An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis

Main editor
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Publishing and version history
v0.8 published on 15.02.2021

Australia & New Zealand Musculoskeletal Clinical Trials Network

An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis seeks to present the best available, current scientific evidence to assist decision making in the pharmacological management of the most common forms of IA, namely rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA). The guideline offers recommended courses of action subject to clinical judgement and patient preferences. Topics and questions identified as having highest clinical relevance to medical practitioners who treat IA are being prioritised. These questions include choice of DMARD, switching, combination therapy and down-titration of treatment. As a living guideline, questions will continue to be addressed, new recommendations developed, and existing recommendations updated on an ongoing basis.

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Sponsors/Funding

An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis is being produced with assistance from the Australian Government's Value in Prescribing (VIP) program grant, managed by the Targeted Therapies Alliance, a consortium coordinated by National Prescribing Service (NPS) MedicineWise. The program grant aims to improve the use of biological disease-modifying anti-rheumatic drugs (bDMARDs), using a variety of interventions and programs. The living guideline and living recommendations component is produced by the Australia and New Zealand Musculoskeletal (ANZMUSC) Clinical Trials Network, Australian Rheumatology Association (ARA), and Cochrane Musculoskeletal, in conjunction with the NPS MedicineWise consortium.

Disclaimer

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Summary of recommendations

1 - How To Use This Guideline

2 - Introduction

3 - Executive Summaries

4 - Dose Reduction and Discontinuation Strategies

4.1 - Rheumatoid Arthritis: Dose Reduction or Discontinuation of bDMARDs and tsDMARDs

Conditional recommendation

In people with RA who have been in sustained low disease activity or remission for at least 6 months, consider stepwise reduction in the dose of b/tsDMARD. Continue dose reduction until cessation is achieved or the lowest effective b/tsDMARD dose is identified, as long as the treatment target is maintained. Abrupt cessation of b/tsDMARDs without prior dose reduction is not recommended.

Remark: *Evidence up to date as at 8 July 2020*

4.2 - Axial Spondyloarthritis: Dose Reduction or Discontinuation of bDMARDs

Conditional recommendation

In people with axial spondyloarthritis who have been in sustained low disease activity or remission for at least 6 months, consider reduction in the dose of bDMARD. Continue at the lower dose as long as the treatment target is maintained. Abrupt cessation of bDMARDs is not recommended.

Remark: *Evidence up to date as at 23 July 2020*

4.3 - Psoriatic Arthritis: Dose Reduction or Discontinuation of bDMARDs and tsDMARDS

Conditional recommendation against

Do not routinely reduce the dose of b/tsDMARDs in patients with psoriatic arthritis who are in low disease activity or remission. Abrupt cessation of b/tsDMARDs is not recommended.

Remark: *Evidence up to date as at 6 August 2020*

5 - Opioids for Pain Management

5.1 - Opioids for Pain in RA

Conditional recommendation against New

Do not routinely use opioids for the treatment of pain in rheumatoid arthritis.
A brief course of a short-acting opioid may be considered for severe pain when other analgesic options have failed.

Remark: *Evidence up to date as at 23 June 2020*

5.2 - Opioids for Pain in Axial Spondyloarthritis

Conditional recommendation against New

Do not routinely use opioids for the treatment of pain in axial spondyloarthritis.

Remark: *Evidence up to date as at 23 November 2020*

5.3 - Opioids for Pain in Psoriatic Arthritis

Conditional recommendation against New

Do not routinely use opioids for the treatment of pain in psoriatic arthritis.

Remark: *Evidence up to date as at 23 November 2020*

6 - Methods and Processes - Evidence Review

6.1 - Clinical Questions (PICO's)

7 - Guideline Panel - Membership and Terms of Reference

8 - Conflict of Interests

9 - Glossary, Abbreviations and Acronyms

10 - Appendices - Figures, Tables and Supplementary Information

1 - How To Use This Guideline

The treatment of Inflammatory Arthritis (IA) has evolved rapidly over the last two decades. New approaches to management (including 'treat-to-target') and a rapid expansion in available disease-modifying antirheumatic drugs (DMARDs) have improved outcomes for many people living with IA. The increasing rate of production of new evidence regarding treatment means that recommendations based on current evidence are likely to become outdated quickly as new studies are published. The living evidence approach facilitates rapid updating of recommendations. By frequently incorporating the most up-to-date evidence, these methods ensure that the currency of each recommendation remains high.

It is anticipated that evidence searches relating to the recommendations in this living guideline will be undertaken monthly and recommendations updated when new evidence emerges. Updates will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted for emphasis.

The guideline consists of two layers:

1. THE RECOMMENDATION

Recommendation for (Green)
A strong recommendation is given when there is high-certainty evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

Recommendation against (Red)
A strong recommendation against the intervention is given when there is high-certainty evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

Conditional Recommendation for (Yellow)
A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.

Conditional Recommendation against (Orange)
A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.

Consensus Recommendation (Bluish-Purple)
A consensus recommendation can be given for or against the intervention. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

2. SUPPORTING INFORMATION

Click on the recommendation to learn more about the basis of the recommendation. Additional information will be added as recommendations are updated in light of new evidence.

Evidence profile: The overall effect estimates and references to the studies.
Summary: Overview and brief review of the underlying evidence.
Certainty of the evidence:

- **High:** We are very sure that the true effect is close to the estimated effect.
- **Moderate:** We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.
- **Low:** We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
- **Very low:** We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Evidence to Decision: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient

preferences.
Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.
Practical information: Practical information regarding the treatment and information on any special patient considerations.
Decision Aids: Tools to assist shared decision making and patient participation in health care decisions.
References: Reference list for the recommendation.
Feedback: If you have a MAGICapp account, you can log in to comment on specific recommendations. To create a free account, click on the 'Account' button in the top right hand corner of the screen.

The grading of evidence quality and recommendation strength is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For a quick and informative introduction to GRADE, the article 'Understanding GRADE: an introduction by Goldet & Howick' is recommended (J Evid Based Med 2013;6(1):50-4). See also http://www.gradeworkinggroup.org.

2 - Introduction

Background

Inflammatory arthritis (IA) is characterized by abnormal inflammation in the joints, ligaments and tendons, resulting in pain, stiffness, swelling and loss of function. Uncontrolled inflammation may result in irreversible joint damage. There are many types of IA including rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), crystal arthritis (including gout and pseudogout) and autoimmune connective tissue diseases such as systemic lupus erythematosus (SLE). In most cases, there is no cure for IA, so treatments aim to relieve pain and stiffness, improve ability to move, and prevent damage to the joints.

Disease-modifying anti-rheumatic drugs (DMARDs) are the cornerstone of pharmacologic treatment for IA. DMARDs control the inflammation and thus reduce symptoms and prevent joint damage. They are categorized according to their structure and mechanisms of action:

- Conventional synthetic DMARDs (csDMARDs) e.g. methotrexate, sulfasalazine and hydroxychloroquine - do not target a specific molecular structure
- Targeted synthetic DMARDs (tsDMARDs) e.g. tofacitinib and baricitinib (a newer class of medications) - designed to target a specific molecular structure
- Biologic DMARDs (bDMARDs) are derived biologically - designed to target specific cells or proteins involved in the inflammatory response present in IA. However, as the complex structure of biologically derived proteins cannot be reproduced exactly, bDMARDs are further classified into bio-originator and biosimilar DMARDs, to specify whether they were made by the first or subsequent manufacturers.

Purpose

The objective of this living guideline is to present the best available, current scientific evidence for pharmacological management of the most common forms of IA (namely RA, PsA and axial SpA), including choice of DMARD, switching, combination therapy and down-titration of treatment.

Target population and audience

This living guideline applies to all adults diagnosed with RA, PsA or SpA. It is intended for use by medical practitioners who treat IA. This is primarily rheumatologists; however, the guideline will also be relevant to GPs and others involved in the care of patients with IA and also for pharmacists and consumers. This is reflected in the multidisciplinary composition of the guideline development working group that includes rheumatologists, GPs, consumer representatives, pharmacy and allied health representatives.

About this living guideline

This living guideline is being produced with assistance from the Australian Government's Value in Prescribing (VIP) program grant, managed by the Targeted Therapies Alliance, a consortium coordinated by National Prescribing Service (NPS) MedicineWise. The program grant aims to improve the use of biological disease-modifying anti-rheumatic drugs (bDMARDs), using a variety of interventions and programs. The living guideline and living recommendations component is produced by the Australia and New Zealand Musculoskeletal (ANZMUSC) Clinical Trials Network, Australian Rheumatology Association (ARA), and Cochrane Musculoskeletal, in conjunction with the NPS MedicineWise consortium.

Public Consultation

The consortium is seeking NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC, see the reading guide in the above section for guidance.

How to cite this Guideline

- APA style] ANZMUSC (2020 version 0.3). An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis. https://mskguidelines.org
- [Vancouver style] ANZMUSC. An Australian Living Guideline for the Pharmacological management of Inflammatory Arthritis. 2020 [version 0.3]. Available from: https://mskguidelines.org

3 - Executive Summaries

PICO 1 Executive Summary: bDMARD or tsDMARD down-titration (dose reduction including disease activity-guided dose reduction, or discontinuation) in adults with RA, with low disease activity or remission:

Compared to continuation of treatment at the standard dose, dose reduction of bDMARDs (mainly anti-TNFs, but with some data on B-lymphocyte, T-lymphocyte and interleukin-6 inhibitors) or tsDMARDs in participants with low disease activity for 3-12 months:

- Is comparable in terms of mean disease activity and function;
- Is probably comparable in terms of proportion of participants with persistent remission, proportion with a flare, quality of life and number of serious adverse events;
- May be comparable in terms of proportion who switch to another treatment, disease progression as measured by proportion with minimal radiographic damage, and number of withdrawals due to adverse events.

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence was only available for anti-TNFs for this question) in participants with low disease activity for 3-12 months:

- Is probably slightly inferior to continuation of treatment in terms of mean disease activity;
- May be inferior with respect to the proportion of participants with persistent remission, proportion with a flare disease progression, disease progression as measured by proportion with minimal radiographic damage, function and quality of life.

We are uncertain if the number of serious adverse events and the number of withdrawals due to adverse events differs with discontinuation compared to continuation, as there were too few events to estimate this with certainty. Furthermore, no studies reported on the number of participants who switched treatments.

PICO 2 Executive Summary: bDMARDs and/or tsDMARD down-titration (fixed dose reduction or discontinuation) in adults with psoriatic arthritis, with low disease activity or remission:

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence limited to anti-TNFs) for 3 months in adults with psoriatic arthritis in remission or with low disease activity:

- We are uncertain of the effect of discontinuation on disease activity, the proportion of participant with persistent remission (PASDAS < 3.2) and flare and the number of serious adverse events, due to the very low certainty evidence.
- We did not find any studies that assessed the effect of discontinuation on function, proportion of participants who switched to another biologic, proportion of participants with minimal radiographic progression or number of withdrawals due to adverse events.

PICO 3 Executive Summary: bDMARD or tsDMARD down-titration (dose reduction or discontinuation) in adults with axial spondyloarthritis (including those with ankylosing spondylitis and non-radiographic axial spondyloarthritis), with low disease activity or remission:

Compared to continuation of treatment at the standard dose, dose reduction of bDMARDs (evidence limited to fixed dose reduction of anti-TNFs) in participants with low disease activity for 6 to 22 months:

- Probably results in slightly fewer people with persistent remission
- May slightly increase the number of people with a flare
- Probably has little or no effect on disease activity or function scores
- May have little or no effect on the number of people with partial remission

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence limited to anti-TNFs) in participants with low disease activity for 10-12 months:

- Probably worsens disease activity
- May result in fewer people with persistent and partial remission and more people with a flare
- Probably has little or no effect on function scores

We are uncertain of the effect of dose reduction or discontinuation on serious adverse events and withdrawals due to adverse events, as there were too few events to estimate these outcomes with certainty.

PICO 4 Executive Summary: Opioids for Pain in RA

In people with rheumatoid arthritis treated with weak opioids for up to six weeks:

Compared with placebo, weak opioids:

- may improve pain and may increase the number of people reporting treatment success
- may have little or no effect on function
- may have little or no effect on the number of people reporting adverse events

We are uncertain of the effect of opioid use results on the number of withdrawals due to inadequate analgesia and withdrawals due to adverse events; and the number of serious adverse events as there were too few events to estimate these outcomes with certainty.

We are uncertain of the benefits and harms of opioids compared with NSAIDs, due to very low quality evidence from a single study.

We did not identify any studies comparing opioids to other analgesics or interventions.

PICO 5 Executive Summary: Opioids for Pain in AxSpA

In people with axial spondyloarthritis (AxSpA), we are uncertain whether opioid use results in fewer or more people reporting treatment success; fewer or more people withdrawing due to adverse events or inadequate analgesia; fewer or more people reporting adverse events; and better or worse pain and function, as the certainty of the evidence is very low.

PICO 6 Executive Summary: Opioids for Pain in PsA

In people with psoriatic arthritis (PsA), we are uncertain whether opioid use is safe or effective as no studies addressing the question were identified.

4 - Dose Reduction and Discontinuation Strategies

Successful treatment, in particular combination treatment, often leads to low disease activity and even remission of disease in some people. An optimal dose of DMARDs is often sought in the individual patient, which is the lowest dose that maintains the targeted low disease activity state. This process, referred to as 'down-titration' might reduce dose-dependent side effects (mainly infections) as well as costs and could involve any type of DMARD.

The best strategies for down-titration are not known. Possible strategies include:
1. Down-titration to either lower dose (e.g. 50mg etanercept once weekly reduced to 25mg once weekly) or an increased interval between doses (e.g. 50mg etanercept once a week reduced to 50mg once every two weeks) which is then the new maintenance dose;
2. Stepwise down-titration similar to 1) but with further dose adjustment according to disease activity (disease activity-guided dose reduction); or
3. Simply discontinuing the medication.

We have specifically avoided the use of the terms 'weaning' or 'tapering' as these terms are commonly understood in the context of weaning or tapering off oral glucocorticoids where the ultimate goal is to completely stop the medication. The ultimate goal of down-titration either alone or according to disease activity is to continue the medication but at a lower total dose.

4.1 - Rheumatoid Arthritis: Dose Reduction or Discontinuation of bDMARDs and tsDMARDs

Executive Summary - bDMARD or tsDMARD down-titration (dose reduction including disease activity-guided dose reduction, or discontinuation) in adults with RA, with low disease activity or remission:

Compared to continuation of treatment at the standard dose, dose reduction of bDMARDs (mainly anti-TNFs, but with some data on B-lymphocyte, T-lymphocyte and interleukin-6 inhibitors) or tsDMARDs in participants with low disease activity for 3-12 months:

- Is comparable in terms of mean disease activity and function;
- Is probably comparable in terms of proportion of participants with persistent remission, proportion with a flare, quality of life and number of serious adverse events;
- May be comparable in terms of proportion who switch to another treatment, disease progression as measured by proportion with minimal radiographic damage, and number of withdrawals due to adverse events.

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence was only available for anti-TNFs for this question) in participants with low disease activity for 3-12 months:

- Is probably slightly inferior to continuation of treatment in terms of mean disease activity;
- May be inferior with respect to the proportion of participants with persistent remission, proportion with a flare disease progression, disease progression as measured by proportion with minimal radiographic damage, function and quality of life.

We are uncertain if the number of serious adverse events and the number of withdrawals due to adverse events differs with discontinuation compared to continuation, as there were too few events to estimate this with certainty. Furthermore, no studies reported on the number of participants who switched treatments.

