MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Project: Clinical Effectiveness of Targeted Immune Modulators for Rheumatoid Arthritis

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Research Protocol

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TABLE OF CONTENTS

BACKGROUND, OBJECTIVES, AND RESEARCH QUESTIONS

Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1,2] RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.[3] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs and skin) may be involved.[3] RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction.[4] The course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations.[3] Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis as well as aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) have greatly improved prognosis in the past 20 years.[5]

The chemotherapeutic agent methotrexate is the most widely used conventional DMARD; it is considered an "anchor drug" because of its effectiveness and tolerability as well as its potential to enhance the effectiveness of biologic and non-biologic drugs that are targeted at certain mediators of inflammation in RA, known collectively as "targeted immune modulators" (TIMs).[3] However, only about 50% of patients treated with methotrexate alone will receive sufficient reduction in disease activity or remission of symptoms. Over the past 18 years, the introduction of TIMs has greatly improved prognosis for many RA patients. Agents with indications for RA include inhibitors or antagonists of multiple mediators of the inflammatory cascade, including tumor necrosis factor (TNF), the B-lymphocyte CD20 antigen, interleukin (IL) 1 and 6, Janus kinase (JAK), and T cells. Novel agents with anti-IL-6 and anti-JAK activity are also currently under regulatory review for an RA indication. Guidelines from the American College of Rheumatology recommend use of TIMs in patients with moderate-to-severe disease activity despite use of conventional DMARDs.[6] Uncertainty remains, however, regarding the relative effectiveness of the different types of TIMs as well as the appropriate sequence of initial and subsequent TIM therapy. In addition, there are long-term safety concerns with chronic use of TIMs in RA that may differ by dose and type of agent.[7] Feedback from patient groups also emphasized the highly individual experience with TIM therapy; some patients see immediate benefit from the first TIM they receive after failure of conventional DMARDs, while others must make multiple attempts before finding an agent that works for them. There is therefore a need to seek evidence on patient subgroups, comorbidities, and other factors that can better inform treatment response and selection of appropriate medications.

Overview

This project will evaluate the health and economic outcomes of multiple TIMs for moderately-to-severely active rheumatoid arthritis, both as monotherapy and in combination with conventional

DMARDs. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated. Studies with a sample size less than 100 will be excluded. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[8]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair*: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs. Specifically, for this review, differences in baseline characteristics and/or duration of follow-up were allowed only if appropriate statistical methods were used to control for these differences (e.g., multiple regression, survival analysis).*

Poor*: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS-related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting.

Population

The population of focus for the review will be adults ages 18 and older with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance of conventional DMARDs. Level of disease activity will be defined according to validated and frequently-used scales in RA (i.e., Disease Activity Score [DAS28], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]).

Note that this focus will not include children, adolescents or adults with juvenile forms of RA or other inflammatory arthritis, now collectively known as juvenile idiopathic arthritis (JIA). Feedback from patient groups and clinicians suggested that the clinical presentation and disease trajectory of these patients differs substantially from those with the adult form of RA.[9]

We will also seek evidence on key subpopulations and/or data stratifications of interest, including (a) evaluation of both TIM-naïve patients *and* those with inadequate response to or intolerance of initial TIM therapy; (b) use of TIMs as monotherapy and in combination with conventional DMARDs; (c) route of administration (i.e., oral vs. self-injected vs. infused); and (d) setting of care (e.g., hospital-based vs. ambulatory infusion centers). Additional subpopulations or stratifications of interest include (e) presence of comorbidities (e.g., cardiovascular, psychiatric, malignancy); (f) both "early" (i.e., within 2 years of symptom onset) and established RA; (g) seropositivity for prognostic markers such as anti-cyclic citrullinated peptide (CCP) antibodies; (h) geography, in particular U.S.-based vs. non-U.S. settings; and (i) study funding (i.e., industry-sponsored vs. other funding sources).

Interventions

Interventions of interest are listed by class below.

