

A Systematic Review and Meta-Analysis of Recent Evidence and Clinical Practice Guidelines for the Medical and Surgical Management of Rheumatoid Arthritis

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic autoimmune and systemic disease in which the synovium of the joints chronically becomes inflamed causing progressive joint destruction, pain and functional disability. Treatment: While disease-modifying antirheumatic drugs (DMARDs), biologic drugs and surgical technique have helped to manage treatment more readily, there are still important decisions to be made regarding therapeutic options, safety and peri-operatively administered drugs. The purpose of the present systematic review with meta-analysis is the analysis of the current clinical guidelines and comparative evidence on the effectiveness, safety, functional results and

perioperative management of medical and surgical management of RA. A systematic literature search will be undertaken on the papers published for the past 5 years using the PubMed/MEDLINE database, Embase, Cochrane CENTRAL, Scopus and Web of Science database for papers that are suitable for inclusion. The included studies will be evaluated on pre-defined eligibility criteria that will also involve randomized controlled trials and comparative observational studies, as well as relevant evidence based clinical practice guidelines. Appropriate and validated methodology tools will be used to assess the methodological quality and risk of bias. When sufficient methodological and clinical comparability is present, quantitative meta analysis will be carried out otherwise findings will be narratively synthesized.

Keywords: *Rheumatoid arthritis; systematic review; meta-analysis; disease-modifying antirheumatic drugs; biologic therapies; surgical management; perioperative care; treatment safety.*

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that involves chronic synovial joints, progressive cartilage and bone destructive disease with symptoms of pain, stiffness and functional problem. The disease may have extra-articular symptoms and present with other chronic problems, and all can affect quality of life and lead to greater long-term health services consumption. The symptoms of RA are different from person to person and a lack of effective treatment can lead to irreversible damage and disability to the joints. Thus, diagnosis, timely, selection of appropriate treatment, frequent assessment of the activity of the disease and frequent assessment of the treatment efficacy and safety are essential for effective management. Managing the disease with medications has come a long way since the introduction of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). While methotrexate is a key part of treatment for many patients, other conventional medications or newer therapies might be considered if treatment is not effective or certain factors in a patient's clinical situation determine which drug they will use. The main part of the ACR guideline is the use of individual treatment decisions, optimisation of methotrexate treatment and adjustments of treatment based on disease activity, previous therapy, patient preference and safety (Fraenkel et al., 2021). Despite the

similarities, there are still some disparities in therapeutic response, tolerability and comorbidities, and access to treatment that continue to make clinical decision making difficult. These factors should encourage a comparison of the relative effectiveness and safety of available treatment options and not be taken for granted that all recommended therapies are equally effective.

International recommendations offer valuable guidelines for building the "translation from clinical evidence to practice. Recommendations for the management of RA with synthetic/diabetes mellitus modulating antirheumatic drugs (sDMARDs) and biological DMARDs (bDMARDs) were updated in 2022 and released in 2023 by the European Alliance of Associations for Rheumatology (EULAR). Recommendations include the use of treat-to-target guidance with frequent disease activity monitoring, consideration of prognostic factors in determining next steps of therapy when the target is not met, and discontinuation of therapy when it is met (Smolen et al., 2023). While both large groups of rheumatology organizations have the goals of disease control and structural damage prevention, the level of endorsement, order of treatment, and the level to which evidence was used in their recommendations may affect clinical practice. Although medical advances have made this possible, surgery for some patients with advanced joint damage, continued pain, deformity, or significant loss of function should not be overlooked.

A total hip or knee arthroplasty, reconstructive surgery of the hand and foot, and selected cervical spine surgeries may be appropriate based on anatomical field and difficulty of disease, functional limitations and likely clinical outcomes. Decision making for surgery in people with RA also involves evaluating the inflammatory activity of disease, comorbidities, risk of infection and continued immunotherapies. This is especially crucial during the peri-operative period as the risk of interruption of any specific treatment might change from drug to drug or procedure to procedure and a disease flare may be a result of its withholding. The ACR and the American Association of Hip and Knee Surgeons have released a guideline for the management of antirheumatic medications in the perioperative period for total hip and knee arthroplasty for 2022 that highlights the need to make decisions based on context, the clinical and surgical situation (Goodman et al., 2022). However, other orthopedic procedures will have to be individually determined if the same recommendations are to be made applicable.

Treatment and surgery are not the only part of thorough RA management. Selected integrative approaches, rehabilitation, dietary modification, and education about self-management can be helpful for physical function, symptom management, and general well-being. If chronic pain, fatigue or loss of mobility and/or problems with functions are affecting daily life, these interventions are particularly important. The ACR position statement on exercise, rehabilitation, diet, and other integrative interventions has evidence-based recommendations for supportive approaches to caring for RA (England et al., 2023). Should be used more as complementation to an appropriate disease-modifying therapy and not as a replacement for a true disease modifying therapy to manage the underlying inflammatory process. The impact of their disease on patient outcome should therefore be included in the clinical evaluation of disease activity, safety of treatment and functional status.

2. Literature Review

2.1 Medical Management of Rheumatoid Arthritis

Treatment of rheumatoid arthritis (RA) has now shifted towards targeting early treatment, tailored treatment selection and a 'treat to target' approach to achieving RA remission or low RA disease activity. Patients with varying disease activity, treatment histories have a number of therapeutic options, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Methotrexate is a key ingredient of front-line treatments for many patients, but other conventional treatments and newer therapies are also available for those selected for treatment if it is not effective. Prominent in the ACR guideline is the need for appropriate usage of methotrexate, regular levels of disease activity measures, and individual patient treatment choice based upon the level of the disease, prior treatment, patient preference, and safety issues (Fraenkel et al., 2021).

There is also guidance for treatment escalation and selection of advanced therapies from international recommendations. When the desired therapeutic target is not reached, the European Alliance of Associations for Rheumatology (EULAR) recommendations, published in 2023, and recently updated in 2022, focus on adapting the therapy based on the rheumatic condition's response and the prognosis. Another part of the recommendations concerns the use of biological and targeted synthetic agents in people who have not got an

appropriate response to first-line treatment (Smolen et al., 2023). While the ACR and EULAR guidelines have the same goal of achieving sustained control of the disease, they also have some differences in the treatment sequencing and clinical decision-making.