Abbreviations used in this recommendation:

- bDMARDs - biological disease-modifying antirheumatic drugs (DMARDs), including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab), IL-6 inhibitors (tocilizumab), T-cell costimulatory signal inhibitor (abatacept), B-cell inhibitors (rituximab)
- tsDMARDs - targeted synthetic DMARDs, including Janus Kinase inhibitors (eg tofacitinib, baricitinib)
- b/tsDMARDs - either bDMARDs or tsDMARDs
- csDMARDs - conventional synthetic DMARDs (e.g. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine)

Conditional recommendation

In people with RA who have been in sustained low disease activity or remission for at least 6 months, consider stepwise reduction in the dose of b/tsDMARD. Continue dose reduction until cessation is achieved or the lowest effective b/tsDMARD dose is identified, as long as the treatment target is maintained. Abrupt cessation of b/tsDMARDs without prior dose reduction is not recommended.

Evidence up to date as at 8 July 2020

Practical Info

- A treat-to-target approach is recommended for all patients with RA, including during dose reduction.
- While this recommendation is based on data from trials in which patients had been in either LDA or remission for 6-12 months, the panel felt that either a 'deep remission' (eg Boolean remission) or persistent LDA for at least 12 months were more likely to represent optimal preconditions for a trial of dose reduction.
- 'Stepwise dose reduction' includes any method that reduces the b/tsDMARD dose in an incremental manner. This may include a reduction in the regular dose (eg a 50% reduction in etanercept dose from 50mg weekly to 25mg weekly) or an increase in the dosing interval (eg from adalimumab 40mg every two weeks to 40mg every three weeks). Further incremental reductions may be possible depending on the particular medication (eg adalimumab 40mg every four weeks). A combination of dose reduction and an increase in dosing interval could also be considered (eg etanercept 25mg every two weeks).
- Following dose reduction, clinical review should occur at least every 3 months and should include measurement of disease activity using a validated composite disease activity measure (e.g., DAS28, SDAI, CDAI). Maintenance of an agreed treatment target state (either remission or low disease activity) should be ensured before considering further dose reduction.
- Patients should be provided with a plan to follow if there is a symptomatic flare following dose reduction, including a mechanism for patients to contact their prescriber between visits if necessary.
- In the event of loss of disease control (e.g., persistent increase in composite disease activity measure or new symptoms that are unacceptable to the patient), we recommend reintroduction of the previous effective dose of b/tsDMARD.
- During b/tsDMARD dose reduction, concurrent csDMARDs should be continued at a stable dose.
- Reduction or cessation of glucocorticoids is also an important goal and ought to be considered before an attempt at b/tsDMARD dose reduction.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In adults with rheumatoid arthritis and low disease activity, reducing the dose of a bDMARD or tsDMARD probably has little effect on control of disease activity, including mean DAS and the proportion who remain in remission (or a low disease activity state). There may be a small negative effect on radiographic progression and function. Based on clinical trials there appears to be little difference in safety or tolerability but adverse event rates in trials are low and therefore data are limited.

Discontinuing a bDMARD or tsDMARD without prior dose reduction may reduce the proportion of participants with persistent remission, probably slightly worsens disease activity, may increase the proportion of people who experience a flare, may slightly increase the proportion of people with minimal radiographic progression, may lead to a slight deterioration in function and may slightly worsen quality of life. Due to the small number of events reported, we are uncertain whether discontinuation results in fewer serious adverse events or whether adverse events differ between groups.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**
Please find Supplementary Figures and Tables (including Forest Plots) **HERE**

Certainty of the Evidence Low

There are some limitations to the certainty of the evidence for dose reduction. First, most of the data are for TNF inhibitors (particularly adalimumab and etanercept), and therefore may not be directly applicable to other b/tsDMARDs. Second, for some outcomes there may not be sufficient precision in the data to demonstrate that dose reduction is an equivalent strategy to b/tsDMARD continuation. Third, the relatively short follow-up period in trials limits the number of important adverse events detected and may reduce the likelihood of detecting radiographic progression, thereby reducing our confidence in the estimates of these outcomes.

There is less certainty in the evidence regarding abrupt b/tsDMARD cessation. Data on drug abrupt cessation were available for TNF inhibitors only, and therefore may not be applicable to other b/tsDMARDs. Most of the evidence for cessation was considered to be low certainty, although there was moderate certainty for mean disease activity score. We have very low confidence in the evidence regarding adverse events due to low event rates.

Preference and values Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. It is likely that individual patient preferences for reduced exposure to medication versus the risk of flare will vary.

A qualitative study of patients with well-controlled RA *[1]* indicated a general preference for reduction of medication burden, particularly in regard to concerns about the cumulative toxicity of DMARDs, but this was tempered by concern about the impact of a possible disease flare. Tolerance for the risk of flare was mediated by social circumstances, including the impact of a disease flare on employment and burden to family. There was variation between individuals in the assessment of competing risks between disease and treatment, suggesting that an individualised shared decision-making framework is of particular importance in this context.

Resources Important issues, or potential issues not investigated

b/tsDMARDs are generally considered to be expensive therapies and therefore strategies to reduce the total cumulative dose are likely to reduce costs for payers (governments and insurers) and may reduce out-of-pocket costs for patients. In the Australian context, the direct cost impact for individual patients is relatively small but this may differ in other contexts. The importance of direct out-of-pocket cost implications of dose reduction versus continuation is likely to vary between individual patients. There are no publicly-available data regarding the actual comparative costs of different bDMARDs to the payer (i.e. the Federal Government) in Australia.

Most trials that have assessed b/tsDMARD dose reduction have not assessed costs or cost-effectiveness. Compared with anti-TNF continuation, two trials found that anti-TNF activity-guided dose reduction significantly reduced costs and resulted in decremental cost-effectiveness ratios but the estimates were very broad *[3]*.

Equity Important issues, or potential issues not investigated

The panel considered that many factors influence individual patient's health opportunities and outcomes. Such factors (based on the PROGRESS-Plus characteristics) might include poor health literacy; residence in rural, remote or relatively under-serviced locations; primary language other than English; low educational attainment; the presence of disability; or adverse socioeconomic or social circumstances. Some of these may affect b/tsDMARD dose reduction, including an impact

on access to urgent specialist care or advice in the event of a flare in disease activity following DMARD dose adjustment.

Acceptability Important issues, or potential issues not investigated

From a recent survey of ARAD participants (unpublished data):

The medication you have taken is known as a biologic or targeted DMARD: Evidence shows that some people with well-controlled disease can safely reduce the dose of their biologic or targeted DMARD or how frequently they take it, without any worsening of their condition. If your treating specialist suggested it, would you be willing to try taking your biologic or targeted DMARD less frequently, or at a reduced dose?

Responses as follows:
Yes: 216 (53%)
No: 66 (16%)
Maybe: 127 (31%)

Feasibility Important issues, or potential issues not investigated

Implementation of the recommendation may be influenced in some cases by local prescribing rules or reimbursement conditions, and by the accessibility of care in the case of a disease flare. Current Australian prescribing and reimbursement rules for b/tsDMARDs are complex. For example, some reimbursement rules are predicated on stable disease control with full-dose medication. In this situation, some patients or prescribers may be concerned about the risk that, in the event of a disease flare with dose reduction, the resumption of a higher dose of the current b/tsDMARD may be prohibited.

Rationale

The panel considered evidence from trials that included patients treated with b/tsDMARDs who had achieved a state of sustained low-disease activity (LDA) or remission. The majority of participants had experienced stable low disease activity for at least 6 months, although the duration varied from 3 to 12 months in the included trials. The expert panel expressed the view that many patients and clinicians may choose to wait for a longer period before a trial of dose reduction. Importantly, there are currently no reliable clinical or laboratory predictors of which patients are most likely to achieve successful dose reduction or cessation.

Data for dose reduction included different approaches to reducing b/tsDMARDs, including both a single reduction in dose or multiple (stepwise) dose reductions, and either a reduction in the regular dose or an increase in the dosing interval. The panel was satisfied that there was sufficient consistency in the data and applicability to clinical practice to warrant combination of the data in this way. It was noted that the data were primarily in patients using TNF inhibitors (especially adalimumab and etanercept) although results for dose reduction appear to be consistent for b/tsDMARDs with other mechanisms of action. There are currently no data on drug cessation for b/tsDMARDs other than TNF inhibitors.

The panel considered data on dose reduction separately from data on complete cessation of b/tsDMARDs but concluded that a single recommendation that incorporated both reduction and cessation was preferable to two separate overlapping recommendations.

While some trials included only patients in remission, many included patients who were in LDA but not remission. Most included trials used the DAS28 to measure remission and LDA. The panel noted that the ACR/EULAR remission criteria (which incorporate either Boolean or SDAI remission) are more stringent and therefore some participants in DAS28 remission may have been in LDA rather than remission if other measures had been used. The treat-to-target approach to RA management recognises that while remission is the preferred state, the treatment target varies between individual patients, and for some patients LDA is a more appropriate target. Given that the trials included patients with both LDA and remission, and recognising the variation in treatment targets between patients, the panel felt that this recommendation should apply to patients in either LDA or remission,

although it was noted that patients in a 'deep' remission (such as Boolean remission) may be more likely to maintain adequate disease control.

The panel noted that the ability to quickly recapture disease control with resumption of a higher dose is high for b/tsDMARDs, although not universal, and that this may be an important consideration in the shared decision-making process for individuals.

Clinical Question/ PICO

Population: Rheumatoid arthritis patients with low disease activity
Intervention: Dose reduction
Comparator: Continuation

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation	Dose reduction	Certainty of the Evidence (Quality of evidence)	Plain text summary
Proportion persistent remission (DAS28 < 2.6) 24 to 52 weeks 9 Critical	Relative risk 0.9 (CI 95% 0.81 - 1) Based on data from 1,783 patients in 7 studies. [1] (Randomized controlled)	543 per 1000	489 per 1000 Difference: **54 fewer** per 1000 (CI 95% 103 fewer - 0 fewer)	**Moderate** Due to possible indirectness [2]	Dose reduction probably has little or no effect on the proportion with persistent remission
Proportion of participants with a flare 52 weeks 9 Critical	Relative risk 1.23 (CI 95% 0.92 - 1.65) Based on data from 880 patients in 7 studies. [3] (Randomized controlled)	220 per 1000	271 per 1000 Difference: **51 more** per 1000 (CI 95% 18 fewer - 143 more)	**Moderate** Imprecision, due to low event rate [4]	Dose reduction probably has little or no effect on the proportion with a flare
Proportion radiographic progression (mSvdH > 0.5) 52 weeks 9 Critical	Relative risk 1.31 (CI 95% 0.96 - 1.81) Based on data from 865 patients in 4 studies. [5] (Randomized controlled)	152 per 1000	199 per 1000 Difference: **47 more** per 1000 (CI 95% 6 fewer - 123 more)	**Low** Due to possible indirectness, and serious imprecision due to low number of events [6]	Dose reduction may result in little or no effect on the proportion with disease progression, as measured by minimal radiographic progression
Proportion switched to another biologic 52 weeks to 3.5 years 6 Important	Relative risk 0.49 (CI 95% 0.27 - 0.91) Based on data from 640 patients in 3 studies. [7] (Randomized controlled)	95 per 1000	47 per 1000 Difference: **48 fewer** per 1000 (CI 95% 69 fewer - 9 fewer)	**Low** Possible indirectness, and serious imprecision due to low event rate [8]	Dose reduction may slightly reduce the proportion who switched to another biologic

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation	Dose reduction	Certainty of the Evidence (Quality of evidence)	Plain text summary
Number of serious adverse events 52 weeks to 3.5 years 9 Critical	Relative risk 0.97 (CI 95% 0.74 - 1.27) Based on data from 2,435 patients in 12 studies. [9] (Randomized controlled)	**79** per 1000	**77** per 1000 Difference: **2 fewer** per 1000 (CI 95% 21 fewer - 21 more)	**Moderate** Due to serious imprecision [10]	Dose reduction probably has little or no effect on the number of serious adverse events
Withdrawals due to adverse events 52 weeks to 3.5 years 9 Critical	Relative risk 1.13 (CI 95% 0.65 - 1.98) Based on data from 1,917 patients in 7 studies. [11] (Randomized controlled)	**24** per 1000	**27** per 1000 Difference: **3 more** per 1000 (CI 95% 8 fewer - 24 more)	**Low** Very serious imprecision due to few events (28 and 23 events per group) [12]	Dose reduction may have little or no effect on the number of withdrawals due to adverse events
Mean disease activity score (DAS28) 26 to 52 weeks 9 Critical	Measured by: DAS28 Scale: 0.9-8 Lower better Based on data from: 1,888 patients in 10 studies. [13]	**2.3** (Mean)	**2.4** (Mean) Difference: **MD 0.13 higher** (CI 95% 0 higher - 0.26 higher)	**High** [14]	Dose reduction has little or no effect on mean disease activity score
Function (Health Assessment Questionnaire) 26 to 52 weeks 9 Critical	Measured by: Health Assessment Questionnaire Scale: 0-3 Lower better Based on data from: 1,666 patients in 8 studies. [15] (Randomized controlled)	**0.52** (Mean)	**0.57** (Mean) Difference: **MD 0.05 higher** (CI 95% 0.01 higher - 0.09 higher)	**High** [16]	Dose reduction results in slight deterioration of function
Quality of life 24 to 52 weeks 6 Important	Measured by: EQ5D 2 trials, SF-12 MCS 1 trial Based on data from: 632 patients in 3 studies. [17] (Randomized controlled)	**41.6** (Mean)	**40.9** (Mean) Difference: **MD 0.07 lower** (CI 95% 4.06 lower - 2.66 higher)	**Moderate** Due to possible imprecision [18]	Dose reduction probably has little or no effect on quality of life

1. Systematic review [4] with included studies: Westhovens 2015, Sanmarti 2019 (TOZURA), Smolen 2013 (PRESERVE), Takeuchi 2019, van Herwaarden 2015 (DRESS), Weinblatt 2017 (C-EARLY), Takeuchi 2019, Mariette 2014 (SMART). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: Serious.** Definition of remission: 6 trials - DAS28 < 2.6; 1 trial CDAI 2.8 or less, follow-up from 24-52 weeks. DMARDS: TNF inhibitors in 4 trials, single trials of baricitinib, ritixumab, abatacept . **Imprecision: No serious. Publication bias: No serious.**
3. Systematic review [4] with included studies: Fautrel 2016 (STRASS), Weinblatt 2017 (C-EARLY), Bejerano 2016