- **TNF inhibitors** (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
- **CD20-directed** cytolytic antibody (rituximab)
- **T-cell inhibitor** (abatacept)
- **IL-6 inhibitors** (tocilizumab, sarilumab [investigational])
- **JAK inhibitors** (tofacitinib, baricitinib [investigational])

We will seek clinical evidence on all forms of the products listed above, including biosimilar and interchangeable biologic forms as data permit. Biosimilar data will be presented separately, given differences in study design and intent (i.e., non-inferiority vs. superiority) relative to clinical studies of the originator products.

Comparators

We will examine studies comparing TIMs to conventional DMARD monotherapy or combination therapy (including triple therapy with the conventional DMARDs methotrexate, sulfasalazine, and hydroxychloroquine) to assess performance versus historical standard treatments, but will also seek head-to-head studies between TIMs to evaluate for more contemporary comparisons. Comparisons of TIMs will be conducted among drugs with similar mechanisms of action (e.g., all TNF inhibitors) as well as between drugs with different mechanisms (e.g., IL-6 inhibitors vs. JAK inhibitors).

While studies with an active comparator arm are preferred, we will also include placebo-controlled trials as necessary to complete a planned network meta-analysis of the effects of treatment on key measures of effectiveness that will combine direct and indirect evidence.

Outcomes

This review will examine key clinical outcomes associated with RA. In conversations held to develop the draft scoping document, patient organizations advised us that clinical trials are often lacking robust information on patient-reported outcomes, and suggested a focus on recently-developed measures such as those described in the federally-funded PROMIS toolkit (http://www.healthmeasures.net/explore-measurement-systems/promis).

- Mortality
- Treatment response (e.g., ACR20, ACR50, and ACR70, area-under-the-curve analysis)
- Measures of disease activity, remission, and remission loss (e.g., DAS28, CDAI, SDAI)
- Radiographic evidence of structural damage
- Key laboratory-based indices (e.g., erythrocyte sedimentation rate, C-reactive protein)
- Disease-specific and general health-related quality of life (e.g., HAQ-DI, SF-36)
- Pain (e.g., visual analog scales)
- Other patient-reported outcomes (e.g., patient satisfaction, measures of fatigue, morning joint stiffness)
- Productivity loss and caregiver burden
- Requirements for joint replacement or other surgical intervention
- Utilization of key healthcare resources (e.g., hospitalization, rehabilitation, assisted living)
- Cardiovascular events
- Treatment-related adverse events (e.g., serious infection, malignancy, liver abnormalities)
- Costs and cost-effectiveness of TIMs

While we will seek to assess these outcomes quantitatively, some measures may not be widely reported and will necessitate descriptive analysis only. Where possible, we will report the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

We will also assess the impact of dose increases, dose decreases, and drug cessation during periods of sustained control or remission on long-term outcomes, as well as the effects of dose levels on the rates of serious adverse events. Where available, we will describe the reported clinical rationale for dose adjustments.

Timing

Evidence on intervention effectiveness will be derived from studies of at least six months' duration, while information on potential harms will be obtained from studies of at least three months' follow-up.