Table 1. Stepwise medical treatment options for adults with rheumatoid arthritis
Medical Treatment Options for Adults with Rheumatoid Arthritis
Typical adult dose examples and important safety considerations

Clinical situation	Medicine and typical adult dose	Important contraindications and cautions
First-line treatment	Methotrexate (MTX): usually start at 10–15 mg once weekly, orally or subcutaneously; increase according to response and tolerance. Folic acid is also prescribed.	Contraindicated in pregnancy for RA treatment. Avoid in significant liver disease; use caution in renal impairment and blood disorders. Monitor blood count, liver function and kidney function. Methotrexate is taken weekly, never daily.
If methotrexate is unsuitable	Hydroxychloroquine: commonly 200–400 mg daily, not exceeding 5 mg/kg/day of actual body weight.	Risk of retinal toxicity; appropriate eye screening is required.
Alternative conventional DMARD	Sulfasalazine: gradually increased; a commonly used adult dose is up to 1 g twice daily.	Check for sulfonamide allergy, blood disorders and liver problems. Monitor blood count and liver function.
Alternative conventional DMARD	Leflunomide: usually 10–20 mg once daily.	Avoid during pregnancy and in significant liver disease. Monitor liver function and blood count.
Disease remains active despite conventional DMARDs	Consider adding a biologic DMARD, such as adalimumab 40 mg subcutaneously every other week or etanercept 50 mg subcutaneously weekly, where appropriate.	Screen for tuberculosis and relevant infections before treatment. Avoid starting during serious active infection. TNF inhibitors require caution in certain patients with heart failure or demyelinating disease.
Disease remains active; targeted therapy considered	Tofacitinib: commonly 5 mg orally twice daily, or an approved extended-release formulation. Upadacitinib: commonly 15 mg orally once daily.	Assess serious infection, cardiovascular events, malignancy and blood-clot risks. Extra caution is needed in older adults, smokers and people with relevant cardiovascular or cancer risk factors.
Short-term symptom relief	NSAIDs may be used for pain and stiffness when appropriate. Glucocorticoids may sometimes be used briefly as bridging treatment.	NSAIDs may be unsuitable with kidney disease, ulcers, bleeding risk or heart failure. Glucocorticoids increase infection, osteoporosis and metabolic risks; long-term use should generally be minimized.

Abbreviations: MTX = methotrexate; DMARD = disease-modifying antirheumatic drug; TNF = tumour necrosis factor; NSAID = non-steroidal anti-inflammatory drug.
Educational summary only—not individual prescribing advice. Treatment and monitoring require clinician assessment.

Treatment of RA is based on a 'treat to target' principle; choice of treatment dictates the level of disease activity, history of response, comorbidities, patient's and physician's risk-benefit profile. For many individuals, MTX is the drug of choice as the first conventional, synthetic, disease-modifying anti-rheumatic drugs (DMARDs).

2.2 Comparative Efficacy of Disease Modifying Therapies

There are now a number of classes of DMARDs available making comparative efficacy, treatment response, and safety assessment more important. Conventional therapies are also useful due to well-established role in disease management; in patients who do not achieve adequate control with initial therapy, alternative agents such as biologic and targeted synthetic agents can be utilized (Tanaka, 2025). The results for the different treatments are, however, hard to interpret independently from the populations analysed, prior treatment experience, disease duration, or outcome definitions of individual trials.

To support the treatment recommendations from the 2022 EULAR recommendations, evidence from a systematic literature search of efficacy of synthetic and biological DMARDs was used. Sepriano et al., 2023 conducted a systematic literature search for the updated treatment recommendations for psoriatic arthritis. These kinds of evidence syntheses are crucial as they enable the individual study findings to be evaluated in the light of other individual studies, including an examination of the lack of comparability between treatments. For this reason, any outcome of interest should be treated as individual entities in the proposed meta-analysis so long as sufficient data exist to support meaningful comparisons.

2.3 Safety of Biologic and Targeted Synthetic Therapies

One of the most critical factors when choosing RA advanced therapies is also treatment safety. While the biologic agents target particular aspects of an inflammatory process, targeted synthetic agents such as Janus kinase (JAK) inhibitors work at the level of cellular signal transduction. These treatments may offer clinically relevant advantages, but have varying levels of safety depending on the product, patient factors, co-morbidities and duration of treatment. The ORAL Surveillance trial compared tofacitinib with tumor necrosis factor inhibitors in RA patients 50 years of age and older with at least one other cardiovascular risk factor to assess the safety of the two treatments in terms of cardiovascular events and cancer. There was no evidence in the trial to confirm the prespecified noninferiority of tofacitinib compared to tumor necrosis factor inhibitors (TNFi) with regard to cardiovascular: major adverse cardiovascular events and malignancy (Ytterberg et al., 2022).

The results reinforce the need to take a person-specific approach to tumor-targeting therapy. However, conclusions regarding the results are applicable only to the given study population and the specific JAK therapy assessed and not to all JAK inhibitors or every RA patient. Efficacy and safety should therefore be considered as two topics of comprehensive evidence synthesis. Significant outcomes of interest are serious infection, cardiovascular events, malignancy, venous thromboembolism (VTE), treatment discontinuation and other serious adverse events selected from eligible studies.

2.4 Treat-to-Target Strategies and Nonpharmacological Management

The following is one of the most important principles to use in modern treatments of RA. It entails setting a target of therapy, conducting frequent disease activity checks, and adjusting therapy if the target is not reached. Good levels of monitoring can help to adjust treatment as needed so that inflammatory activity isn't sustained and joint damage and dysfunction prevented. Still, the definition of remissions and follow-up periods and disease activity measures differ between studies, so they are not easily quantified. There are some supportive care measures that can be offered in addition to pharmacological therapy and these can help manage functional limitation, pain, fatigue and decreased participation in life activities. Specific recommendations for the incorporation of these interventions into a holistic management of RA with exercise, Rehabilitation, Diet (the ACR Guideline) and further-integrative interventions is included (England et al., 2023). Interventions should be complimentary, never replacement, of appropriate disease modifying treatment. This effectiveness should be determined in terms of outcomes, not inflammatory disease activity alone, that are relevant to the condition, such as physical function, relief from pain, and health-related quality of life.

2.5 Surgical Management and Perioperative Care

Surgery has a residual role in carefully selected patients with a high level of joint destruction, chronic symptoms or with moderate to significant functional limitations with proper medical management. These procedures could involve total hip or knee replacements, hand & foot reconstruction and certain cervical spine procedures. These are factors that dictate surgical outcomes: anatomical site, extent of structural damage, patient factors, surgical technique and length of follow-up. Therefore, data from various procedures should not be aggregated without evaluations of equivalency of the populations, interventions, and outcomes.