(OPTIBIO), van Herwaarden 2015 (DRESS), Westhovens 2015, Ibrahim 2017 (OPTTIRA), Ibrahim 2017 (OPTTIRA), van Vollenhoven 2016 (DOSERA). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious.** One trial included abatacept; TNFi in all other trials. **Imprecision: Serious.** Small event rate. **Publication bias: No serious.**
5. Systematic review [4] with included studies: Fautrel 2016 (STRASS), Weinblatt 2017 (C-EARLY), Smolen 2013 (PRESERVE), van Herwaarden 2015 (DRESS). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNF inhibitors. **Imprecision: Serious.** Low number of events. **Publication bias: No serious.**
7. Systematic review [4] with included studies: Raffeiner 2015, van Herwaarden 2015 (DRESS), Fautrel 2016 (STRASS). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNF inhibitors. **Imprecision: Serious.** Low number of events. **Publication bias: No serious.**
9. Systematic review [4] with included studies: van Herwaarden 2015 (DRESS), van Vollenhoven 2016 (DOSERA), Mariette 2014 (SMART), Fautrel 2016 (STRASS), Ibrahim 2017 (OPTTIRA), l'Ami 2018, Smolen 2013 (PRESERVE), Takeuchi 2019, Sanmarti 2019 (TOZURA), Raffeiner 2015, Weinblatt 2017 (C-EARLY), Westhovens 2015. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: No serious. Indirectness: No serious.** Nine studies assessed TNFi, one each assessed rituximab, baracitinib, abatacept. **Imprecision: Serious.** Low number of events. **Publication bias: No serious.**
11. Systematic review [4] with included studies: Mariette 2014 (SMART), Weinblatt 2017 (C-EARLY), Sanmarti 2019 (TOZURA), Takeuchi 2019, Raffeiner 2015, Westhovens 2015, Smolen 2013 (PRESERVE). **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: No serious. Indirectness: No serious.** Four studies assessed TNFi, one each assessed rituximab, baracitinib, abatacept. **Imprecision: Very Serious.** Low number of events. **Publication bias: No serious.**
13. Systematic review [4] with included studies: Westhovens 2015, Takeuchi 2019, Takeuchi 2019, Ibrahim 2017 (OPTTIRA), Bejerano 2016 (OPTIBIO), Fautrel 2016 (STRASS), l'Ami 2018, van Herwaarden 2015 (DRESS), Sanmarti 2019 (TOZURA), Mariette 2014 (SMART), Smolen 2013 (PRESERVE). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: No serious. Indirectness: No serious.** Seven studies assessed TNFi, one each assessed rituximab, baracitinib, abatacept. **Imprecision: No serious. Publication bias: No serious.**
15. Systematic review [4] with included studies: Takeuchi 2019, Fautrel 2016 (STRASS), Westhovens 2015, Mariette 2014 (SMART), Takeuchi 2019, l'Ami 2018, Sanmarti 2019 (TOZURA), Smolen 2013 (PRESERVE), Ibrahim 2017 (OPTTIRA). **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: No serious.** Six trials assessed TNF inhibitors, one each assessed baracitinib and abatacept. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
17. Systematic review [4] with included studies: Ibrahim 2017 (OPTTIRA), Smolen 2013 (PRESERVE), Mariette 2014 (SMART). **Baseline/comparator:** Primary study.
18. **Inconsistency: No serious. Indirectness: No serious.** Two trials assessed TNF inhibitors and one assessed rituximab - is result applicable to other DMARDs?. **Imprecision: Serious.** Three trials, query if sufficient participants. **Publication bias: No serious.**

References

4. Down-titration and discontinuation strategies of tumour necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity. 2019;

Clinical Question/ PICO

Population: Rheumatoid arthritis patients with low disease activity
Intervention: Discontinuation
Comparator: Continuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation	Discontinuation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion persistent remission (DAS28) 28 to 52 weeks 9 Critical	Relative risk 0.56 (CI 95% 0.41 - 0.75) Based on data from 1,188 patients in 6 studies. [1] (Randomized controlled)	619 per 1000	347 per 1000 Difference: 272 fewer per 1000 (CI 95% 365 fewer - 155 fewer)	**Low** Due to serious inconsistency and potential indirectness [2]	Discontinuation may reduce the proportion of participants with persistent remission
Proportion of participants with a flare 24 to 52 weeks 9 Critical	Relative risk 2.04 (CI 95% 1.77 - 2.34) Based on data from 1,388 patients in 5 studies. (Randomized controlled)	236 per 1000	481 per 1000 Difference: 245 more per 1000 (CI 95% 182 more - 316 more)	**Low** Due to serious inconsistency and limited to TNF inhibitors [3]	Discontinuation may increase the proportion of participants with a flare
Proportion radiographic progression (mSvdH > 0.5) 52 weeks 9 Critical	Relative risk 1.69 (CI 95% 1.1 - 2.59) Based on data from 549 patients in 3 studies. [4] (Randomized controlled)	105 per 1000	177 per 1000 Difference: 72 more per 1000 (CI 95% 11 more - 167 more)	**Low** Due to serious imprecision and possible indirectness [5]	Discontinuation may slightly increase the proportion of participants with disease progression, as measured by minimal radiographic progression
Proportion switched to another biologic 6 Important				No studies reported this outcome	No studies were found that reported proportion switching to another biologic
Number of serious adverse events 28 to 52 weeks 9 Critical	Relative risk 1.29 (CI 95% 0.82 - 2.03) Based on data from 2,095 patients in 8 studies. [6] (Randomized controlled)	57 per 1000	74 per 1000 Difference: 17 more per 1000 (CI 95% 10 fewer - 59 more)	**Very Low** Due to possible indirectness, and very serious imprecision due to low event rates [7]	We are uncertain whether discontinuation results in fewer serious adverse events, due to the small number of events reported

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation Discontinuation	Certainty of the Evidence (Quality of evidence)	Plain text summary
Withdrawals due to adverse events 28 to 52 weeks 9 Critical	Relative risk 1.46 (CI 95% 0.75 - 2.84) Based on data from 1,116 patients in 4 studies. [8] (Randomized controlled)	27 per 1000 39 per 1000 Difference: 12 more per 1000 (CI 95% 7 fewer - 50 more)	**Very Low** Due to possible indirectness and very serious imprecision due to low event rates [9]	We are uncertain whether withdrawal due to adverse events differs between groups, due to the small number of events reported
Mean disease activity score (DAS28) 28 to 52 weeks 9 Critical	Measured by: DAS Scale: 0.9-8 Lower better Based on data from: 733 patients in 2 studies. [10] (Randomized controlled)	2.82 (Mean) 3.78 (Mean) Difference: MD 0.96 higher (CI 95% 0.67 higher - 1.25 higher)	**Moderate** Due to serious indirectness [11]	Discontinuation probably slightly worsens disease activity
Function (Health Assessment Questionnaire) 28 to 52 weeks 9 Critical	Measured by: Health Assessment Questionnaire Scale: 0-3 Lower better Based on data from: 1,498 patients in 4 studies. [12] (Randomized controlled)	0.52 (Mean) 0.7 (Mean) Difference: MD 0.18 higher (CI 95% 0.05 higher - 0.31 higher)	**Low** Due to possible indirectness and serious inconsistency [13]	Discontinuation may lead to a slight deterioration in function
Quality of life 28 to 52 weeks 6 Important	Measured by: EQ5D Scale: 0-1 High better Based on data from: 733 patients in 2 studies. [14] (Randomized controlled)	0.6 (Mean) 0.5 (Mean) Difference: MD 0.1 lower (CI 95% 0.13 lower - 0.07 lower)	**Low** Due to possible indirectness and imprecision [15]	Discontinuation may worsen quality of life slightly

1. Systematic review [4] with included studies: Yamanaka 2016 (ENCOURAGE), Smolen 2013 (PRESERVE), Chatzidionysiou 2016 (ADMIRE), Smolen 2014 (OPTIMA), Weinblatt 2017 (C-EARLY), Pavelka 2017. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 80%. **Indirectness: Serious.** Evidence limited to TNF-inhibitors. **Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 79%. **Indirectness: Serious.** Outcome defined as DAS28 ≥ 3.2 in 3 trials, DAS28 ≥ 2.6 in 1 trial, participant or physician reported in 1 trial. Evidence limited to TNF inhibitors. **Imprecision: No serious. Publication bias: No serious.**
4. Systematic review [4] with included studies: Smolen 2013 (PRESERVE), Weinblatt 2017 (C-EARLY), Yamanaka 2016 (ENCOURAGE). **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNF inhibitors; unclear how these small changes in radiographic progression affect disease activity. **Imprecision: Serious.** Low event rates. **Publication bias: No serious.**
6. Systematic review [4] with included studies: Chatzidionysiou 2016 (ADMIRE), Ghiti Moghadam 2016 (POEET), Pavelka 2017, Smolen 2013 (PRESERVE), Yamanaka 2016 (ENCOURAGE), Weinblatt 2017 (C-EARLY), Smolen 2014 (OPTIMA), van Vollenhoven 2016 (DOSERA). **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: No serious. Indirectness: Serious.** Evidence restricted to TNF inhibitors. **Imprecision: Very Serious.** Low

event rates.
8. Systematic review [4] with included studies: Weinblatt 2017 (C-EARLY), Smolen 2013 (PRESERVE), Smolen 2014 (OPTIMA), Pavelka 2017. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Inconsistency: No serious. Indirectness: Serious.** Evidence only available for TNF inhibitors. **Imprecision: Very Serious.** Very few events were reported. **Publication bias: No serious.**
10. Systematic review [4] with included studies: Smolen 2013 (PRESERVE), Pavelka 2017. **Baseline/comparator:** Systematic review.
11. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNF inhibitors; and data from a third trial was precluded as participants could restart a full dose after flare which would likely impact disease activity measures, Differences between the intervention/comparator of interest and those studied. **Imprecision: No serious. Publication bias: No serious.**
12. Systematic review [4] with included studies: Pavelka 2017, Smolen 2013 (PRESERVE), Ghiti Moghadam 2016 (POEET), Smolen 2014 (OPTIMA). **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 79%.. **Indirectness: Serious.** Evidence limited to TNF inhibitors. **Imprecision: No serious. Publication bias: No serious.**
14. Systematic review [4] with included studies: Pavelka 2017, Smolen 2013 (PRESERVE). **Baseline/comparator:** Control arm of reference used for intervention.
15. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNF inhibitors, due to [reason], Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Reported in only two studies. **Publication bias: No serious.**

4.2 - Axial Spondyloarthritis: Dose Reduction or Discontinuation of bDMARDs

Axial spondyloarthritis (axSpA) is an umbrella term for different types of inflammatory arthritis that affect the spine and other joints. There are two subtypes:

- Ankylosing spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-axSpA)

Most commonly, axSpA affects the spine and the sacroiliac (SI) joints that connect the lower spine to the pelvis, resulting in pain in the lower back, hips, and buttocks. Inflammation in axSpA primarily occurs at sites where ligaments or tendons attach to bones, so many sites other than the spine can also be affected including the heels, chest wall and joints of the upper and lower limbs. In some cases inflammation can occur in other organs, most commonly the eyes, skin and the gut.

Prolonged inflammation in the SI joints, spine or other joints may result in permanent changes to the structure of the ligaments and joints in these sites, and may progress to complete fusion (ankylosis) of joints or the spine. The term ankylosing spondylitis (AS) is used to describe the subset of patients with axSpA in whom these x-ray (radiographic) changes are visible. The term non-radiographic axial spondyloarthritis (nr-axSpA) is used when patients display the clinical features of axSpA but do not have definite x-ray changes, although in many cases inflammatory changes in the bones or joints are seen on other forms of imaging such as MRI scans. In many but not all cases, nr-axSpA may eventually progress to AS. Unless otherwise indicated, the term axSpA, which encompasses both nr-axSpA and AS, is used here because the symptoms, the impact on function, and treatment of axSpA are generally the same regardless of the presence of x-ray changes. Physical therapy is the primary non-pharmacological management strategy in axSpA. NSAIDs remain the first-line medication.

Executive Summary - bDMARD or tsDMARD down-titration (dose reduction or discontinuation) in adults with axial spondyloarthritis (including those with ankylosing spondylitis and non-radiographic axial spondyloarthritis), with low disease activity or remission:

Compared to continuation of treatment at the standard dose, dose reduction of bDMARDs (evidence limited to fixed dose reduction of anti-TNFs) in participants with low disease activity for 6 to 22 months:

- Probably results in slightly fewer people with persistent remission

- May slightly increase the number of people with a flare
- Probably has little or no effect on disease activity or function scores
- May have little or no effect on the number of people with partial remission

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence limited to anti-TNFs) in participants with low disease activity for 10-12 months:

- Probably worsens disease activity
- May result in fewer people with persistent and partial remission and more people with a flare
- Probably has little or no effect on function scores

We are uncertain of the effect of dose reduction or discontinuation on serious adverse events and withdrawals due to adverse events, as there were too few events to estimate these outcomes with certainty.

Abbreviations used in this recommendation:

- bDMARDs - biological disease-modifying antirheumatic drugs (DMARDs), including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab), IL-17 inhibitors (secukinumab, ixekizumab)
- tsDMARDs - targeted synthetic DMARDs, including Janus Kinase inhibitors (eg tofacitinib, baricitinib)
- b/tsDMARDs - either bDMARDs or tsDMARDs
- csDMARDs - conventional synthetic DMARDs (e.g. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine)

Conditional recommendation

In people with axial spondyloarthritis who have been in sustained low disease activity or remission for at least 6 months, consider reduction in the dose of bDMARD. Continue at the lower dose as long as the treatment target is maintained. Abrupt cessation of bDMARDs is not recommended.

Evidence up to date as at 23 July 2020

Practical Info

- A treat-to-target approach within a shared decision-making framework is recommended for all patients with axial spondyloarthritis, including during dose reduction.
- Although we have included a conditional recommendation against complete discontinuation of bDMARDs due to the substantially higher proportion of disease flares in patients who discontinue bDMARDs compared with those who continue at a full or reduced dose, there is a small proportion of patients with axial spondyloarthritis who are able to achieve disease-free remission (i.e., complete withdrawal from bDMARDs after achieving a clinical remission). Therefore, a discussion of the potential benefits and risks of bDMARD discontinuation after dose reduction may form part of the shared decision-making process.
- TNFi dose reduction may include a decrease in the regular dose (e.g., a 50% reduction in etanercept dose from 50mg weekly to 25mg weekly) or an increase in the dosing interval (e.g., from adalimumab 40mg every two weeks to 40mg every three weeks).
- Following dose reduction, clinical review should occur at least every 3 months and should include measurement of disease activity using a validated composite disease activity measure that includes patient-reported outcomes (e.g., BASDAI, ASDAS) and escalation to the full dose should be considered if the treatment target has not been maintained.
- The presence of extraspinal features of axial spondyloarthritis (e.g., enthesitis) and extraskeletal manifestations (including psoriasis, uveitis and inflammatory bowel disease) during the disease course should be considered when contemplating dose reduction and clinical review after dose reduction should include surveillance for the emergence of these clinical features.
- Patients should be provided with a plan to follow if there is a symptomatic flare following dose reduction, including a mechanism for patients to contact their prescriber between visits if necessary.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In adults with axial spondyloarthritis and sustained low disease activity, reducing the dose of bDMARD probably results in fewer patients with persistent remission and may slightly increase the proportion of patients with a disease flare, but probably has little or no effect on disease activity as measured by BASDAI and may have little or no effect on the number of patients in ASAS partial remission. Dose reduction probably has little or no effect on function.

Abrupt cessation of bDMARD may result in fewer people with persistent remission or ASAS partial remission, probably worsens disease activity, may increase the number of people who experience a flare, and probably worsens function.

The effect of either dose reduction or discontinuation on the safety or tolerability of bDMARDs is difficult to estimate due to low rates of adverse events in the included clinical trials.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**
Please find Supplementary Figures and Tables (including Forest Plots) **HERE**

Certainty of the Evidence

Low

There are some limitations to our confidence in the evidence. There was moderate certainty for most of the evidence for the effect of dose reduction on disease activity, although certainty in the evidence was low for the number of patients with a disease flare and the proportion with ASAS partial remission. Confidence in the evidence for the effect of bDMARD discontinuation was moderate for disease activity (measured by BASDAI) and function, but was otherwise low. We have very low confidence in the evidence regarding adverse events following either dose reduction or discontinuation due to low event rates.

Importantly, all of the data are from trials of TNF inhibitors and therefore may not be applicable to other b/tsDMARDs. We combined data from trials that included patients with either ankylosing spondylitis, non-radiographic axial spondyloarthritis or both, on the assumption that these represent aspects of the same disease spectrum, although we recognise that not all patients with non-radiographic axial spondyloarthritis will progress to radiographic disease (i.e., ankylosing spondylitis).