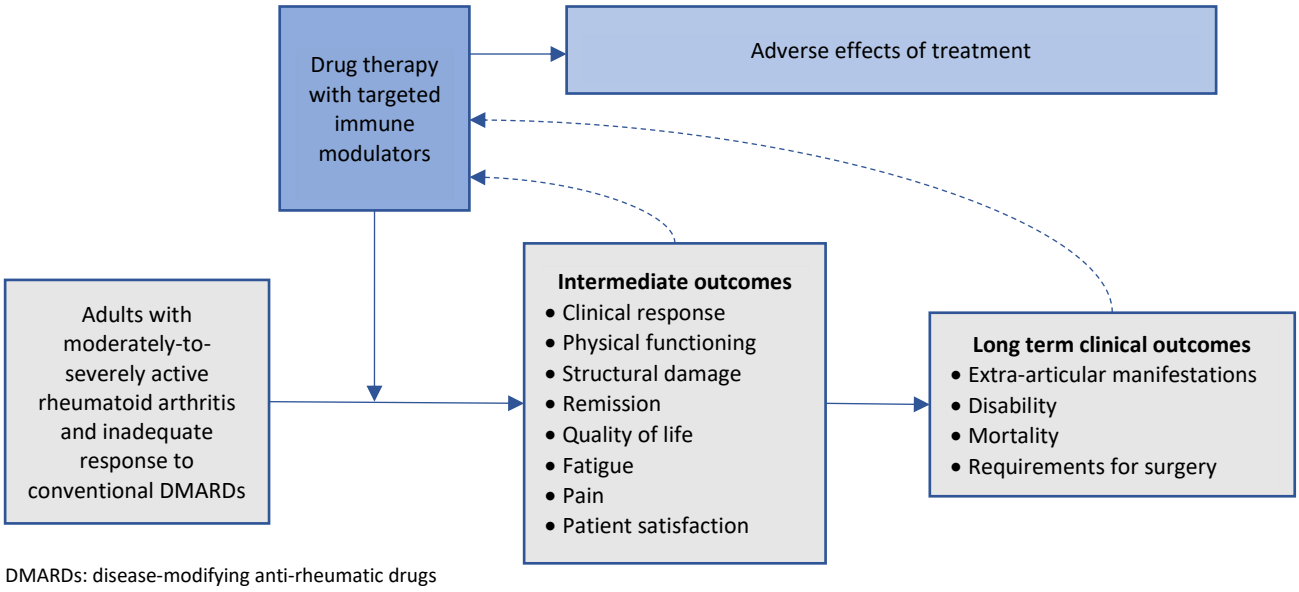
Setting

All relevant settings will be considered, including outpatient as well as ambulatory and hospital-based infusion centers. We will focus attention on studies pertinent to the U.S. setting; however, we recognize that studies conducted outside the U.S. will likely be required for a complete review of the evidence.

Analytic Framework

The proposed analytic framework for this project is depicted below.

Figure 1. Analytic Framework: Targeted Immune Modulators for Moderately-to-Severely Active Rheumatoid Arthritis



DMARDs: disease-modifying anti-rheumatic drugs

EVIDENCE REVIEW METHODS

Search Methods and Data Sources

The Agency for Healthcare Research and Quality (AHRQ) published a review in 2012 entitled "Drug Therapy for Rheumatoid Arthritis in Adults," which followed a similar scope to the one planned for this review.[10] We will therefore summarize the AHRQ review's findings and present new evidence that has emerged since 2012 by conducting an updated systematic literature search.

Procedures for the systematic literature review assessing the evidence on targeted immune modulators for rheumatoid arthritis will follow established best methods.[11,12] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies published since 2010. We will overlap the search timeframe with that of the AHRQ review in order to account for delays in indexing. As tofacitinib and the two investigational therapies of focus for

our review (sarilumab and baricitinib), were not included in the AHRQ review, we will not restrict the search period for studies of these agents. Each search will be limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items.

The search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 on the following pages. We will also include abstracts from conference proceedings in the literature search for drugs that are approaching an FDA approval decision (i.e., sarilumab and baricitinib) or that have received approval within the past five years (i.e., tofacitinib). In order to supplement the above searches and ensure optimal and complete literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

Table 1: Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials

1	exp Arthritis, Rheumatoid/
2	((rheumatoid or rheumatic or rheumat$) adj3 (arthrit$ or diseas$ or condition$)).ti,ab.
3	1 or 2
4	exp abatacept/
5	(abatacept or orencia).ti,ab.
6	exp rituximab/
7	(rituximab or rituxan or mabthera).ti,ab.
8	(tocilizumab or atlizumab or actemra or roactemra).ti,ab.
9	exp infliximab/
10	(infliximab or remicade).ti,ab.
11	exp etanercept/
12	(etanercept or enbrel).ti,ab.
13	exp adalimumab/
14	(adalimumab or humira).ti,ab.
15	exp certolizumab pegol/
16	(certolizumab pegol or cimzia).ti,ab.
17	(golimumab or simponi).ti,ab.
18	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	3 and 18
20	limit 19 to yr="2010 -Current"
21	(tofacitinib or tasocitinib or tofacitinib citrate or Xeljanz).ti,ab.
22	(sarilumab or REGN88).ti,ab.
23	(baricitinib or LY3009104 or INCB028050).ti,ab.
24	21 or 22 or 23
25	24 and 3
26	25 or 20
27	(animals not (humans and animals)).sh.
28	26 not 27
29	limit 28 to english language
30	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate

	publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
31	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt
32	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
33	31 or 32
34	29 not 30
35	34 and 33
36	Remove duplicates from 35