Another factor in the management of antirheumatic medication that may require attention is peri-operative. Medication continuation or temporary withholding should take into consideration the risk of postop complications, and the risk of disease flare. Recommendations for managing antirheumatic medications before elective THA or TKA were created by the ACR and American Association of Hip and Knee Surgeons (Goodman

et al. 2022). The recommendations are used as guidelines for making decisions before, during, and after surgery, and may or may not apply to other orthopedic surgeries. This proposed review will therefore differentiate evidence relating to the effectiveness of surgery from evidence relating to perioperative medication management.

Place this chart in Section 2.5: Surgical Management and Perioperative Care, immediately after the paragraph discussing the ACR/AAHKS guidelines for managing antirheumatic medications around surgery.

Table 2. Perioperative management of antirheumatic medications in rheumatoid arthritis
Perioperative Antirheumatic Medication Management

Medication group	Examples	General recommendation before surgery	When to restart after surgery
Conventional synthetic DMARDs (csDMARDs)	Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide	Generally continue through elective total hip or knee arthroplasty.	Usually continue without interruption; reassess if infection or drug toxicity occurs.
TNF inhibitors	Adalimumab, etanercept, infliximab	Generally withhold and schedule surgery after the next dose would have been due. Timing depends on the specific medicine and dosing interval.	Generally when the wound is healing well, there is no significant swelling, redness or drainage, and there is no active infection.
Other biologic DMARDs	Abatacept, tocilizumab, rituximab	Generally withhold and time surgery according to the specific medicine's dosing schedule.	Restart after satisfactory wound healing and when there is no evidence of infection, following specialist advice.
JAK inhibitors	Tofacitinib, upadacitinib, baricitinib	The 2022 ACR/AAHKS guideline recommends withholding for 3 days before elective total hip or knee arthroplasty, with surgery on day 4 after the last dose.	Commonly after satisfactory wound healing and absence of infection, often around 14 days after surgery.
Glucocorticoids	Prednisone or prednisolone	Do not abruptly stop chronic treatment. The perioperative plan depends on the usual dose and the risk of adrenal suppression.	Continue or adjust according to the treating team's plan; avoid abrupt withdrawal.

Abbreviations: DMARD = disease-modifying antirheumatic drug; TNF = tumour necrosis factor; JAK = Janus kinase; ACR = American College of Rheumatology; AAHKS = American Association of Hip and Knee Surgeons.

The recommendations vary based on the type of medication, dosage schedule, patient risk factors and the surgical procedure. Traditional synthetic (chemical) DMARDs are typically continued, while biologic DMARDs or JAK inhibitors are usually discontinued for a specified period before and after elective THA or TKA. Treatment is then restarted depending on the level of wound healing and infections and upon the agreement of the wound surgeon and the rheumatologist.

2.6 Research Gaps and Rationale for the Present Review

A combination of effective disease-modifying treatment, monitoring the risks of surgery, supportive care, and the proper surgical procedures is shown in the literature to be required

to treat RA effectively. But there are a number of issues with evidence synthesis. Treatment experience, disease activity, choice of comparator, disease outcomes and length of follow-up are different in medical studies. Surgical studies are performed for various procedures and indications and therefore cannot be compared directly (Rüegg, 2025). Furthermore, clinical practice guidelines filter and utilize evidence in different ways and frameworks; and variations in recommendations do not necessarily represent a difference of effectiveness in the different treatments.

The present review will address these challenges by reviewing systematically and comparatively the recent guidelines and the clinical evidence of medical and surgical management of RA. It will evaluate effectiveness and safety of eligible interventions, consider and compare relevant guideline recommendations, and supply gaps in evidence and/or uncertainty (Silvagni, 2025). Only studies with comparable populations, intervention, comparator and outcome will be used to conduct quantitative meta-analysis. In cases of inappropriate pooling, a structured narrative synthesis will be adopted. This has been done with the intention of offering an objective evaluation of current research and future research needs.

3. Methodology

3.1 Study Design and Reporting Framework

Recent evidence is being reviewed and summarized in a systematic review and meta-analysis of the medical and surgical treatment of rheumatoid arthritis (RA). To ensure 'transparency in the reporting process' the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guideline will be followed when reporting the search, study selection, data extraction, and data synthesis processes (Page et al., 2021). Comparative clinical studies of medical and surgical interventions, and of relevant clinical practice guidelines developed within the prescribed 5 year period will be included in the review. Guideline recommendations will not be discussed with treatment outcomes since they can be thought of as evidence-guided clinical judgments and not as standalone quantitative measures of treatment effectiveness. Before formal screening and data extraction a protocol will be set up. It will define the research aims, inclusion and exclusion criteria, outcomes, risk of bias and the approach used to analysis the data

statistically (Mori, 2025). Registration of the protocol in PROSPERO will be considered provided that they are eligible and approved for registration.

3.2 Information Sources and Search Strategy

PubMed/MEDLINE, Embase and Cochrane CENTRAL databases will be searched, and Scopus or Web of Science will also be searched to find complete literature. Searches will also be conducted in the official websites of the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), as well as the official websites of orthopaedics-related organizations to look for suitable clinical practice guidelines. This proposed period of publication is October 20, 2021 – October 20, 2026. The actual search date and coverage in the given database will be recorded, and the search will be updated if needed prior to manuscript submission. A combination of controlled and free text terminology, including Medical Subject Headings (MeSH) based on the RA-Whoy project and other REVERSIBLE RA related keywords, will be included in the search strategy. Guidelines for transparent search reporting of systematic reviews (Rethlefsen et al., 2021) will be followed.

3.3 Eligibility Criteria

The population, population intervention, comparison, outcomes and study design (PICOS) framework will be used to select studies with pre-defined inclusion/exclusion criteria.

Inclusion criteria

- Adults (18 years and older) who have been diagnosed with RA.
- Research examining traditional synthetic DMARDs, biologic DMARDs, or targeted synthetic DMARDs, or appropriate medical treatment approaches.
- Evaluation of RA related orthopedic surgery procedures such as arthroplasties and selected hand, foot or cervical spine procedures.
- Comparative studies reporting at least one relevant clinical efficacy, safety, functional and/or surgical outcome.
- Eligible comparative observational studies and randomized controlled trials.