There were some differences between the trials in the definition of low disease activity or remission, the amount of time participants were in a low disease activity state before dose reduction, and the method used for dose reduction (such as increased dosing interval versus a lower dose of drug at the same interval). There are no data regarding the effect of further dose adjustments based on the response to an initial dose reduction (i.e., 'stepwise' dose reduction). All patients in the trials of bDMARD discontinuation stopped the drug without a prior dose taper.

Preference and values

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. It is likely that individual patient preferences for reduced exposure to medication versus the risk of flare will vary.

There are no data on the effect of dose reduction on important non-musculoskeletal features of spondyloarthritis (including inflammatory disorders of the eye, intestinal tract and skin). The presence of these clinical features may also influence individual patients' preferences regarding DMARD dose reduction.

A qualitative study *[6]* of British patients with inflammatory arthritis - including ankylosing spondylitis - found that patients who were using bDMARDs were interested in reducing their dose when the disease was under control in the hope that this would reduce inconvenience and potential toxicity while maintaining disease control, and reduce overall cost to society. However this was balanced by concerns that dose reduction might result in a disease flare and that resumption of the full

dose, if required, might be limited due to the high cost of bDMARDs or might not achieve the previous level of disease control. Shared decision-making, including control over flexible dosing, was identified as an important theme.

Resources

Important issues, or potential issues not investigated

Most trials that have assessed bDMARD dose reduction have not assessed costs or cost-effectiveness. bDMARDs are generally considered to be expensive therapies and therefore strategies to reduce the total cumulative dose are likely to reduce costs for payers (governments and insurers) and may reduce out-of-pocket costs for patients. In the Australian context, the direct cost impact for individual patients is relatively small but this may differ in other contexts. The importance of direct out-of-pocket cost implications of dose reduction versus continuation is likely to vary between individual patients. There are no publicly-available data regarding the actual comparative costs of different bDMARDs to the payer (i.e., the Federal Government) in Australia.

Equity

Important issues, or potential issues not investigated

The panel considered that many factors influence individual patients' health opportunities and outcomes. Such factors (based on the PROGRESS-Plus characteristics) might include poor health literacy; residence in rural, remote or relatively under-serviced locations; primary language other than English; low educational attainment; the presence of disability; or adverse socioeconomic or social circumstances. Some of these may affect bDMARD dose reduction, including an impact on access to urgent specialist care or advice in the event of a flare in disease activity following DMARD dose adjustment.

Acceptability

Important issues, or potential issues not investigated

Evidence for acceptability of the intervention to consumers comes from a recent survey of ARAD participants (unpublished data):

The medication you have taken is known as a biologic or targeted DMARD: Evidence shows that some people with well-controlled disease can safely reduce the dose of their biologic or targeted DMARD or how frequently they take it, without any worsening of their condition. If your treating specialist suggested it, would you be willing to try taking your biologic or targeted DMARD less frequently, or at a reduced dose?

Responses as follows:
Yes: 95 (50%)
No: 45 (23%)
Maybe: 51 (27%)

There is little evidence regarding the acceptability of bDMARD dose reduction or discontinuation to clinicians, policymakers or other stakeholders, although the panel felt that consideration of reduction of medication burden in a shared decision-making framework would likely be acceptable to all stakeholders.

Feasibility

Important issues, or potential issues not investigated

Implementation of the recommendation may be influenced in some cases by local prescribing rules or reimbursement conditions, and by the accessibility of care in the case of a disease flare. Current Australian prescribing and reimbursement rules for bDMARDs are complex. For example, some reimbursement rules are predicated on stable disease control with full-dose medication. In this situation, some patients or prescribers may be concerned about the risk that, in the event of a

disease flare with dose reduction, the resumption of a higher dose of the current bDMARD may be prohibited.

Rationale

The panel considered data on dose reduction separately from data on complete discontinuation of bDMARDs but concluded that a single recommendation that incorporated both reduction and discontinuation was preferable to two separate overlapping recommendations. Data for dose reduction included different approaches to reducing bDMARDs, including a reduction in the regular dose or an increase in the dosing interval. There were no trials that tested the effect of further dose adjustments based on the response to an initial dose reduction (i.e., 'stepwise' dose reduction) or dose reduction prior to discontinuation.

The panel acknowledged that the evidence regarding adverse drug effects following dose reduction or cessation was of very low certainty. Furthermore, the long-term effects of bDMARD dose reduction on either the disease (including structural damage) or the risk of adverse drug effects remain unknown. Ideally, all patients using a b/tsDMARD should be offered the opportunity to participate in a registry in order to provide long-term data.

The panel felt that the potential for a flare in disease activity following a reduction in bDMARD dose might be balanced by the potential benefits of a lower burden of immunosuppressant medication, but that the decision to reduce the dose would be influenced by individual circumstances, preferences and values, and that a continuous, open and informed shared decision-making process should underpin any such decision. The data regarding bDMARD discontinuation suggested a higher likelihood of loss of disease control and the panel believed that the balance of benefits and harms would be unlikely to favour discontinuation for most patients, however it was noted that some trial participants were able to achieve a drug-free remission.

The panel noted that the ability to quickly recapture disease control with resumption of the normal dose of TNFi is high but not universal, and that this may be an important consideration in the shared decision-making process for individuals.

Another consideration in shared decision-making for the individual patient with axial spondyloarthritis may be the presence of extraskeletal manifestations such as psoriasis, uveitis and inflammatory bowel disease. The balance of risks and benefits may be different in patients for whom bDMARDs have also been an effective therapy for these disease manifestations.

All of the data considered by the panel were from patients treated with TNF inhibitors (TNFi). While drugs with other mechanisms of action (such as IL-17 inhibitors) are now used for the treatment of axial spondyloarthritis, it is not clear to what extent the estimated effects of dose reduction or cessation apply to people who have achieved low disease activity following treatment with IL-17 inhibitors or b/tsDMARDS with other mechanisms of action.

The panel considered evidence from trials that included patients treated with bDMARDs who had achieved a state of sustained low-disease activity, inactive disease or remission. Different definitions of this disease state were used but all used composite measures that included patient-reported pain and inflammatory symptoms and in most cases included blood markers of inflammation. All were considered to be appropriate targets within a treat-to-target framework. All participants had received bDMARDs in full dose for at least six months, although the duration varied between trials. The expert panel expressed the view that many patients and clinicians may choose to wait for longer than six months before a trial of dose reduction. While there are currently no reliable clinical or laboratory predictors of which patients are most likely to achieve successful dose reduction or cessation, the panel considered that a prolonged period of inactive disease may represent the optimum circumstances under which to develop a plan for dose reduction.

Clinical Question/ PICO

Population: Axial spondyloarthritis patients with low disease activity
Intervention: Dose reduction
Comparator: Continuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation — Dose reduction	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion persistent remission (ASDAS <1.3 or as defined by study) [1] 6 to 22 months 9 Critical	Relative risk 0.84 (CI 95% 0.74 - 0.96) Based on data from 380 patients in 4 studies. [2] (Randomized controlled)	786 per 1000 — 660 per 1000 Difference: **126 fewer** per 1000 (CI 95% 204 fewer - 31 fewer)	**Moderate** Due to possible indirectness [3]	Dose reduction probably results in fewer people with persistent remission.
Proportion ASAS partial remission (<2 units for each of the four domains identified for ASAS20/40) 10 to 12 months 9 Critical	Relative risk 0.47 (CI 95% 0.08 - 2.92) Based on data from 256 patients in 2 studies. [4] (Randomized controlled)	688 per 1000 — 585 per 1000 Difference: **103 fewer** per 1000 (CI 95% 193 fewer - 0 fewer)	**Low** Due to possible indirectness and imprecision [5]	Dose reduction may have little or no effect on the number of people with ASAS partial remission.
Proportion of participants with a flare [6] 12 to 22 months 9 Critical	Relative risk 1.89 (CI 95% 1 - 3.59) Based on data from 372 patients in 3 studies. [7] (Randomized controlled)	70 per 1000 — 132 per 1000 Difference: **62 more** per 1000 (CI 95% 0 fewer - 181 more)	**Low** Due to possible indirectness and imprecision [8]	Dose reduction may slightly increase the number with a flare
Number of serious adverse events 6 to 22 months 9 Critical	Relative risk 0.48 (CI 95% 0.03 - 7.51) Based on data from 412 patients in 4 studies. [9] (Randomized controlled)	77 per 1000 — 37 per 1000 Difference: **40 fewer** per 1000 (CI 95% 75 fewer - 501 more)	**Very Low** Due to indirectness and very serious imprecision [10]	We are very uncertain whether dose reduction results in fewer serious adverse events, due to the small number of events reported
Withdrawals due to adverse events 6 to 22 months 9 Critical	Relative risk 2.3 (CI 95% 1 - 5.29) Based on data from 332 patients in 2 studies. [11] (Randomized controlled)	42 per 1000 — 97 per 1000 Difference: **55 more** per 1000 (CI 95% 0 fewer - 180 more)	**Very Low** Due to indirectness and very serious imprecision [12]	We are very uncertain whether dose reduction results in fewer withdrawals due to adverse events, due to the small number of events reported

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation	Dose reduction	Certainty of the Evidence (Quality of evidence)	Plain text summary
Disease activity score (BASDAI) [13] 6 to 22 months 9 Critical	Measured by: BASDAI Scale: 0-10 Lower better Based on data from: 404 patients in 4 studies. (Randomized controlled)	1 (Mean)	1.15 (Mean) Difference: MD 0.15 higher (CI 95% 0.15 lower - 0.44 higher)	Moderate Due to possible indirectness [14]	Dose reduction probably has little or no effect on disease activity
Function (BASFI) [15] 6 to 22 months 9 Critical	Measured by: BASFI Scale: 0-10 Lower better Based on data from: 412 patients in 4 studies. [16] (Randomized controlled)	0.7 (Mean)	1.07 (Mean) Difference: MD 0.37 higher (CI 95% 0.17 lower - 0.9 higher)	Moderate Due to possible indirectness [17]	Dose reduction probably has little or no effect on function

1. Defined variably as.....
2. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Cantini 2013 AS ETN, Gratacos 2019 aSpA TNFi, Yates 2015 AS ETN. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of bias: No serious.** Three of the four studies may be subject to detection bias but the larger study was well designed and all studies showed a similar effect. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: No serious.** Possibly slightly low event rate, but as all studies show similar effects with narrow CI's we didn't downgrade . **Publication bias: No serious.**
4. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Yates 2015 AS ETN. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious.** I2 is 72% but based on two studies both of which showed a similar direction. **Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Serious.** Low number of patients and wide confidence intervals. **Publication bias: No serious.**
6. Defined variably as not remission, ASDAS CRP 1.1 or more, ASDAS 2.1 or more for two consecutive visits or 3.5 or more at any time
7. Systematic review [5] with included studies: Gratacos 2019 aSpA TNFi, Landewe 2020 aSpA CZP, Cantini 2013 AS ETN. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Serious.** Low number of patients and wide confidence intervals. **Publication bias: No serious.**
9. Systematic review [5] with included studies: Cantini 2013 AS ETN, Landewe 2020 aSpA CZP, Yates 2015 AS ETN, Gratacos 2019 aSpA TNFi. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: No serious.** I2 was high but only two studies contributed data. **Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Low number of patients and two studies reported zero events. **Publication bias: No serious.**
11. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Yates 2015 AS ETN, Gratacos 2019 aSpA TNFi, Cantini 2013 AS ETN. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Low number of patients. **Publication bias: No serious.**
13. MCID 1.0
14. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: No serious. Publication bias: No serious.**
15. MCID 0.7
16. Systematic review [5] with included studies: Gratacos 2019 aSpA TNFi, Cantini 2013 AS ETN, Yates 2015 AS ETN, Landewe 2020 aSpA CZP. **Baseline/comparator:** Control arm of reference used for intervention.

17. **Inconsistency: No serious.** One study (Yates) reported a decrease in function with dose reduction but possibly due to a worse function score at baseline. **Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

Population: Axial spondyloarthritis patients with low disease activity
Intervention: Discontinuation
Comparator: Continuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation	Discontinuation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion persistent remission (ASDAS<1.3) 40 to 48 weeks	Relative risk 0.61 (CI 95% 0.5 - 0.76) Based on data from 416 patients in 2 studies. [1] (Randomized controlled)	678 per 1000	414 per 1000 Difference: **264 fewer** per 1000 (CI 95% 339 fewer - 163 fewer)	**Low** Due to possible indirectness and imprecision [2]	Discontinuation may result in fewer people with persistent remission
Proportion ASAS partial remission (<2 units for each of the four domains identified for ASAS20/40) 40 to 48 weeks	Relative risk 0.38 (CI 95% 0.13 - 1.08) Based on data from 513 patients in 2 studies. [3] (Randomized controlled)	566 per 1000	215 per 1000 Difference: **351 fewer** per 1000 (CI 95% 492 fewer - 45 more)	**Low** Due to possible indirectness and imprecision [4]	Discontinuation may result in fewer people with ASAS partial remission. The 95% CI includes little or no effect but we suspect the true effect favours continuation of treatment
Proportion of participants with a flare 40 to 48 weeks	Relative risk 4.3 (CI 95% 0.71 - 26.04) Based on data from 513 patients in 2 studies. [5] (Randomized controlled)	168 per 1000	722 per 1000 Difference: **554 more** per 1000 (CI 95% 10 fewer - 850 more)	**Low** Due to possible indirectness and imprecision [6]	Discontinuation may result in more flares. The 95% CI includes little or no effect but we suspect the true effect favours continuation of treatment
Number of serious adverse events 40 to 48 weeks	Relative risk 1.06 (CI 95% 0.01 - 108.42) Based on data from 513 patients in 2 studies. [7] (Randomized controlled)	23 per 1000	24 per 1000 Difference: **1 more** per 1000 (CI 95% 23 fewer - 2,471 more)	**Very Low** Due to indirectness and very serious imprecision [8]	We are very uncertain whether discontinuation results in fewer serious adverse events, due to the small number of events reported

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation	Discontinuation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Withdrawals due to adverse events 40 to 48 weeks	Relative risk 1.84 (CI 95% 0.07 - 47.51) Based on data from 513 patients in 2 studies. [9] (Randomized controlled)	4 per 1000	7 per 1000 Difference: 3 more per 1000 (CI 95% 4 fewer - 186 more)	**Very Low** Due to possible indirectness and serious imprecision [10]	We are very uncertain whether discontinuation results in fewer withdrawals due to adverse events, due to the small number of events reported
Disease activity score (BASDAI) 40 to 48 weeks	Measured by: BASDAI Scale: 0-10 Lower better Based on data from: 208 patients in 1 studies. [11] (Randomized controlled)	1 (Mean)	3.4 (Mean) Difference: MD 2.4 higher (CI 95% 1.85 higher - 2.95 higher)	**Moderate** Due to possible indirectness [12]	Discontinuation probably worsens disease activity
Function (BASFI) 40 to 48 weeks	Measured by: BASFI Scale: 0-10 Lower better Based on data from: 513 patients in 2 studies. [13] (Randomized controlled)	0.7 (Mean)	1.71 (Mean) Difference: MD 1.01 higher (CI 95% 0.11 lower - 2.12 higher)	**Moderate** Due to possible indirectness [14]	Discontinuation probably worsens function. The 95% CI includes little or no effect but we suspect the true effect favours continuation of treatment

1. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Landewe 2018 nraSpA ADA. **Baseline/ comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi . **Imprecision: Serious.** Low number of events. **Publication bias: No serious.**
3. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Landewe 2018 nraSpA ADA. **Baseline/ comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious.** Substantial heterogeneity might be explained by the different participants investigated in the two studies. **Indirectness: Serious.** Evidence limited to TNFi, Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Event rates are low and wide confidence intervals. **Publication bias: No serious.**
5. Systematic review [5] with included studies: Landewe 2018 nraSpA ADA, Landewe 2020 aSpA CZP. **Baseline/ comparator:** Systematic review.
6. **Inconsistency: No serious.** Substantial heterogeneity might be explained by the different participants investigated in the two studies. **Indirectness: Serious.** Evidence limited to TNFi, Differences between the intervention/comparator of interest and those studied, Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Event rates low and wide confidence intervals. **Publication bias: No serious.**
7. Systematic review [5] with included studies: Landewe 2018 nraSpA ADA, Landewe 2020 aSpA CZP. **Baseline/ comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious.** Substantial heterogeneity might be explained by the different participants investigated in the two studies. **Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Event rate very low. **Publication bias: No serious.**

9. Systematic review [5] with included studies: Landewe 2018 nraSpA ADA, Landewe 2020 aSpA CZP. **Baseline/ comparator:** Control arm of reference used for intervention.
10. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Event rate very low .
11. Systematic review [5] with included studies: Landewe 2018 nraSpA ADA, Landewe 2020 aSpA CZP. **Baseline/ comparator:** Primary study.
12. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: No serious.** Assume number of participants sufficient to detect a clinically important difference. **Publication bias: No serious.**
13. Systematic review [5] with included studies: Landewe 2020 aSpA CZP, Landewe 2018 nraSpA ADA. **Baseline/ comparator:** Control arm of reference used for intervention.
14. **Inconsistency: No serious.** Substantial heterogeneity might be explained by difference in the disease across the two studies . **Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: No serious. Publication bias: No serious.**

4.3 - Psoriatic Arthritis: Dose Reduction or Discontinuation of bDMARDs and tsDMARDS

Psoriatic arthritis (PsA) is an inflammatory joint disease that causes painful and swollen joints, as well as enthesitis and inflammatory back symptoms. It occurs in approximately 25% to 30% of people with the autoimmune disease of the skin, psoriasis. There are several subtypes of psoriatic arthritis characterised by different patterns of disease that may overlap. These include subtypes similar to rheumatoid arthritis or spondyloarthritis, an asymmetrical phenotype often involving lower limb joints, involvement specifically of the distal interphalangeal joints often with psoriatic nail disease and a rare severely destructive disease. It leads to impaired function and reduced quality of life. There is no cure for PsA, so treatments aim to relieve pain and stiffness, improve function and prevent joint and tendon damage.

Executive Summary - bDMARDs and/or tsDMARD down-titration (fixed dose reduction or discontinuation) in adults with psoriatic arthritis, with low disease activity or remission:

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence limited to anti-TNFs) for 3 months in adults with psoriatic arthritis in remission or with low disease activity:

- We are uncertain of the effect of discontinuation on disease activity, the proportion of participant with persistent remission (PASDAS < 3.2) and flare and the number of serious adverse events, due to the very low certainty evidence.
- We did not find any studies that assessed the effect of discontinuation on function, proportion of participants who switched to another biologic, proportion of participants with minimal radiographic progression or number of withdrawals due to adverse events.

Abbreviations used in this recommendation:

- bDMARDs - biological disease-modifying antirheumatic drugs (DMARDs), including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitor (ustekinumab)
- tsDMARDs - targeted synthetic DMARDs, including Janus Kinase inhibitors (eg tofacitinib, baricitinib)
- b/tsDMARDs - either bDMARDs or tsDMARDs
- csDMARDs - conventional synthetic DMARDs (e.g. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine)

Conditional recommendation against

Do not routinely reduce the dose of b/tsDMARDs in patients with psoriatic arthritis who are in low disease activity or remission. Abrupt cessation of b/tsDMARDs is not recommended.

Evidence up to date as at 6 August 2020

Practical Info

- A treat-to-target approach within a shared decision-making framework is recommended for all patients with psoriatic arthritis, including consideration of dose reduction.
- Although we have conditionally recommended against reducing the dose of b/tsDMARDs in patients with psoriatic arthritis who are in a stable low-disease activity state, there may be some patients for whom the potential benefits of using a lower dose may outweigh the potential risk of a disease flare. The potential for flare, the risk of failure to regain remission with resumption of a higher dose, and the current lack of evidence to help estimate these risks should all be discussed.
- In patients who choose to attempt dose reduction, clinical review should occur at least every 3 months and should include measurement of disease activity using a validated composite disease activity measure that includes patient-reported outcomes (e.g., PASDAS) and escalation to the full dose should be considered if the treatment target has not been maintained.
- The presence of extra-articular features of psoriatic arthritis (e.g., psoriasis, nail dystrophy) should also be considered when contemplating dose reduction and clinical review after dose reduction should include surveillance for the emergence of these clinical features.
- Patients should be provided with a plan to follow if there is a symptomatic flare following dose reduction, including a mechanism for patients to contact their prescriber between visits if necessary.

Evidence To Decision

Benefits and harms

There are no data on the effect of dose reduction of b/tsDMARDs in patients with psoriatic arthritis.

In patients with psoriatic arthritis in sustained minimal disease activity, we are uncertain about the effect of discontinuation of TNF inhibitors (TNFi) on disease activity, the chance of staying in remission or experiencing a disease flare, or the risk of adverse effects. There are no data on the effect of discontinuation of b/tsDMARDs other than TNFi.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**
Please find Supplementary Figures and Tables (including Forest Plots) **HERE**

Certainty of the Evidence

Very Low

There are no data on the effect of dose reduction of b/tsDMARDs in patients with psoriatic arthritis.

We are uncertain about the effect of discontinuation of TNF inhibitors (TNFi) in patients with psoriatic arthritis in sustained minimal disease activity. A pilot RCT (of 17 patients on various treatment regimens including 10 participants on TNFi alone or in combination with csDMARDs) measured the proportion of participants with persistent remission, the proportion of participants with a flare, disease activity (PASDAS) and adverse events but the results do not provide sufficient certainty to estimate the likely benefits or harms of TNFi discontinuation in this population. There are no trials that measure other important outcomes (including radiographic progression and function). There are no trials of discontinuation of b/tsDMARDs other than TNFi.

Preference and values

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. It is likely that individual patient preferences for reduced exposure to medication versus the risk of flare will vary. The presence of non-musculoskeletal features of psoriatic arthritis (particularly psoriasis) may also influence individual patients' preferences regarding DMARD dose reduction.

A qualitative study *[6]* of British patients with inflammatory arthritis - including psoriatic arthritis - found that patients who were using bDMARDs were interested in reducing their dose when the disease was under control in the hope that this would reduce inconvenience and potential toxicity while maintaining disease control, and reduce overall cost to society. However this was balanced by concerns that dose reduction might result in a disease flare and that resumption of the full dose, if required, might be limited due to the high cost of bDMARDs or might not achieve the previous level of disease control. Shared decision-making, including control over flexible dosing, was identified as an important theme.

Resources

Important issues, or potential issues not investigated

There are no data on the cost-effectiveness of b/tsDMARD dose reduction for psoriatic arthritis. b/tsDMARDs are generally considered to be expensive therapies and therefore strategies to reduce the total cumulative dose are likely to reduce costs for payers (governments and insurers) and may reduce out-of-pocket costs for patients. In the Australian context, the direct cost impact for individual patients is relatively small but this may differ in other contexts. The importance of direct out-of-pocket cost implications of dose reduction versus continuation is likely to vary between individual patients. There are no publicly-available data regarding the actual comparative costs of different b/tsDMARDs to the payer (i.e., the Federal Government) in Australia.

Equity

Important issues, or potential issues not investigated

The panel considered that many factors influence individual patients' health opportunities and outcomes. Such factors (based on the PROGRESS-Plus characteristics) might include poor health literacy; residence in rural, remote or relatively under-serviced locations; primary language other than English; low educational attainment; the presence of disability; or adverse socioeconomic or social circumstances. Some of these may affect bDMARD dose reduction, including an impact on access to urgent specialist care or advice in the event of a flare in disease activity following DMARD dose adjustment.

Acceptability

Important issues, or potential issues not investigated

Evidence for acceptability of the intervention to consumers comes from a recent survey of ARAD participants (unpublished data):

"The medication you have taken is known as a biologic or targeted DMARD: Evidence shows that some people with well-controlled disease can safely reduce the dose of their biologic or targeted DMARD or how frequently they take it, without any worsening of their condition. If your treating specialist suggested it, would you be willing to try taking your biologic or targeted DMARD less frequently, or at a reduced dose?"

Responses as follows:
Yes: 74 (46%)
No: 31 (19%)
Maybe: 55 (34%)

There is little evidence regarding the acceptability of b/tsDMARD dose reduction or discontinuation to clinicians, policymakers or other stakeholders, although the panel felt that consideration of reduction of medication burden in a shared decision-making framework would likely be acceptable to all stakeholders.

Feasibility Important issues, or potential issues not investigated

Implementation of the recommendation may be influenced in some cases by local prescribing rules or reimbursement conditions, and by the accessibility of care in the case of a disease flare. Current Australian prescribing and reimbursement rules for b/tsDMARDs are complex. For example, some reimbursement rules are predicated on stable disease control with full-dose medication. In this situation, some patients or prescribers may be concerned about the risk that, in the event of a disease flare with dose reduction, the resumption of a higher dose of the current bDMARD may be prohibited.

Rationale

There is very little evidence from clinical trials on which to base a recommendation regarding tapering or discontinuation of b/tsDMARDs in patients with psoriatic arthritis who have achieved their treatment target (i.e., clinical remission or a similar low disease activity state). There are no published trials of tapering in this patient population. A pilot RCT of discontinuation versus continuation of DMARDs in patients with psoriatic arthritis who had achieved stable minimal disease activity enrolled only 17 participants on a variety of treatment regimens. The panel considered that this single small trial provided very low certainty evidence regarding the benefits and harms of b/tsDMARD discontinuation in this population.

Due to the lack of evidence, there was considerable discussion among the panel regarding the relative merits of a conditional recommendation for or against a trial of b/tsDMARD dose reduction in patients who have been in a stable low disease activity state for at least six months. The panel considered that a cautious trial of dose reduction may be a suitable option for patients who place a high value on reduced exposure to medication (e.g., to reduce overall medication burden, personal or societal cost, or due to concerns about current or potential adverse effects). They considered that this would be reasonable to consider within a shared decision-making framework, but that the lack of data regarding the risks of such an approach precluded a conditional recommendation in favour of dose reduction. In particular, there may be a risk of disease flare with b/tsDMARD dose reduction and a proportion of patients who flare may not regain a low disease activity state with resumption of a higher dose. There is a lack of data regarding the proportion who fail to regain a low disease activity state.

It was also noted that psoriatic arthritis is a disease that varies considerably in its clinical manifestations both between patients and also within the same patient over time, and therefore decisions regarding dose modification will depend heavily on the individual context. The panel felt that data regarding the potential benefits and harms of b/tsDMARD dose reduction in other inflammatory arthropathies (rheumatoid arthritis and axial spondyloarthritis) could not be reliably applied to the unique clinical syndrome of psoriatic arthritis.

Another consideration in shared decision-making for the individual patient with psoriatic arthritis may be the presence of extraskeletal manifestations, particularly psoriasis. The balance of risks and benefits may be different in patients for whom b/tsDMARDs have also been an effective therapy for skin disease or other symptoms.

Abrupt discontinuation of b/tsDMARDs is likely to increase the risk of disease flare compared with gradual dose reduction, and is therefore not recommended.

The panel felt that this was likely to be a question of importance to patients with psoriatic arthritis and therefore clinical trials of dose reduction are strongly encouraged. It is noted that two trials are currently registered which may inform future versions of this conditional living recommendation.

Clinical Question/ PICO

Population: Psoriatic arthritis patients with low disease activity
Intervention: Dose reduction
Comparator: Continuation

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation Dose reduction	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion with persistent remission (PASDAS <3.2) 9 Critical				No studies were found that looked at proportion with persistent remission
Proportion of participants with a flare 9 Critical				No studies were found that looked at withdrawals due to adverse events
Proportion switched to another biologic 6 Important				No studies were found that looked at proportion switched to another biologic
Proportion of participants with minimal radiographic progression 9 Critical				No studies were found that looked at proportion of participants with minimal radiographic progression
Number of serious adverse events 9 Critical				No studies were found that looked at number of serious adverse events
Withdrawals due to adverse events 9 Critical				No studies were found that looked at withdrawals due to adverse events
Disease activity score (PASDAS)				No studies were found that looked at disease activity score

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation Dose reduction	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical **Function** 9 Critical				No studies were found that looked at function

Clinical Question/ PICO

Population: Psoriatic arthritis patients with low disease activity
Intervention: Discontinuation
Comparator: Continuation

Outcome Timeframe	Study results and measurements	Absolute effect estimates Continuation Discontinuation	Certainty of the Evidence (Quality of evidence)	Plain text summary
Proportion with persistent remission (PASDAS <3.2) 3 months 9 Critical	Relative risk 0.49 (CI 95% 0.26 - 0.94) Based on data from 17 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	803 per 1000 393 per 1000 Difference: **410 fewer** per 1000 (CI 95% 594 fewer - 48 fewer)	**Very Low** Due to risk of bias, possible indirectness and very serious imprecision [1]	We are uncertain whether discontinuation results in more people with persistent remission
Proportion of participants with a flare 3 months 9 Critical	Relative risk 7.58 (CI 95% 0.5 - 115) Based on data from 17 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	1 per 1000 8 per 1000 Difference: **7 more** per 1000 (CI 95% 0 more - 114 more)	**Very Low** Due to risk of bias, possible indirectness and very serious imprecision [2]	We are uncertain whether discontinuation results in more people with a flare
Proportion switched to another biologic 6 Important				No studies were found that looked at proportion of participants switched to another biologic

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuation	Discontinuation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion of participants with minimal radiographic progression 9 Critical					No studies were found that looked at proportion of participants with minimal radiographic progression
Number of serious adverse events 3 months 9 Critical	Relative risk Based on data from 17 patients in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95%	**Very Low** Due to risk of bias, possible indirectness and very serious imprecision [3]	There were no serious adverse events reported. 5/6 participants in the continuation group and 2/11 participants in the discontinuation group reported mild adverse events likely unrelated to treatment
Withdrawals due to adverse events 9 Critical					It is unclear if withdrawals due to adverse events were measured
Disease activity score (PASDAS)	Measured by: PASDAS Scale: 0-10 Lower better Based on data from: 17 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	1.33 (Mean)	2.23 (Mean) Difference: **MD 0.9 higher** (CI 95% 0.36 higher - 1.44 higher)	**Very Low** Due to risk of bias, possible indirectness and very serious imprecision [4]	We are uncertain whether discontinuation improves or worsens disease activity score
Function					No studies were found that looked at function

1. **Risk of bias: Serious.** Potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Single, small study (17 participants). **Publication bias: No serious.**
2. **Risk of bias: Serious.** Potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Single, small study (17 participants). **Publication bias: No serious.**
3. **Risk of bias: Serious.** Potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Single, small study (17 participants). **Publication bias: No serious.**
4. **Risk of bias: Serious.** Potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** Evidence limited to TNFi. **Imprecision: Very Serious.** Single, small study (17 participants). **Publication bias: No serious.**

5 - Opioids for Pain Management

5.1 - Opioids for Pain in RA

People with rheumatoid arthritis perceive pain to be their predominant impairment and report pain management as their highest priority (Heiberg 2002). The cornerstone of pharmacologic treatment for rheumatoid arthritis is disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), which primarily control the inflammation and to some extent the pain associated with the inflammation. There are, however, multiple contributors to the genesis of pain in RA in addition to inflammation, including joint damage or destruction and peripheral and central sensitisation (McDougall 2006), which may not be responsive to treatment with DMARDs and/or NSAIDs. Despite recent improvements in the management of RA, including earlier intervention, more aggressive use of DMARDs and the use of the biologic disease-modifying therapies (bDMARDs), many patients with RA continue to experience musculoskeletal pain even when inflammation is well-controlled (Kvien 2004).