Table 2. Search strategy of EMBASE SEARCH

#1	'rheumatoid arthritis'/exp
#2	((rheumatoid OR rheumatic OR rheumat*) NEAR/3 (arthrit* OR diseas* OR condition*)):ab,ti
#3	#1 OR #2
#4	'abatacept'/exp OR abatacept:ab,ti OR orencia:ab,ti
#5	'rituximab'/exp OR rituximab:ab,ti OR rituxan:ab,ti OR mabthera:ab,ti
#6	'tocilizumab'/exp OR tocilizumab:ab,ti OR atlizumab:ab,ti OR actemra:ab,ti OR roactemra:ab,ti
#7	'infliximab'/exp OR infliximab:ab,ti OR remicade:ab,ti
#8	'etanercept'/exp OR etanercept:ab,ti OR enbrel:ab,ti
#9	'adalimumab'/exp OR adalimumab:ab,ti OR humira:ab,ti
#10	'certolizumab pegol'/exp OR 'certolizumab pegol':ab,ti OR cimzia:ab,ti
#11	'golimumab'/exp OR golimumab:ab,ti OR simponi:ab,ti
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	#3 AND #12
#14	#13 AND [2010-2016]/py
#15	#14 AND ('chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#16	#14 NOT #15
#17	'tofacitinib'/exp OR tofacitinib:ab,ti OR tasocitinib:ab,ti OR 'tofacitinib citrate':ab,ti OR xeljanz:ab,ti
#18	'baricitinib'/exp OR baricitinib:ab,ti
#19	'sarilumab'/exp OR sarilumab:ab,ti
#20	#17 OR #18 OR #19
#21	#3 AND #20
#22	#21 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#23	#21 NOT #22
#24	#16 OR #23
#25	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#26	'human'/exp
#27	#25 AND #26

#28	#25 NOT #27
#29	#24 NOT #28
#30	#29 AND [english]/lim
#31	#30 AND [medline]/lim
#32	#30 NOT #31

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will screen the titles and abstracts of all publications identified through electronic searches according to the inclusion and exclusion criteria defined by the PICOTS elements; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

1. Two reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Information from the accepted studies will be extracted into data extraction forms.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies, in order to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. Evidence table shells are presented in Appendix B. Data Extraction Summary Table Shells

In addition, we will conduct network meta-analyses (NMA) using a mixed treatment comparison approach, where possible.[14] Quantitative analyses will focus attention on the effects of the regimens of interest on treatment response and/or disease activity, and will be conducted using WinBUGS statistical software for Bayesian analysis (MRC Biostatistics Unit, Cambridge, UK). We will fit both fixed and random treatment effect models using non-informative normal priors. A total of 40,000 iterations each will be used for both "burn-in" (for model convergence) and model (for model results) simulations.

Given the relatively long timeline for consideration of evidence (i.e., the first TNF-α inhibitors were approved in the US in the late 1990s), consequent changes in diagnostic and clinical practice in RA, and possible heterogeneity within and across trial populations, we will explore whether various covariates appear to be modifiers of treatment effect. For example, it is possible that duration of RA can have an impact on relative effectiveness across treatments,[15] and it is well known that baseline risk (as proxied by the trial-specific baseline in the control arm) is an important clinical variable in broad research synthesis of almost any chronic disease.[16] In such meta-regression models, we will assume a common interaction term for the effect of any treatment modifier, and use any appropriate data transformations to ensure covariate centering.[15]

Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points will be used to assess model fit under multiple alternative assumptions. We will also explore whether the inclusion or exclusion of potential covariates as discussed above has an important impact on measures of model fit.

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APPENDIX A. PRISMA CHECKLIST

The checklist below is drawn from Moher et al. 2009.[13] Additional explanation of each item can be found in Liberati et al. 2009.[25]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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APPENDIX B. DATA EXTRACTION SUMMARY TABLE SHELLS

Table B1. Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics

Table B2. Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Radiographic Evidence of Structural Damage	Laboratory-based indices	Mortality

Table B3. Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes

Table B4. Healthcare Utilization and Non-Healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes

Table B5. Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation & Serious AE rate