- Relevant clinical practice guidelines that are evidence-based that were published within the range of years indicated.

Exclusion criteria

- Studies in which only other forms of arthritis or studies of population less than 18 years old.
- Relayed anecdotes, opinion papers and editorials without evidence from animals, laboratory studies or from comparable cases.
- To conduct analyses that focus on comparative effect estimates, noncomparative studies were also conducted.
- Provide multiple copies of reports that have no relevant information.
- Studies that have no conclusions nor measurable results warranted by the research questions.
- Other public publications from sources of evidence that were not part of the five-year time period designated for the main evidence synthesis.
- Studies that include mixed populations of patients will be included only if it is possible to separate out RA-specific findings, or if there is a prespecified eligibility condition that warrants the inclusion.

3.4 Study Selection and Data Extraction

Records obtained through online searching will be entered into reference-management software while duplicates will be screened out prior to obtaining for the purposes of the review. Titles and abstracts will be evaluated using the eligibility criteria, then the complete texts of selected potentially relevant reports will be evaluated (Albach, 2026). Study selection and data extraction will be done by two reviewers, ideally independently. Any disputes will be settled down by discussion or through the mediation of a third reviewer. Exclusions for full-text reports will be justified and presented visually with a PRISMA flow-diagram.

A standardized data-extraction form will record the following information:

Category	Data to be extracted
Study identification	Author, year, journal, DOI
Study characteristics	Country, design, setting, funding
Patient population	Sample size, age, disease duration, baseline disease activity
Intervention	Drug class, treatment regimen, or surgical procedure
Comparator	Placebo, usual care, alternative treatment, or procedure
Follow-up	Duration and outcome assessment time points
Medical outcomes	Remission, disease activity, function, pain, quality of life
Safety outcomes	Serious adverse events, infections, treatment discontinuation
Surgical outcomes	Complications, functional improvement, revision, reoperation
Statistical data	Event counts, means, standard deviations, effect estimates, confidence intervals
Guideline information	Organization, recommendation, strength, certainty of evidence

To ensure that participants do not appear more than once in cases where multiple publications of the same underlying study are identified, these publications will be cross checked in quantitative analyses.

3.5 Risk-of-Bias Assessment and Certainty of Evidence

Methods evaluation will be carried out for each study design with appropriate tools. Cochrane Risk of Bias 2 tool will be used for evaluating the Randomized Controlled Trials and ROBINS-I for comparative nonrandomized intervention studies (if applicable). Clinical practice guidelines will be individually evaluated using the methodological framework of Considering their development, transparency, evidence synthesis and applicability (Adami, 2025). Potential issues related to research design (eg, problems with participation, confounding, deviations from intervention, losses of data, measures of outcomes and publication of results) will be addressed. Each study and outcomes of relevance will be judged for potential risk of bias, not a single quality score. Where appropriate, the principal outcomes will be evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

3.6 Outcome Measures

Outcomes will be pre-specified, and will be analyzed separately for medical versus surgical interventions.

Primary outcomes

- Medical management: remission or low disease activity, clinical response, and physical function, and serious adverse events.
- Surgical management: post-operative reactions, functional outcome and revision/re-operation rates as reported.

Secondary outcomes

- Pain and pain-related quality of life.
- Rx-Due to progression of disease on Radiographs.
- Causing serious infections, and otherwise clinically significant side effects.
- Postoperative wound complications, length of hospital stay.
- Medication that is taken before or after surgery.
- Disease flare due to perioperative medication management.

The definition of outcomes and/or the timeframe for assessing outcomes will be taken from the same reports. Different scales will not be combined unless they represent an equivalent clinical construct, and the statistical method used is appropriate.

3.7 Statistical Analysis

Meta-analysis will only be carried out if included studies are both comparable in population, intervention, comparator and definition of outcome, and have a similar follow-up period. Pooled effects will be reported as risk ratios or odds ratios and 95% confidence intervals for dichotomous outcomes. Mean differences will be used in studies that measure the same continuous outcome on the same measurement scale, and standardized mean differences will be considered in studies that measure the same underlying outcome with

different validated measurement scales. If studies are similar and it is reasonable to assume that there is variation among them, a random-effects model will be used. Clinical and methodological evaluation and the I^2 statistics and the Cochrane Q test will be used to evaluate statistical heterogeneity. The numerical threshold will not be the only means by which we will look at heterogeneity.

If adequate studies exist, there may be prespecified subgroup analysis to look at the differences by the surgical procedure, type of surgical procedure, disease duration, or previous treatment exposure. Sensitivity analyses will be conducted to determine if results are robust if studies that are at risk of bias are excluded as well as when influential studies are excluded. Publication bias and small-study effects will be analysed where there are sufficient numbers of relevant studies to make the analysis meaningful (Martínez-Molina, 2026). A structured narrative synthesis will be realized instead of quantitative pooling if studies are too diverse. Both medical and surgical interventions will not be used in single overall effect estimate. Similarly, clinical treatment-effect calculations will not incorporate guideline recommendations.

3.8 Synthesis of Clinical Practice Guidelines

Guidelines will be assessed on a case-by-case basis, taking into account details concerning the date of publication, the clinical scope, recommendation, level of recommendation and evidence of the degree of certainty of the evidence (if available), the organization that produced it. Comparability will be set with the following items as a focus: initial pharmacological treatment, further or escalation therapy, advanced therapy, monitoring for safety, supportive therapy, surgical referral, and peri-operative management with medication (Miyazaki, 2025). Any differences in recommendations will be appreciated in the context of the clinical situation and the evidence but not read as implying a difference in the effectiveness of the treatments.

