituximab, <em>Rituxan</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunex</td>
<td>Etanercept, <em>Enbrel</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen Biotech</td>
<td>Golimumab, <em>Simponi</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicis</td>
<td>Minocycline, <em>Solodyn</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merck (Investigational)</td>
<td>MK-8457</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer</td>
<td>Etanercept, <em>Enbrel</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer (Investigational)</td>
<td>Oral CP-690550, Tofacitinib citrate, a Janus kinase (JAK) 3 inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacia and UpJohn</td>
<td>Sulfasalazine, <em>Azulfidine</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi Aventis US</td>
<td>Hydroxychloroquine, <em>Plaquenil</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S*BIO Pte. Ltd, Singapore</td>
<td>SB1578, a novel inhibitor of JAK2, FLT3, and c-Fms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCB</td>
<td>Certolizumab Pegol, <em>Cimzia</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertex Pharmaceuticals Inc.</td>
<td>VX-509, an Oral JAK3 Inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>