Opioids may successfully control pain in rheumatoid arthritis, however, the potential for adverse effects, particularly addiction and drug interactions, limit their regular use in this patient population.

Executive Summary - Opioids for pain management in adults with rheumatoid arthritis

In people with rheumatoid arthritis treated with weak opioids for up to six weeks:

Compared with placebo, weak opioids:
- may improve pain and may increase the number of people reporting treatment success
- may have little or no effect on function
- may have little or no effect on the number of people reporting adverse events

We are uncertain of the effect of opioid use results on the number of withdrawals due to inadequate analgesia and withdrawals due to adverse events; and the number of serious adverse events as there were too few events to estimate these outcomes with certainty.

We are uncertain of the benefits and harms of opioids compared with NSAID, due to very low quality evidence from a single study.

We did not identify any studies comparing opioids to other analgesics or interventions.

Conditional recommendation against

New

Do not routinely use opioids for the treatment of pain in rheumatoid arthritis.
A brief course of a short-acting opioid may be considered for severe pain when other analgesic options have failed.

Evidence up to date as at 23 June 2020

Practical Info

- Any decision regarding the use of opioids should be made within a shared decision-making framework following a clear discussion of potential benefits and harms, tailored to the individual's circumstances (including comorbidities and concomitant medications)

- In patients who are already using opioids, the lowest effective dose should be sought, and opportunities for reduction in dose or cessation should be considered at each visit

- In all patients for whom opioids are being considered or currently prescribed:
  - Consider age, other pharmacotherapy and important comorbidities (e.g., cognitive impairment, falls risk, active mental

illness, history of drug or alcohol misuse) and avoid any opioid use in individuals at increased risk of harm from opioids
    - Actively enquire about the individual patient's prior or current experience with opioid analgesics (including effectiveness, adverse effects, and dose used), and current use of other centrally-acting drugs
    - Consider the pain phenotype: make sure inflammatory pain is adequately treated, and be alert for comorbid fibromyalgia or nociplastic pain (for which opioids are generally not recommended). Ensure that other treatable or reversible pathology (e.g., occult insufficiency fracture) has been adequately considered and investigated

- In patients for whom a trial of opioids is being considered:
    - Ensure that appropriate non-pharmacological therapies and other analgesic strategies have been optimised prior to consideration of opioid prescription
    - Before commencing treatment with opioids, the prescriber and patient should agree on the goals of therapy and the method for measuring outcomes

- If a decision is made to proceed with a trial of opioids, the following should be considered:
    - Commence at a low dose of a short-acting opioid
    - A written treatment plan should be agreed upon by the patient and prescriber, and this should be provided to other relevant parties (e.g., the GP)
    - Discuss the risks of driving a motor vehicle and operating heavy machinery during initiation and dose adjustment of opioids, and develop a plan to mitigate this risk
    - The primary prescriber and the dispensing pharmacy should also be identified in the written plan and all parties should be informed
    - Establish a clear plan for discontinuation of opioids if the treatment goals are not met

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There was considerable debate among the panel about whether the potential benefits and harms of opioids are balanced or whether there is net harm on average. There was a majority (but not unanimous) panel vote for "Small net benefit, or little difference between the alternatives", based on the data from trials of short-term use of opioids in people with rheumatoid arthritis. Some panellists were of the opinion that, on balance, there were important harms that outweighed the potential benefits.

Evidence regarding opioid analgesics in patients with rheumatoid arthritis (RA) comes mostly from short-term trials comparing various opioids with placebo: opioids may improve mean pain and increase the number of people who report treatment success but may have little or no effect on function. Opioids may have a small or no effect on the number of people reporting adverse events in short-term clinical trials (up to 6 weeks). We are uncertain of the effect of opioids on serious adverse events or withdrawals from treatment due to either inefficacy or adverse effects.

There is very little evidence regarding the efficacy and safety of opioids compared with other types of analgesic medications in patients with RA.

The Cochrane review of opioids for RA pain *[7]* used a 'net efficacy adjusted for risk' (NEAR) analysis to estimate the balance of benefits and harms of opioids in RA. The NEAR calculation combines efficacy and adverse event outcomes into a single estimate of the proportion of participants in each treatment group who achieve the clinically desirable state of both analgesic response and avoidance of important adverse effects. By this measure, there was no evidence of a difference between opioids and placebo: the NEAR relative risk (that is, the chance of achieving benefit without harm for those treated with opioids versus placebo) was 1.20 (95% CI, 0.89–1.61).

Although there was relatively little high-quality data specific to RA, the widespread use of opioids for chronic non-cancer pain, including in patients with RA, has been increasingly recognised in recent years and use is increasing. The prevalence of opioid use among Australians with RA has been estimated at 32.9% (95% CI 31.6, 34.2) *[15]* . The use of high-potency opioids in this group has increased over time and now represents approximately a third of all opioid use. Across all

indications, over 1.9 million Australians initiate treatment with opioids each year, the majority for non-cancer pain *[13]*. 2.6% of people who initiate opioids in Australia for non-cancer pain will go on to become persistent users over a 12-month period *[16]*. In a US emergency department setting, for every 48 patients given an initial opioid prescription, one will become a long-term opioid user *[23]*. Rheumatological conditions may be a risk factor for transition from first use to long-term opioid use for non-cancer pain *[17]*.

Use of low-potency or low-dose opioids is also associated with a risk of transition to high-dose therapy. Tolerance with long-term use of opioids often leads to a requirement for dose escalation. Almost one percent of Australians who commence weak opioids may escalate to high-dose opioid therapy (equivalent to at least 90mg oral morphine per day) and approximately one in 13 will transition to a strong opioid during a 12-month period *[21]*. Older people are at increased risk of transition to higher doses or more potent opioids. Higher doses are associated with an increased risk of opioid-related morbidity and mortality.

All of the trials included in the evidence summary for this recommendation evaluated short-term use (up to 6 weeks); the effectiveness of opioids for RA pain beyond 6 weeks is unknown. Potential harms from chronic use of opioids are well recognised but are unlikely to be adequately captured in short-term trials. Evidence is available regarding harms in trials of medium-term use of opioids (2 weeks to 13 months) for chronic non-cancer pain *[18]*: opioid use is associated with an increased risk of any adverse event (RR versus placebo 1.42, 95% CI 1.22, 1.66) and serious adverse events (RR 2.75, 95% CI 2.06, 3.67). Adverse effects that occurred at significantly increased rates in opioid users included nausea and vomiting, constipation, dizziness, drowsiness and fatigue, pruritus, hot flushes and sweating.

Evidence for opioid harms in the longer term comes from observational studies. Data from a study of almost 100,000 UK patients treated with opioids for musculoskeletal conditions and followed for a median of 3.4 years indicate that long-term opioid use is associated with a dose-dependent increase in the risk of fractures and other major trauma, overdose, falls, gastrointestinal pathology and addiction *[19]*. Episodes of major trauma increased by 84 for every 10,000 person-years of use of low-dose opioids (equivalent to <20mg morphine per day) and by 139/10,000 for doses equivalent to at least 50mg morphine per day. While the risk of dependence, addiction and overdose is generally well recognised, the potential for other important harms associated with opioid use, including fractures, endocrine dysfunction, and worsening of chronic pain (opioid-induced hyperalgesia), is frequently underestimated.

Opioid prescription is also associated with an increased risk of mortality. Treatment with opioids for chronic non-cancer pain is associated with a 58% increase in the risk of all-cause mortality compared with other analgesic therapies (HR 1.58, 95% CI 1.38 to 1.82), equivalent to 148 excess deaths per 10,000 person-years of treatment *[20]*.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**
Please find Supplementary Figures and Tables (including Forest Plots) **HERE**

Certainty of the Evidence Low

Evidence from trials regarding benefits and harms of opioids in patients with RA was generally of low certainty. Important outcomes for which there was low certainty evidence included pain, function and the number of participants reporting treatment success. There was very low certainty evidence for serious adverse events and withdrawals due to either adverse events or inadequate analgesia.

We included trials of any opioid, including medications with other mechanisms of action in addition to opioid receptor effects (i.e. tramadol) and compound analgesics (e.g. an opioid plus paracetamol). Some of the opioids included in these trials are not currently available in Australia. Importantly, most of the evidence comes from trials that pre-date the modern era of treat-to-target management of RA, and none of the participants in the included trials were using biologic or targeted synthetic DMARDs for the treatment of their RA, so the results may not necessarily generalise to people with RA who have been treated with an intensive disease-modifying strategy. No trials were longer than 6 weeks in duration.

Preference and values

Substantial variability is expected or uncertain

Patients with rheumatoid arthritis report relief of pain to be their highest priority *[9]*. A 2018 systematic review of patient values and preferences regarding chronic non-cancer pain *[8]* included 6 studies involving patients with various forms of chronic non-cancer pain (CNCP). While none of the included studies specifically recruited patients with RA, one included patients with other forms of musculoskeletal pain, including osteoarthritis and fibromyalgia. It is likely that the preferences and values of patients with various forms of CNCP are broadly applicable to people with RA pain.

Across the included studies, pain relief was consistently reported as being of high importance to patients. The most important adverse effects were nausea/vomiting and alteration of mental state. Other adverse effects, including risk of addiction, were of lesser importance.

Included studies that evaluated the trade-off between benefits and harms indicated that substantial pain relief (at least 2 points on a 10-point numerical scale) would be required for a net benefit in the presence of adverse effects (particularly nausea or vomiting).

No studies considered the risk of overdose or death, although these outcomes and deliberate misuse or diversion of prescription opioids are common concerns at a societal level. Similarly, while opioid prescribers also view CNCP as an important problem, they are more likely to report concerns about the risk of opioid misuse or addiction *[10]*.

Resources

Important issues, or potential issues not investigated

Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs or may have an impact on work.

The societal costs of chronic non-cancer pain are significant. Approximately 3 million Australian adults use prescription opioids *[13]*. The majority of these are people with non-cancer pain, although it is likely that opioid use for rheumatoid arthritis represents only a small fraction of these cases. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity.

Equity

Important issues, or potential issues not investigated

Socioeconomic factors are important determinants of chronic pain, opioid use and opioid-related adverse outcomes *[11][22]*. Variation in access to rheumatologists for people with early inflammatory arthritis may lead to delayed treatment with DMARDs in some settings, which may increase the risk of persistent pain throughout the disease course. Access to comprehensive and multidisciplinary chronic pain management services varies within Australia. In particular, access may be limited for socially-disadvanted people and those in regional and remote areas *[12]*. This may affect pain management strategies in general and, specifically, may alter the balance of potential benefits and harms of opioid analgesics.

Acceptability

Important issues, or potential issues not investigated

It is likely that the option of short-term use of opioids guided by an explicit management plan in a shared decision-making framework would be acceptable to both patients and prescribers. Evidence from qualitative studies suggests that while patients strongly value relief of pain, this is balanced by concerns about adverse effects (particularly nausea and vomiting) and that patients feel that opioids should be used with caution *[14]*. Given the potential net harms of opioids use at the population level, widespread use of opioids for RA pain may be less acceptable to policy-makers.

Feasibility

No important issues with the recommended alternative

Opioids are a widely-available and feasible treatment option.

Rationale

The panel noted the lack of high quality evidence regarding the use of opioids for RA pain. On balance, there may be some short-term improvement in pain but for many patients this may be at the cost of unpleasant adverse effects. Importantly, there are no data on the benefits of long-term use of opioids, but there is a large body of literature that highlights the potential long-term harms of opioid use for chronic non-cancer pain in general. Therefore, any decision to use opioids in RA should take place within a clear shared decision-making framework that acknowledges the relative lack of specific data on short-term risks and benefits and the large body of literature regarding the potential risks of long-term opioid use.

While the panel was of the view that, on average, the potential benefits of opioids are unlikely to outweigh the potential harms, it was also recognised that some individuals may derive a net benefit from a short course of opioids. Therefore, while there is a general recommendation against the use of opioids in the setting of RA pain, in some situations the patient and doctor may elect to trial a short course of opioids. For example, if there is disabling pain due to untreated inflammation and while waiting for DMARDs to take effect and NSAIDs, glucocorticoids or other analgesic strategies have been ineffective or are contraindicated, a brief course of opioids may be warranted. It is likely that such situations would be uncommon in contemporary rheumatology practice. The panel recognised, however, that opioid use among patients with RA appears to be relatively prevalent which suggests that opioids are being used for longer durations or different indications in many patients. In recent years, the persistence of joint pain in a proportion of people with RA despite effective treatment of inflammation has been increasingly recognised. It is unlikely that this type of pain is suited to opioid therapy due to both its chronicity (which would imply a need for long-term opioid use) and its clinical and mechanistic resemblance to 'nociplastic' pain (similar to the centrally-mediated pain in fibromyalgia) for which opioids are considered to be ineffective or harmful.

The panel also noted that an important proportion of patients who initiate short-term opioid therapy will go on to become long-term users, therefore caution is required even when a brief course of opioids is intended, and mechanisms to prevent transition to chronic use should be established, particularly in patients with a chronic disease such as RA.

The panel was strongly of the view that some attempt should be made to identify the phenotype of the pain in the patient with RA. In general, inflammatory pain is best treated with anti-inflammatory strategies (including DMARDs, glucocorticoids and NSAIDs). Pain due to joint damage may occasionally warrant a trial of opioids, although the risks of long-term use should be carefully considered in this setting. Pain that is thought to be related to activation of central mechanisms (i.e. nociplastic pain) is often associated with other clinical features, including widespread tenderness, allodynia, sleep disturbance and cognitive clouding; in such cases the potential risks of opioids typically outweigh any potential benefits.

The panel also noted that there are some populations for whom the risks of opioids more clearly outweigh the potential benefits (e.g. the elderly, individuals with active mental illness, those with multiple comorbidities, and those with a history of substance misuse). The panel more strongly recommends against the use of opioids in such cases.