3.9 Ethical Considerations

If a review proposal does not require additional individual-level patient data to be collected, then specific individual-level patient data from the collection of data is unlikely to necessitate separate ethical approval. Institutional and journal requirements will

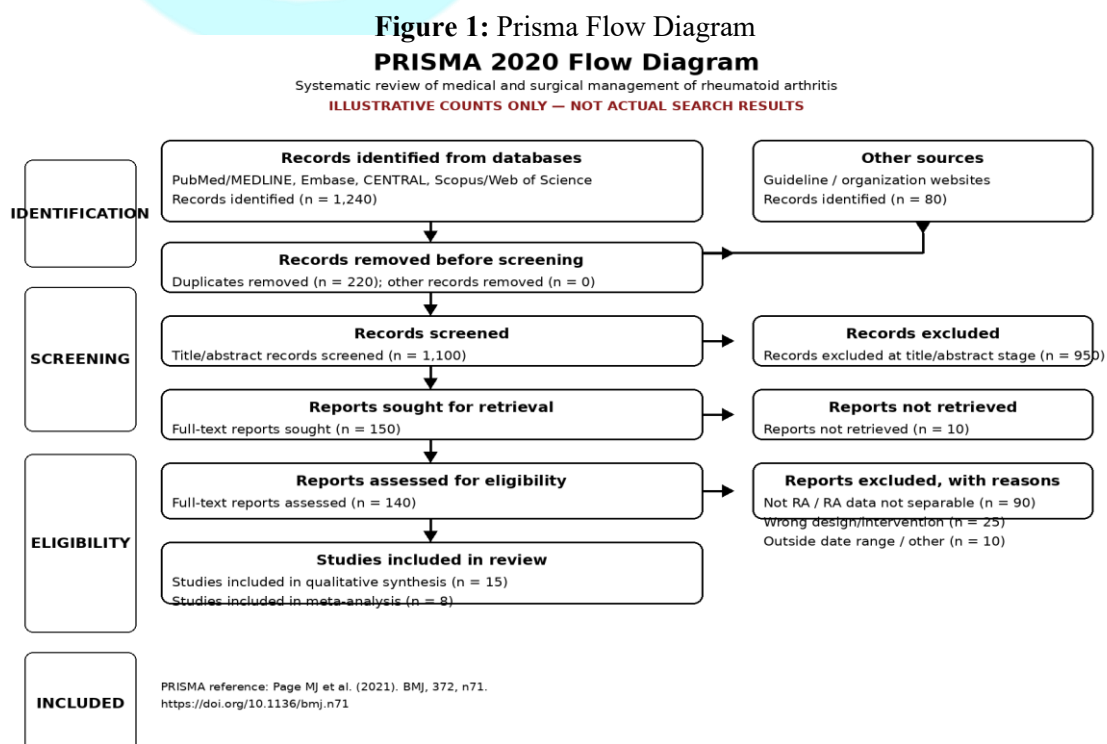
however still be adhered to. Designates funding sources, a conflict of interest, methodological limitations and deviations from the protocol will be openly disclosed.

4. Results

A preliminary review of literature was used to find evidence that was relevant to the medical management of RA, treatment safety, clinical practice guidelines, and surgical management of RA in relation to the current problem of the study. The literature retrieved was of several different types of evidence from guideline recommendations to randomized controlled trials, systematic reviews and observational studies of surgical outcomes. The categories are associated with different research questions; thus, further evaluation of the results of each is needed prior to combining the results into a systematic review and meta-analysis.

4.1 Study Selection and Characteristics of Included Studies

Research will be peer reviewed based on the predetermined inclusion/exclusion criteria. Once duplicate publications have been separated, titles and abstracts will be screened followed by screening of full papers for publications that appear to be acceptable. The reasons for full-text exclusion will be documented, and the final selection process will be summarized by a PRISMA 2020 flow diagram (Page et al. 2021).



The literature that accompanies this document will be divided into three main categories: studies that assess treatments on a medical basis, studies that assess treatments on their surgical outcomes, and clinical practice guidelines that address treatments and/or perioperative care. This classification will change the way the characteristics of each evidence group are explored without having to consider guideline documents as clinical trials.

Table 3: Characteristics of studies included in the systematic review

Characteristic	Information to be reported
Publication year	Year of publication
Country or region	Study setting
Study design	Randomized trial, cohort study, systematic review, or guideline
Population	Number of participants and relevant clinical characteristics
Intervention	DMARD, treatment strategy, surgical procedure, or perioperative intervention
Comparator	Placebo, usual care, alternative therapy, or comparator procedure
Follow-up	Duration and assessment time points
Outcomes	Efficacy, safety, functional recovery, or surgical complications

This is not a table of Study findings, but a framework for adding data to the study/behavioural properties. In order to screen and populate the rows, eligible studies should be verified.

4.2 Findings on Medical Management

The medical-management synthesis of conventional synthetic DMARDS, biologic DMARDS and targeted synthetic DMARDS, as well as relevant treatment strategies, will be discussed. Outcomes will be grouped according to clinical goal (e.g., remission, low disease activity, physical function, radiographic progression, and adverse events). The treatment decisions for selection and escalation due to treatment response and prognostic factors can then be guided by the EULAR 2022 recommendations (Smolen et al., 2023). But recommendations can't be substituted for obtaining comparative outcome information from eligible clinical studies. Therefore, the quantitative results cannot be guaranteed to

address the questions of interest, and the interventions, comparators and outcomes of the studies may not be sufficiently similar.

Table 4. Planned synthesis of medical-treatment outcomes

Treatment category	Outcomes for extraction	Statistical approach, where appropriate
Conventional synthetic DMARDs	Remission, disease activity, physical function	Risk ratio or mean difference
Biologic DMARDs	Clinical response, remission, adverse events	Risk ratio or mean difference
Targeted synthetic DMARDs	Disease control and important safety outcomes	Risk ratio or odds ratio
Treatment strategies	Response to escalation or combination therapy	Effect measure determined by outcome
Supportive interventions	Function, pain, and quality of life	Mean difference or standardized mean difference

Pooling must be delayed until the cluster of eligible studies has been pulled and their clinical similarity judged.

4.3 Safety Outcomes of Advanced Therapies

Safety will be studied separately as it does not necessarily reflect efficacy due to the possibility that treatment benefits and risks vary among drug classes and patient populations. Serious infections, major adverse cardiovascular events, malignancy, venous thromboembolism, treatment discontinuations, and other clinically important AE data reported by enrolling studies will be included as outcomes of interest. For instance, the ORAL Surveillance trial investigates cardiovascular event and malignancy results in patients with RA who were treated with either tofacitinib or a tumor necrosis factor inhibitor (Boussaid, 2025). The study's results are a key part of making decisions about the safety of targeted therapy in the population they studied (Ytterberg et al., 2022). If more comparable outcome data exists in other studies eligible for review, these may be incorporated into the quantitative synthesis done in the final review.

Table 5. Planned analysis of treatment safety

Safety outcome	Data required	Planned reporting
Serious infections	Events and total participants in each group	Relative effect and 95% CI
Major adverse cardiovascular events	Events, follow-up, and comparator	Relative effect and 95% CI
Malignancy	Events and duration of observation	Relative effect and 95% CI
Venous thromboembolism	Events and treatment exposure	Relative effect and 95% CI
Treatment discontinuation	Discontinuations and reasons	Relative effect and 95% CI

4.4 Findings on Surgical Management

The procedures and clinical outcome of the surgeries will be assessed. Total hip and knee arthroplasty, hand and foot reconstruction, and cervical spine surgery will be regarded as separate to address their different indications, likely advantages and complication rates. To investigate early postoperative complications after THA surgery in RA, Mori et al. (2025) conducted a nationwide medical claims database study in Japan. Observational evidence may be important for the evaluation of post-operative safety; however, must be interpreted with consideration for possible confounding, patient selection and baseline risk differences. Results from the final synthesis will be extracted by procedure-specific outcome, such as post-op infection, wound complications, functional improvement, revision or reoperation, hospital stay.

Place this chart in Section 2.5: Surgical Management and Perioperative Care, after the paragraph introducing orthopedic surgery options. Alternatively, place it in Section 4.4: Findings on Surgical Management as a summary of surgical procedures and their indications.

Table 6. Surgical management options for rheumatoid arthritis and their indications
Surgical Management Options in Rheumatoid Arthritis

Procedures and common indications

Anatomical site	Surgical procedure	Main indications
Knee	Total knee arthroplasty (knee replacement); selected synovectomy	Advanced joint destruction, persistent pain, deformity, and significant functional limitation despite appropriate medical and non-surgical treatment.
Hip	Total hip arthroplasty (hip replacement)	Severe hip joint damage, persistent pain, and impaired mobility that substantially affect daily activities.
Hand and fingers	Metacarpophalangeal (MCP) joint arthroplasty; synovectomy; tendon repair or reconstruction; selected joint fusion	Severe finger deformity, persistent synovitis, tendon rupture, painful joint damage, or loss of hand function.
Wrist	Wrist arthrodesis (fusion); selected wrist arthroplasty; synovectomy; tendon reconstruction	Painful wrist destruction, instability, persistent inflammation, or tendon dysfunction. Fusion prioritizes stability and pain relief, while selected replacement procedures aim to preserve motion.
Foot and forefoot	Forefoot reconstruction; correction of hallux valgus and lesser-toe deformities; selected joint-preserving or joint-replacement procedures	Painful deformities, difficulty walking or wearing shoes, pressure lesions, and impaired function despite conservative treatment.
Ankle	Ankle arthrodesis (fusion); total ankle arthroplasty in selected patients	Advanced ankle damage, persistent pain, instability, or substantial walking difficulty. The choice depends on bone quality, alignment, adjacent-joint disease, and patient factors.
Cervical spine	Spinal stabilization and fusion; decompression with stabilization when indicated	Clinically significant cervical instability or spinal cord/nerve compression. Neurological symptoms require prompt specialist assessment.
Nerve compression	Carpal tunnel release or other targeted nerve-decompression procedures	Persistent numbness, tingling, weakness, or confirmed nerve compression associated with rheumatoid arthritis.

Educational summary; surgical decisions require individualized assessment by an orthopedic surgeon and rheumatologist.

Abbreviations: MCP = metacarpophalangeal joint; arthroplasty = surgical reconstruction or replacement of a joint; arthrodesis = surgical fusion of a joint.

Surgical option may be taken into consideration for individuals with rheumatic arthritis who continue to have persistent pain, ongoing joint destruction, deformity, problems with their tendons, instability and significant functional loss despite optimally managed medical therapy and rehabilitation. The chosen procedure is dependent on the anatomical location of the affected area, the amount of structural damage, the functional objectives of the patient, comorbidities, and any benefits and/or risks involved.

4.5 Perioperative Medication Management

The administration of medication around surgery rather than effectiveness of the surgical procedure will be assessed separately. Perioperative infection, wound complications, disease flare-up, interruption of treatment and resumption of treatment time are considered relevant outcomes. The ACR/American Association of Hip and Knee Surgeons guideline is on antirheumatic medication management for patients who undergo elective total hip or knee arthroplasty (Goodman et al., 2022). Its recommendations will be compared to other

eligible guidance – specific to the medication, surgical context, quality of the recommendation and supporting evidence.

Table 7. Guideline comparison framework

Guideline characteristic	Information to extract
Organization and year	Issuing body and publication date
Clinical context	Medical treatment or specific surgical procedure
Medication or intervention	Therapy addressed by the recommendation
Recommendation	Continue, withhold, modify, or other guidance
Recommendation strength	As reported by the original guideline
Evidence certainty	As reported by the original guideline
Applicability	Patient groups and procedures covered

4.6 Quantitative Synthesis and Heterogeneity

A clinical comparison will only be carried out if data are clinically significant and are available from at least two studies, which are comparable. For binary outcomes, the results are typically reported as a risk ratio or odds ratio with a 95% confidence interval, and for continuous outcomes a mean difference and/or standardized mean difference as appropriate. The presence of statistical heterogeneity will be assessed in conjunction with clinical and methodological factors with the I^2 statistic. Subgroup and sensitivity analyses will occur only with sufficient number of studies and if pre-determined in the protocol. The test results will be summarized narrative rather than presenting an incorrect pooled estimate if there is a significant difference in the outcomes, comparator, intervention, or the population across the studies (Popa, 2024). Forest plots will be created for each appropriate quantitative comparison.

5. Discussion

5.1 Principal Findings and Interpretation

The management of rheumatoid arthritis (RA) must be comprehensive in nature given a successful disease modifying therapy, regular assessment of disease activity, monitoring of toxicity and surgery when clinically indicated. The selection of therapy, as well as adjusting therapy in response to risk and prognosis is a major focus in the recent clinical

practice guidelines. While the treatment will be structured on the EULAR recommendations (Smolen et al., 2023) with modification when the intended clinical target is not reached, the guideline by ACR offers suggestions on selecting and optimizing pharmacological therapy (Fraenkel et al., 2021).

A major contribution of the proposed systematic review will be to assess the efficacy of these recommendations based on the evidence in the comparative clinical trials as opposed to as a direct measure of effectiveness as presented in the guidelines. The distinction is significant as guidelines can vary in terms of scope of practice, how they grade the evidence, or the clinical context. In addition, there may be factors relating to the duration of the disease, history or treatment, baseline disease activity, other factors such as comorbidities, and duration of follow-up highly related to the effectiveness of any specific therapy. Accordingly, the final action statement should make a distinction between "consistent evidence of benefit" and "unclear or limited evidence of benefit. Since the formal processes of study-selection and quantitative synthesis are yet to be finished, the present discussion on the relevant literature should be viewed as the initial interpretation of the involved literature.