Clinical Question/ PICO

Population: Adults with rheumatoid arthritis
Intervention: Opioids
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Opioids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Participant-reported treatment success	Relative risk 1.41 (CI 95% 1.07 - 1.87) Based on data from 325 patients in 3 studies.	387 per 1000	546 per 1000	**Low** Due to potential risk of bias and imprecision [1]	Opioid use may increase the number of people who report treatment success

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo	Opioids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Up to 6 weeks 9 Critical	(Randomized controlled)	Difference: **159 more** per 1000 (CI 95% 27 more - 337 more)			
Total withdrawals due to adverse events or inadequate analgesia Up to 6 weeks 9 Critical	Relative risk 1.9 (CI 95% 0.85 - 4.27) Based on data from 431 patients in 6 studies. (Randomized controlled)	**105** per 1000	**199** per 1000 Difference: **94 more** per 1000 (CI 95% 16 fewer - 334 more)	**Very Low** Due to potential risk of bias and very serious imprecision [2]	We are uncertain whether opioid use results in more people withdrawing due to adverse events or inadequate analgesia
Withdrawals due to inadequate analgesia Up to 6 weeks 9 Critical	Relative risk 0.66 (CI 95% 0.21 - 2.06) Based on data from 346 patients in 4 studies. (Randomized controlled)	**58** per 1000	**38** per 1000 Difference: **20 fewer** per 1000 (CI 95% 46 fewer - 61 more)	**Very Low** Due to potential risk of bias and very serious imprecision [3]	We are uncertain whether opioid use results in more people withdrawing due to inadequate analgesia
Number of participants reporting adverse events Up to 6 weeks 9 Critical	Relative risk 1.76 (CI 95% 0.82 - 3.8) Based on data from 410 patients in 5 studies. (Randomized controlled)	**346** per 1000	**609** per 1000 Difference: **263 more** per 1000 (CI 95% 62 fewer - 968 more)	**Low** Due to potential risk of bias and imprecision [4]	Opioid use may have little or no effect on the number of people reporting adverse events
Number of serious adverse events Up to 6 weeks 9 Critical	Relative risk 1.7 (CI 95% 0.18 - 15.97) Based on data from 317 patients in 2 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **0 more** per 1000 (CI 95% 1 more - 163 more)	**Very Low** Due to potential risk of bias and very serious imprecision [5]	We are uncertain whether opioid use results in more people reporting serious adverse events
Mean Pain Up to 6 weeks 9 Critical	Measured by: VAS Scale: 0-10 Lower better Based on data from: 301 patients in 3 studies. (Randomized controlled)	**5.4** (Mean)	**3.8** (Mean) Difference: **MD 1.62 lower** (CI 95% 2.94 lower - 0.3 lower)	**Low** Due to potential for bias and imprecision [6]	Opioid use may improve pain

Outcome Timeframe	Study results and measurements	Absolute effect estimates Placebo	 Opioids	Certainty of the Evidence (Quality of evidence)	Plain text summary
Mean Function Up to 6 weeks 9 Critical	Measured by: HAQ Scale: 0-3 Lower better Based on data from: 243 patients in 2 studies. (Randomized controlled)	1.09 (Mean)	0.99 (Mean) Difference: MD 0.1 lower (CI 95% 0.33 lower - 0.13 higher)	Low Due to potential for bias and imprecision [7]	Opioid use may have little or no effect on function

1. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Small number of events; confidence intervals include both a small number and a larger number of people reporting success. **Publication bias: No serious.**
2. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Very low number of events. **Publication bias: No serious.**
3. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Very small number of events. **Publication bias: No serious.**
4. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Small number of events. **Publication bias: No serious.**
5. **Risk of bias: Serious.** Possible selection and detection bias . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Very small number of events. **Publication bias: No serious.**
6. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Confidence intervals include both a small improvement and a clinically important improvement. **Publication bias: No serious.**
7. **Risk of bias: Serious.** Possible selection and detection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

5.2 - Opioids for Pain in Axial Spondyloarthritis

The cornerstone of pharmacologic treatment for axial spondyloarthritis (axSpA) is disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), which primarily control the inflammation and to some extent the pain associated with the inflammation. There are, however, multiple contributors to the genesis of pain in AS in addition to inflammation, including joint damage or destruction and peripheral and central sensitisation, which may not be responsive to treatment with DMARDs and/or NSAIDs. Opioids may successfully control pain in axial spondyloarthritis; however, the potential for adverse effects, particularly addiction and drug interactions, limit their regular use in this patient population.

Executive Summary - Opioids for pain management in adults with axial spondyloarthritis

In people with axial spondyloarthritis, we are uncertain whether opioid use results in fewer or more people reporting treatment success; fewer or more people withdrawing due to adverse events or inadequate analgesia; fewer or more people reporting adverse events; and better or worse pain and function, as the certainty of the evidence is very low.

Conditional recommendation against

New

Do not routinely use opioids for the treatment of pain in axial spondyloarthritis.

Evidence up to date as at 23 November 2020

Practical Info

- Any decision regarding the use of opioids should be made within a shared decision-making framework following a clear discussion of potential benefits and harms, tailored to the individual's circumstances (including comorbidities and concomitant medications)
- In patients who are already using opioids, the lowest effective dose should be sought, and opportunities for reduction in dose or cessation should be considered at each visit
- In all patients for whom opioids are being considered or currently prescribed:
  - Consider age, other pharmacotherapy and important comorbidities (e.g., cognitive impairment, falls risk, active mental illness, history of drug or alcohol misuse) and avoid any opioid use in individuals at increased risk of harm from opioids
  - Actively enquire about the individual patient's prior or current experience with opioid analgesics (including effectiveness, adverse effects, and dose used), and current use of other centrally-acting drugs
  - Consider the pain phenotype: make sure inflammatory pain is adequately treated, and be alert for comorbid fibromyalgia or nociplastic pain (for which opioids are generally not recommended). Ensure that other treatable or reversible pathology (e.g., occult insufficiency fracture) has been adequately considered and investigated
- In patients for whom a trial of opioids is being considered:
  - Ensure that appropriate non-pharmacological therapies and other analgesic strategies have been optimised prior to consideration of opioid prescription
  - Before commencing treatment with opioids, the prescriber and patient should agree on the goals of therapy and the method for measuring outcomes
- If a decision is made to proceed with a trial of opioids, the following should be considered:
  - Commence at a low dose of a short-acting opioid
  - A written treatment plan should be agreed upon by the patient and prescriber, and this should be provided to other relevant parties (e.g., the GP)
  - Discuss the risks of driving a motor vehicle and operating heavy machinery during initiation and dose adjustment of opioids, and develop a plan to mitigate this risk
  - The primary prescriber and the dispensing pharmacy should also be identified in the written plan and all parties should be informed
  - Establish a clear plan for discontinuation of opioids if the treatment goals are not met

Evidence To Decision

Benefits and harms

Important harms

Benefits:
In adults with axial spondyloarthritis (including ankylosing spondylitis), we are uncertain of the benefits of opioid use compared with other analgesics (i.e. NSAIDs) or in addition to NSAIDs versus NSAIDs alone, with regards to treatment success, pain or function, due to very low certainty evidence.

Harms:
In adults with axial spondyloarthritis (including ankylosing spondylitis), we are uncertain of the harms of opioid use compared with other analgesics (i.e. NSAIDs) or in addition to NSAIDs versus NSAIDs alone, with regards to the number of adverse events, ineffective analgesia and withdrawals due to either or both of these outcomes. No serious adverse events were reported in two randomised controlled trials.

There was considerable debate among the panel regarding the balance of potential benefits and harms of opioid therapy in people with axial spondyloarthritis pain. Only two randomised controlled trials were available, which provided very low certainty evidence regarding efficacy or short-term harms. Given the lack of evidence regarding efficacy and the known risk of long-term harm associated with opioid use in the broader population of people with chronic non-cancer pain, the panel formed the consensus view that the known risks outweigh the potential benefits in this setting.

There are few data regarding the prevalence of opioid use among people with axial spondyloarthritis, particularly in the Australian setting. Observational data from the US suggests that opioid use for spondyloarthritis pain is common. Data from a claims database indicated that patients with various forms of inflammatory arthritis are at higher risk of receiving long-term opioid prescriptions, and that the risk was highest for patients with ankylosing spondylitis *[26]*. In a cohort of US patients with ankylosing spondylitis, 9.5% were taking chronic opioids (defined as taking opioids daily for at least 6 months) and 21.7% were using intermittent or "on demand" opioids *[27]*. Opioid use was higher among those with multiple comorbidities, polypharmacy (including anxiolytics and hypnotics), higher functional impairment and depression.

Across all indications, over 1.9 million Australians initiate treatment with opioids each year, the majority for non-cancer pain *[13]*. 2.6% of people who initiate opioids in Australia for non-cancer pain will go on to become persistent users over a 12-month period *[16]*. In a US emergency department setting, for every 48 patients given an initial opioid prescription, one will become a long-term opioid user *[23]*. Rheumatological conditions may be a risk factor for transition from first use to long-term opioid use for non-cancer pain *[17]*.

Use of low-potency or low-dose opioids is also associated with a risk of transition to high-dose therapy. Tolerance with long-term use of opioids often leads to a requirement for dose escalation. Almost one percent of Australians who commence weak opioids may escalate to high-dose opioid therapy (equivalent to at least 90mg oral morphine per day) and approximately one in 13 will transition to a strong opioid during a 12-month period *[21]*. Older people are at increased risk of transition to higher doses or more potent opioids. Higher doses are associated with an increased risk of opioid-related morbidity and mortality.

Although there is little trial evidence regarding harms of opioids that is specific to spondyloarthritis, data are available regarding harms in patients with chronic non-cancer pain from trials of medium-term use of opioids (2 weeks to 13 months) *[18]*: opioid use is associated with an increased risk of any adverse event (RR versus placebo 1.42, 95% CI 1.22, 1.66) and serious adverse events (RR 2.75, 95% CI 2.06, 3.67). Adverse effects that occurred at significantly increased rates in opioid users included nausea and vomiting, constipation, dizziness, drowsiness and fatigue, pruritus, hot flushes and sweating.

Evidence for opioid harms in the longer term comes from observational studies. Data from a study of almost 100,000 UK patients treated with opioids for musculoskeletal conditions and followed for a median of 3.4 years indicate that long-term opioid use is associated with a dose-dependent increase in the risk of fractures and other major trauma, overdose, falls, gastrointestinal pathology and addiction *[19]*. Episodes of major trauma increased by 84 for every 10,000 person-years of use of low-dose opioids (equivalent to <20mg morphine per day) and by 139/10,000 for doses equivalent to at least 50mg morphine per day. While the risk of dependence, addiction and overdose is generally well recognised, the potential for other important harms associated with opioid use, including fractures, endocrine dysfunction, and worsening of chronic pain (opioid-induced hyperalgesia), is frequently underestimated.

Opioid prescription is also associated with an increased risk of mortality. Treatment with opioids for chronic non-cancer pain is associated with a 58% increase in the risk of all-cause mortality compared with other analgesic therapies (HR 1.58, 95% CI 1.38 to 1.82), equivalent to 148 excess deaths per 10,000 person-years of treatment *[20]*.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**
Please find Supplementary Figures and Tables (including Forest Plots) **HERE**

Certainty of the Evidence Very Low

There is *very low certainty evidence* for the effect of opioid use compared with other analgesics (i.e. NSAIDs) or in addition to NSAIDs versus NSAIDs alone, for:

- participant-reported treatment success
- total withdrawals due to adverse events or inadequate analgesia
- withdrawals due to adverse events
- withdrawals due to inadequate analgesia
- number of participants reporting adverse events
- number of serious adverse events
- mean change in pain from baseline
- mean change in function from baseline.

Preference and values

Substantial variability is expected or uncertain

A 2018 systematic review of patient values and preferences regarding chronic non-cancer pain (CNCP) *[8]* included 6 studies involving patients with various forms of CNCP. While none of the included studies specifically recruited patients with axial spondyloarthritis, one included patients with other forms of musculoskeletal pain, including osteoarthritis and fibromyalgia. It is likely that the preferences and values of patients with various forms of CNCP are broadly applicable to people with spondyloarthritis pain.

Across the included studies, pain relief was consistently reported as being of high importance to patients. The most important adverse effects were nausea/vomiting and alteration of mental state. Other adverse effects, including risk of addiction, were of lesser importance.

Included studies that evaluated the trade-off between benefits and harms indicated that substantial pain relief (at least 2 points on a 10-point numerical scale) would be required for a net benefit in the presence of adverse effects (particularly nausea or vomiting).

No studies considered the risk of overdose or death, although these outcomes and deliberate misuse or diversion of prescription opioids are common concerns at a societal level. Similarly, while opioid prescribers also view CNCP as an important problem, they are more likely to report concerns about the risk of opioid misuse or addiction *[10]*.

Resources

Important issues, or potential issues not investigated

Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs or may have an impact on work.

The societal costs of chronic non-cancer pain are significant. Approximately 3 million Australian adults use prescription opioids *[13]*. The majority of these are people with non-cancer pain, although it is likely that opioid use for axial spondyloarthritis represents only a small fraction of these cases. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity. There was concern among some panellists that the societal costs of opioid therapy may be disproportionately high compared with other analgesic strategies in axial spondyloarthritis, and that this may therefore represent an important argument against the use of opioids in this setting.

Equity

Important issues, or potential issues not investigated

Socioeconomic factors are important determinants of chronic pain, opioid use and opioid-related adverse outcomes *[11][22]*. Variation in access to rheumatologists for people with inflammatory back pain or other features of axial spondyloarthritis may lead to delayed diagnosis and treatment in some settings, which may increase the risk of persistent pain throughout the disease course.

Access to comprehensive and multidisciplinary chronic pain management services varies within Australia. In particular, access may be limited for socially-disadvantaged people and those in regional and remote areas *[12]*. This may affect pain management strategies in general and, specifically, may alter the balance of potential benefits and harms of opioid analgesics.

Acceptability Important issues, or potential issues not investigated

It is likely that the option of short-term use of opioids guided by an explicit management plan in a shared decision-making framework would be acceptable to both patients and prescribers. Evidence from qualitative studies in patients with musculoskeletal disease suggests that while patients strongly value relief of pain, this is balanced by concerns about adverse effects (particularly nausea and vomiting) and that patients feel that opioids should be used with caution *[14]*. Given the potential net harms of opioids use at the population level, widespread use of opioids for axial spondyloarthritis pain may be less acceptable to policy-makers.

Feasibility Important issues, or potential issues not investigated

Opioids are generally a widely-available and feasible treatment option. In some settings, alternatives to opioids, particularly for chronic pain, including multidisciplinary and multimodal pain management services, may be difficult to access or implement. This may particularly be the case in rural or remote areas *[12]*, among socially-disadvantaged individuals, or in primary care settings where resources or access to multidisciplinary or specialist services are limited. In such cases the barriers to opioid avoidance or deprescribing may make a recommendation against opioid use difficult to implement without additional resources. The panel strongly supported the development of implementation initiatives that seek to facilitate either avoidance of opioid initiation or deprescribing in those already using opioids.

Rationale

The panel discussed at length the balance between the potential benefits and harms of opioids for axial spondyloarthritis pain. In particular, given that the only evidence regarding efficacy in this population was of very low certainty, the panel carefully considered the extent to which the balance of potential benefits and harms can be inferred from other data, including the large body of literature regarding the risks associated with prescription opioids. On balance, due to the lack of evidence regarding efficacy and the known risk of long-term harm associated with opioid use in the broader population of people with chronic non-cancer pain, the panel formed the consensus view that the known risks are likely to outweigh the potential benefits for axial spondyloarthritis.

As a result, the panel recommended against the routine use of opioids for axial spondyloarthritis pain. This recommendation differs slightly from the recommendation for rheumatoid arthritis pain which, while still a conditional recommendation against opioids, also recommends that "a brief course of a short-acting opioid may be considered for severe pain when other analgesic options have failed". The rheumatoid arthritis recommendation is based on low certainty evidence of short-term efficacy of opioids in a proportion of patients; no such evidence currently exists for patients with axial spondyloarthritis.

Importantly, this living recommendation has been made in the setting of very low certainty evidence, and therefore is susceptible to change if new evidence emerges.

The lack of evidence regarding benefits does not exclude the possibility that opioids may be beneficial in some patients with axial spondyloarthritis. There was considerable discussion within the panel regarding the relative lack of evidence regarding

opioids in this population, and the difficulty of generating a recommendation that appropriately acknowledges the known short- and long-term risks of opioid use while allowing for the possibility that there may be some circumstances in which (short-term) opioid therapy may be an appropriate choice within a shared decision-making framework, even without a precise estimate of the potential benefits and risks.

The panel acknowledged that there may be some situations in which the patient and doctor may elect to consider a short course of opioids. For example, if there is disabling pain due to untreated inflammation and while waiting for b/tsDMARDs to take effect and NSAIDs or other analgesic strategies have been ineffective or are contraindicated, consideration of a brief course of opioids may be warranted. It is likely that such situations would be uncommon in contemporary rheumatology practice. Any decision to use opioids in axial spondyloarthritis should take place within a clear shared decision-making framework that acknowledges the lack of specific data on short-term risks and benefits and the large body of literature regarding the potential risks of long-term opioid use.