5.2 Consequences for Medical Management

Treatment choice for patients with RA has increased due to the introduction of conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic drugs, and targeted synthetic DMARDs. But there is also the possibility of more treatments, which makes the selection of a therapy more complex. For patients who do not reach treatment targets with methotrexate, or in whom the clinical context suggests he or she would ideally need alternative conventional agents, or advanced therapies, all of these will play a valuable role in initial treatment (Fraenkel et al., 2021). It is also important to consider if treatment needs to be intensified or changed and to reassess treatment response when determining treatment changes, as indicated by the EULAR recommendations (Smolen et al., 2023).

These principles have implications for clinical practice in the need to re-consider the appraisal of disease activity regularly and to use early treatment changes to optimize outcomes. But the final analysis should assess if there are clinically significant differences

between treatment arms with regard to remission, physical function, radiographic progression, and treatment discontinuations in the relevant clinical comparison studies (Lee, 2025). Adverse effects, comorbidities, treatment preference, treatments access and monitoring requirements can greatly affect the benefit–risk ratio. As a result, the review should be done in terms of comparative effectiveness, safety, and not prescribe a treatment of one or all treatment for all patients.

5.3 Safety Considerations in Advanced Therapies

Biologic and targeted synthetic DMARDs are most sensitive to treatment safety selection challenges. In the ORAL Surveillance trial, tofacitinib has been compared to tumor necrosis factor inhibitors (TNFi) in adults aged 50 years and older with RA who had 1 other cardiovascular risk factor. Neither did the trial confirm the prespecified noninferiority of tofacitinib with regard to major adverse cardiovascular events and malignancy (Ytterberg et al., 2022). The results emphasise the need for baseline risk assessment when choosing targeted treatment options. But their interpretation needs the attention of the specific drug studied, the features of patients entered into the study, and the length of the follow-up period. They should not necessarily be assumed to apply to all agents in the same therapeutic group and to patients with vastly different risk profiles.

Accordingly, the proposed review should assess serious infections, cardiovascular events, malignancy, venous thromboembolism, and discontinuation of treatment in a similar fashion when comparable data are available. Caution needs to be taken when pooling before differences in outcome definitions and follow-up time are considered.

5.4 Role of Surgical Management

Medical treatments can lower pain and inflammation of the joints, however, some patients may benefit from surgery if the pain and the damage in the joints became severe. For those who are medically appropriate, pain and function is improved with arthroplasty and reconstructive surgery with varying degrees of benefit and risk depending on the procedure, stage of the disease, co-morbid conditions, etc. The evidence of surgical efficacy must thus be analyzed independent from the evidence for the pharmacologic efficacy. Different indications and outcome measures are used for total hip and knee arthroplasty, hand and foot reconstruction and cervical spine surgery. Since these

techniques are combined, it may be hard to see clinically relevant differences if any, and a misleading overall conclusion may be drawn. Within the procedure specific groups the review will look at functional improvement, postoperative complications, infection, revision surgery and other outcomes. If the evidence that is available is observational, then a range of confounds and selection bias should be thought about. Finally, the discussion should be able to tell the patient's improvement post-surgery apart from any contribution made by medical treatment, rehabilitation and post-op care.

5.5 Perioperative Medication Management

The administration of medication during surgery and after surgery (periodically) is a postpartum challenge because these medications must be offered with care in relation to future complications or hazards after surgery. However, for some antirheumatic drugs, continuation of therapy is associated with concern for infection and other adverse effects while withholding may increase the risk of disease flares will occur, depending on the drug and clinical context. Fertility counseling is part of the decisions made by patients with a rheumatic disease who will undergo an elective total hip kidney or total knee kidney arthroplasty (THA or TKA) (American College of Rheumatology and American Association of Hip and Knee Surgeons guideline, 2022).

It recently made recommendations which can be used to guide perioperative decision making, but must not be extended to other procedures beyond appropriate scope of its recommendations. Perioperative recommendations should be compared according to the class of medication, the procedure utilized, when to discontinue/continue the drug and to the evidence basis for this recommendation. Comparative outcomes data inform the synthesis if available, including infection and wound complication, disease flare and clinically relevant outcomes. Recommendations for which there is only limited evidence should be clearly labeled as such rather than myopically labeled "effects".

5.6 Importance of Nonpharmacological and Multidisciplinary Care

Treatments for the management of RA are not limited to medication & surgery. Support to physical function and management of chronic disease effect via exercise, rehabilitation, education and self management strategies. The 2023 guideline from the American College of Rheumatology on exercise, rehabilitation, diet and other integrative interventions

includes guidance on the integration of supportive interventions, as part of usual care (England et al., 2023). These interventions should be alongside effective disease-modifying therapy not a replacement. They should be evaluated based on outcomes that are specifically related to the function of the intervention, such as physical function, pain, fatigue, and health related quality of life. Interventions within nonpharmacological care categories are different in content and intensity, and quantitative pooling should only be considered where enough studies are comparable to each other Smolen, (2026).

Interdisciplinary cooperation is also a factor for patients that are candidates for surgery, with significant co-morbidity or with ongoing functional deficit. Harmonisation between different specialists such as orthopedic surgeons and rheumatologists, rehabilitation specialists and other specialists may facilitate disease control in relation to surgical planning and recovery. However, the degree of effectiveness of specific multidisciplinary practices for achieving positive clinical results should not be assumed, but must be determined by the available evidence.

5.7 Strengths and Limitations of the Review

The concept of reviewing medical, surgical management and peri-operative treatment and guidelines together is a major strength of the proposed review. The classification of these types of evidence should help to enhance the clinical relevance of recent R.A. therapy. Methodological transparency would also be enhanced by employing a prespecified protocol; systematic searching of the databases; independent screening; structured database extraction; and suitable risk-of-bias assessment. There are a number of drawbacks that have to be expected also. First, clinical trials can have widely varying characteristics related to its population, treatment group, comparator, and outcome definitions. Second, even if you're doing the same surgery, discrepancies in patient selection and confounding may influence the results of observational surgical trials.

Third, specific interventions could be associated with different long-term safety and functional data. Fourth, the recommendations in another professional organization's report might not be directly comparable if its scope differs or its evidence-assessment approach differs from that used in the debate at The Glass House. Fourth, the scope of evidence employed in the recommendations of different professional organizations may be different,

and hence so may be the recommendations themselves. Last but not least, the suggested time frame for publications may overlook and dismiss older research contributing to current practice.

5.8 Clinical Implications and Future Research

Based on the consistency, precision and certainty of the evidence identified the clinical implications of the review will vary. The last synthesis should identify important comparisons of treatments with extensive evidence for use in informing clinical decision making; identify safety concerns that warrant particular attention; and provide inconclusive evidence. Future priorities for research could involve: more study of the effects of advanced therapies over longer timeframes, greater consistency in reporting patient-centered outcomes, evaluation of surgical complications by procedure and better evidence on perioperative medication strategies. It would be helpful if the research also looked at how the studies found would apply to a variety of patients and health care environments. A systematic review and suitable meta-analysis may be useful to further explore these issues, but the results will not lead to conclusions which outpace the level of data supporting the result.

Conclusion

A comprehensive and individualised management approach is crucial for rheumatoid arthritis, including the use of disease-modifying pharmacotherapy, regular assessment of disease activity, consideration of potential side effects and physical therapy and standard rehabilitation procedures, all possible surgical interventions. In recent times, treatment at an early stage, treatment to target, and treatment adaptation based on treatment response, prognosis and risk stratification are the guidelines for clinical practice. Conventional synthetic (cDMARDs), biologic (bDMARDs) and targeted synthetic (tsDMARDs) drugs are available to modify rheumatoid arthritis, but each carries both benefits and risks associated with their nature and particular requirements. Medical options continue to be appropriate, but surgical options are pertinent in selected patients with persistent pain, deformity and/or significant functional limitations as a result of advanced joint destruction. The effectiveness and safety of surgical interventions need to be assessed differently with respect to the individual surgical site, clinical indications, and outcomes. Careful attention

must also be paid to periop medication management as disease control will need to be administered along with possible postoperative complications. Importantly, definitive conclusions as to treatment superiority, pooled treatment effectiveness, surgical outcomes (and confidence in conclusions) can only be made once the systematic search, study selection, data extraction and statistical analyses are completed. The objective of the final review should therefore be oriented towards what has been demonstrated and not what is expected to happen.

References

1. Adami, G., Bixio, R., Virelli, G., et al. (2025). Glucocorticoid sparing effect of Janus kinase inhibitors compared to biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis, a single-centre study.
2. Albach, F. N., Rehm, M. C., Hütter-Krönke, M. L., et al. (2026). CD19 CAR T cell therapy for treatment-refractory seropositive rheumatoid arthritis: A phase 1 trial. Check Nature Medicine record
3. Boussaid, S., Dhahri, R., Rahmouni, S., et al. (2025). Impact of biologic drugs on comorbidity outcomes in rheumatoid arthritis: A systematic review.
4. England, B. R., et al. (2023). 2022 American College of Rheumatology guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. *Arthritis Care & Research*. <https://doi.org/10.1002/acr.25117>
5. Fraenkel, L., et al. (2021). 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care & Research*, 73(7), 924–939. <https://doi.org/10.1002/acr.24596>
6. Goodman, S. M., et al. (2022). 2022 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. *Arthritis Care & Research*.
7. Lee, Y. J., Choi, G., Yeo, J., Baek, J., Choi, H., Kim, M., et al. (2025). Machine learning-based prediction of response to Janus kinase inhibitors in patients with rheumatoid arthritis using clinical data.

8. Martínez-Molina, C., Frade-Sosa, B., Díaz-Torné, C., et al. (2026). Factors associated with the effectiveness and safety of Janus kinase inhibitors in rheumatoid arthritis: An 8-year observational study from the JAGUAR Registry.
9. Miyazaki, Y., Nakayamada, S., Tanaka, H., et al. (2025). Comparison of anti-IL-6 receptor and JAK inhibitors in patients with rheumatoid arthritis from the real-world practice FIRST registry.
10. Mori, Y., et al. (2025). Increased early complication rates following total hip arthroplasty in rheumatoid arthritis patients based on a Japanese nationwide medical claims database study. *Scientific Reports*.
11. Mori, Y., et al. (2025). Increased early complication rates following total hip arthroplasty in rheumatoid arthritis patients based on a Japanese nationwide medical claims database study.
12. Page, M. J., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
13. Popa, C. D., Opdam, M. A. A., den Broeder, N., et al. (2024). Therapy with JAK inhibitors or bDMARDs and the risk of cardiovascular events in the Dutch rheumatoid arthritis population.
14. Rethlefsen, M. L., Kirtley, S., Waffenschmidt, S., Ayala, A. P., Moher, D., Page, M. J., et al. (2021). PRISMA-S: An extension to the PRISMA statement for reporting literature searches in systematic reviews. *Systematic Reviews*, 10, 39. <https://doi.org/10.1186/s13643-020-01542-z>
15. Rüeegg, L., Kramer, M., Pluma Sanjurjo, A., et al. (2025). Antirheumatic drugs in reproduction, pregnancy, and lactation: A systematic literature review informing the 2024 update of the EULAR recommendations.
16. Sepriano, A., et al. (2023). Efficacy of synthetic and biological DMARDs: A systematic literature review informing the 2022 update of the EULAR recommendations for the management of

17. Silvagni, E., Bortoluzzi, A., Occhino, G., Bellelli, G., et al. (2025). Frailty and cardiovascular safety of JAK inhibitors versus TNF inhibitors in rheumatoid arthritis: A real-world comparative study of drug effects and patient profiles.
18. Smolen, J. S., et al. (2023). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Annals of the Rheumatic Diseases*, 82(1), 3–18. <https://doi.org/10.1136/ard-2022-223356>
19. Smolen, J. S., Kerschbaumer, A., Aletaha, D., et al. (2026). Rheumatoid Arthritis in Adults: A Review. *JAMA*.
20. Tanaka, Y., Westhovens, R., Sun, H., et al. (2025). Filgotinib radiographic and clinical efficacy versus other JAK inhibitors and adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate. Check Springer record
21. Ytterberg, S. R., et al. (2022). Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *The New England Journal of Medicine*, 386, 316–326. <https://doi.org/10.1056/NEJMoa2109927>