The panel also noted that opioid use among patients with axial spondyloarthritis appears to be relatively prevalent which suggests that opioids are being used for longer durations or in place of other evidence-based therapies in many patients. The panel also noted that an important proportion of patients who initiate short-term opioid therapy for any indication will go on to become long-term users, therefore caution is required even when a brief course of opioids is intended, and mechanisms to prevent transition to chronic use should be established, particularly in patients with a chronic disease such as axial spondyloarthritis. Similarly, consideration should be given to deprescribing opioids in current users. The "Practical Info" section provides some further guidance for patients and practitioners who are considering a trial of opioids or who are currently using opioids.

The panel was also of the view that some attempt should be made to identify the phenotype of the pain in patients with inflammatory arthritis and persistent pain. In general, inflammatory pain is best treated with anti-inflammatory strategies (including NSAIDs and DMARDs). Pain due to joint damage or spinal ankylosis may very occasionally warrant a trial of opioids, although the risks of long-term use should be carefully considered in this setting. Pain that is thought to be related to activation of central mechanisms (i.e. nociplastic pain) is often associated with other clinical features including widespread tenderness, allodynia, sleep disturbance and cognitive clouding; in such cases the risks of opioids typically outweigh any potential benefits.

The panel also noted that there are some populations for whom the risks of opioids more clearly outweigh the potential benefits (e.g. the elderly, individuals with active mental illness, those with multiple comorbidities, and those with a history of substance misuse). The panel more strongly recommends against the use of opioids in such cases.

5.3 - Opioids for Pain in Psoriatic Arthritis

The cornerstone of pharmacologic treatment for psoriatic arthritis (PsA) is disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), which primarily control the inflammation and to some extent the pain associated with the inflammation. There are, however, multiple contributors to the genesis of pain in PsA in addition to inflammation, including joint damage or destruction and peripheral and central sensitisation, which may not be responsive to treatment with DMARDs and/or NSAIDs. Opioids may successfully control pain in psoriatic arthritis; however, the potential for adverse effects, particularly addiction and drug interactions, limit their regular use in this patient population.

Executive Summary - Opioids for pain management in adults with psoriatic arthritis

In people with psoriatic arthritis (PsA), we are uncertain whether opioid use is safe or effective as no studies addressing the question were identified.

Conditional recommendation against

New

Do not routinely use opioids for the treatment of pain in psoriatic arthritis.

Evidence up to date as at 23 November 2020

Practical Info

- Any decision regarding the use of opioids should be made within a shared decision-making framework following a clear discussion of potential benefits and harms, tailored to the individual's circumstances (including comorbidities and concomitant medications)
- In patients who are already using opioids, the lowest effective dose should be sought, and opportunities for reduction in dose or cessation should be considered at each visit
- In all patients for whom opioids are being considered or currently prescribed:
  - Consider age, other pharmacotherapy and important comorbidities (e.g., cognitive impairment, falls risk, active mental illness, history of drug or alcohol misuse) and avoid any opioid use in individuals at increased risk of harm from opioids
  - Actively enquire about the individual patient's prior or current experience with opioid analgesics (including effectiveness, adverse effects, and dose used), and current use of other centrally-acting drugs
  - Consider the pain phenotype: make sure inflammatory pain is adequately treated, and be alert for comorbid fibromyalgia or nociplastic pain (for which opioids are generally not recommended). Ensure that other treatable or reversible pathology (e.g., occult insufficiency fracture) has been adequately considered and investigated
- In patients for whom a trial of opioids is being considered:
  - Ensure that appropriate non-pharmacological therapies and other analgesic strategies have been optimised prior to consideration of opioid prescription
  - Before commencing treatment with opioids, the prescriber and patient should agree on the goals of therapy and the method for measuring outcomes
- If a decision is made to proceed with a trial of opioids, the following should be considered:
  - Commence at a low dose of a short-acting opioid
  - A written treatment plan should be agreed upon by the patient and prescriber, and this should be provided to other relevant parties (e.g., the GP)
  - Discuss the risks of driving a motor vehicle and operating heavy machinery during initiation and dose adjustment of opioids, and develop a plan to mitigate this risk
  - The primary prescriber and the dispensing pharmacy should also be identified in the written plan and all parties should be informed
  - Establish a clear plan for discontinuation of opioids if the treatment goals are not met

Evidence To Decision

Benefits and harms

Important harms

In people with psoriatic arthritis (PsA), we are uncertain whether opioid use is safe or effective as no studies addressing the question were identified.

There are few data regarding the prevalence of opioid use among people with psoriatic arthritis, however across all indications over 1.9 million Australians initiate treatment with opioids each year, the majority for non-cancer pain *[13]*. 2.6% of people who initiate opioids in Australia for non-cancer pain will go on to become persistent users over a 12-month period *[16]*. In a US emergency department setting, for every 48 patients given an initial opioid prescription, one will become a long-term opioid user *[23]*. Rheumatological conditions may be a risk factor for transition from first use to long-term opioid use for non-cancer pain *[17]*.

Use of low-potency or low-dose opioids is also associated with a risk of transition to high-dose therapy. Tolerance with

long-term use of opioids often leads to a requirement for dose escalation. Almost one percent of Australians who commence weak opioids may escalate to high-dose opioid therapy (equivalent to at least 90mg oral morphine per day) and approximately one in 13 will transition to a strong opioid during a 12-month period *[21]*. Older people are at increased risk of transition to higher doses or more potent opioids. Higher doses are associated with an increased risk of opioid-related morbidity and mortality.

Although there is little trial evidence regarding harms of opioids that is specific to psoriatic arthritis, data are available regarding harms in patients with chronic non-cancer pain from trials of medium-term use of opioids (2 weeks to 13 months) *[18]*: opioid use is associated with an increased risk of any adverse event (RR versus placebo 1.42, 95% CI 1.22, 1.66) and serious adverse events (RR 2.75, 95% CI 2.06, 3.67). Adverse effects that occurred at significantly increased rates in opioid users included nausea and vomiting, constipation, dizziness, drowsiness and fatigue, pruritus, hot flushes and sweating.

Evidence for opioid harms in the longer term comes from observational studies. Data from a study of almost 100,000 UK patients treated with opioids for musculoskeletal conditions and followed for a median of 3.4 years indicate that long-term opioid use is associated with a dose-dependent increase in the risk of fractures and other major trauma, overdose, falls, gastrointestinal pathology and addiction *[19]*. Episodes of major trauma increased by 84 for every 10,000 person-years of use of low-dose opioids (equivalent to <20mg morphine per day) and by 139/10,000 for doses equivalent to at least 50mg morphine per day. While the risk of dependence, addiction and overdose is generally well recognised, the potential for other important harms associated with opioid use, including fractures, endocrine dysfunction, and worsening of chronic pain (opioid-induced hyperalgesia), is frequently underestimated.

Opioid prescription is also associated with an increased risk of mortality. Treatment with opioids for chronic non-cancer pain is associated with a 58% increase in the risk of all-cause mortality compared with other analgesic therapies (HR 1.58, 95% CI 1.38 to 1.82), equivalent to 148 excess deaths per 10,000 person-years of treatment *[20]*.

Please find Evidence Tables & Systematic Search-related Criteria & Results **HERE**

Certainty of the Evidence Very Low

No studies addressing this question were identified.

Preference and values Substantial variability is expected or uncertain

A 2018 systematic review of patient values and preferences regarding chronic non-cancer pain *[8]* included 6 studies involving patients with various forms of chronic non-cancer pain (CNCP). While none of the included studies specifically recruited patients with psoriatic arthritis, one included patients with other forms of musculoskeletal pain, including osteoarthritis and fibromyalgia. It is likely that the preferences and values of patients with various forms of CNCP are broadly applicable to people with psoriatic arthritis pain.

Across the included studies, pain relief was consistently reported as being of high importance to patients. The most important adverse effects were nausea/vomiting and alteration of mental state. Other adverse effects, including risk of addiction, were of lesser importance.

Included studies that evaluated the trade-off between benefits and harms indicated that substantial pain relief (at least 2 points on a 10-point numerical scale) would be required for a net benefit in the presence of adverse effects (particularly nausea or vomiting).

No studies considered the risk of overdose or death, although these outcomes and deliberate misuse or diversion of prescription opioids are common concerns at a societal level. Similarly, while opioid prescribers also view CNCP as an important problem, they are more likely to report concerns about the risk of opioid misuse or addiction *[10]*.

Resources Important issues, or potential issues not investigated

Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs or may have an impact on work.

The societal costs of chronic non-cancer pain are significant. Approximately 3 million Australian adults use prescription opioids *[13]*. The majority of these are people with non-cancer pain, although it is likely that opioid use for psoriatic arthritis represents only a small fraction of these cases. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity. There was concern among some panellists that the societal costs of opioid therapy may be disproportionately high compared with other analgesic strategies in psoriatic arthritis, and that this may therefore represent an important argument against the use of opioids in this setting.

Equity Important issues, or potential issues not investigated

Socioeconomic factors are important determinants of chronic pain, opioid use and opioid-related adverse outcomes*[11] [22]*. Variation in access to rheumatologists for people with psoriatic arthritis may lead to delayed diagnosis and treatment in some settings, which may increase the risk of persistent pain throughout the disease course.

Access to comprehensive and multidisciplinary chronic pain management services varies within Australia. In particular, access may be limited for socially-disadvantaged people and those in regional and remote areas *[12]*. This may affect pain management strategies in general and, specifically, may alter the balance of potential benefits and harms of opioid analgesics.

Acceptability Important issues, or potential issues not investigated

It is likely that the option of short-term use of opioids guided by an explicit management plan in a shared decision-making framework would be acceptable to both patients and prescribers. Evidence from qualitative studies in patients with musculoskeletal disease suggests that while patients strongly value relief of pain, this is balanced by concerns about adverse effects (particularly nausea and vomiting) and that patients feel that opioids should be used with caution *[14]*. Given the potential net harms of opioids use at the population level, widespread use of opioids for psoriatic arthritis pain may be less acceptable to policy-makers.

Feasibility Important issues, or potential issues not investigated

Opioids are generally a widely-available and feasible treatment option. In some settings, alternatives to opioids, particularly for chronic pain, including multidisciplinary and multimodal pain management services, may be difficult to access or implement. This may particularly be the case in rural or remote areas *[12]*, among socially-disadvantaged individuals, or in primary care settings where resources or access to multidisciplinary or specialist services are limited. In such cases the barriers to opioid avoidance or deprescribing may make a recommendation against opioid use difficult to implement without additional resources. The panel strongly supported the development of implementation initiatives that seek to facilitate either avoidance of opioid initiation or deprescribing in those already using opioids.

Rationale

The panel discussed at length the balance between the potential benefits and harms of opioids for psoriatic arthritis pain. In particular, given the absence of randomised controlled trials in this population, the panel carefully considered the extent to which the balance of potential benefits and harms can be inferred from other data, including the large body of literature regarding the risks associated with prescription opioids. On balance, due to the lack of evidence regarding efficacy and the known risk of long-term harm associated with opioid use in the broader population of people with chronic non-cancer pain, the panel formed the consensus view that the known risks are likely to outweigh the potential benefits for psoriatic arthritis.

As a result, the panel recommended against the routine use of opioids for psoriatic arthritis pain. This recommendation differs slightly from the recommendation for rheumatoid arthritis pain which, while still a conditional recommendation against opioids, also recommends that "a brief course of a short-acting opioid may be considered for severe pain when other analgesic options have failed". The rheumatoid arthritis recommendation is based on low certainty evidence of short-term efficacy of opioids in a proportion of patients; no such evidence currently exists for patients with psoriatic arthritis.

Importantly, this living recommendation has been made in the absence of evidence from randomised controlled trials in people with psoriatic arthritis, and therefore is susceptible to change if new evidence emerges.

The lack of evidence regarding benefits does not exclude the possibility that opioids may be beneficial in some patients with psoriatic arthritis. There was considerable discussion within the panel about the lack of evidence regarding opioids in this population, and the difficulty of generating a recommendation that appropriately acknowledges the known short- and long-term risks of opioid use while allowing for the possibility that there may be some circumstances in which (short-term) opioid therapy may be an appropriate choice within a shared decision-making framework, even without a precise estimate of the potential benefits and risks.

The panel acknowledged that there may be some situations in which the patient and doctor may elect to consider a short course of opioids. For example, if there is disabling pain due to untreated inflammation and while waiting for DMARDs to take effect and NSAIDs or other analgesic strategies have been ineffective or are contraindicated, consideration of a brief course of opioids may be warranted. It is likely that such situations would be uncommon in contemporary rheumatology practice. Any decision to use opioids in psoriatic arthritis should take place within a clear shared decision-making framework that acknowledges the lack of specific data on short-term risks and benefits and the large body of literature regarding the potential risks of long-term opioid use.

The panel also noted that an important proportion of patients who initiate short-term opioid therapy for any indication will go on to become long-term users, therefore caution is required even when a brief course of opioids is intended, and mechanisms to prevent transition to chronic use should be established, particularly in patients with a chronic disease such as psoriatic arthritis. Similarly, consideration should be given to deprescribing opioids in current users. The "Practical Info" section provides some further guidance for patients and practitioners who are considering a trial of opioids or who are currently using opioids.

The panel was also of the view that some attempt should be made to identify the phenotype of the pain in patients with inflammatory arthritis and persistent pain. In general, inflammatory pain is best treated with anti-inflammatory strategies (including NSAIDs and DMARDs). Pain due to joint damage may very occasionally warrant a trial of opioids, although the risks of long-term use should be carefully considered in this setting. Pain that is thought to be related to activation of central mechanisms (i.e. nociplastic pain) is often associated with other clinical features including widespread tenderness, allodynia, sleep disturbance and cognitive clouding; in such cases the risks of opioids typically outweigh any potential benefits.

The panel also noted that there are some populations for whom the risks of opioids more clearly outweigh the potential benefits (e.g. the elderly, individuals with active mental illness, those with multiple comorbidities, and those with a history of substance misuse). The panel more strongly recommends against the use of opioids in such cases.

6 - Methods and Processes - Evidence Review

Search Methods

Each clinical question was broken down into specific participants (P), interventions (I), comparisons (C), outcomes (O) of interest. Search strategies were based on the specific PICO elements of each question. We used a hierarchical approach when identifying the evidence, first seeking evidence from systematic reviews. In our initial searches for systematic review evidence, we did not impose any date or language restrictions. Any updated searches for systematic reviews will be conducted from the date of the last search. We intentionally designed our searches not to include terms for the 'intervention'. This allowed us to identify trials of all current and future approved treatments, necessary for our living evidence process. Screening of all search results and extraction of data from eligible systematic reviews and primary studies was carried out independently by two researchers. Any disagreements were resolved by discussion or by a third researcher.

1. We searched for existing Cochrane reviews in the Cochrane Database of Systematic Reviews (CDSR) (via Ovid or via The Cochrane Library)
2. If we found a recent (published in the last 2 years) Cochrane Review that wholly addressed our question we extracted the data from the Cochrane Review into the Key Findings of the Evidence Summary, Summary of Findings, and evidence tables. Using the search strategy outlined in the CR, we searched forward from the date of the last search to identify any new, potentially eligible primary studies. Data from newly identified eligible primary studies were incorporated into the Key Findings of the Evidence Summary, Summary of Findings and evidence tables
3. In the absence of recent Cochrane reviews, or if a Cochrane Review only partially addressed our question, we searched for non-Cochrane systematic reviews (via Ovid Medline and Ovid Embase), using the search filters at https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/.
4. We also searched reference lists of relevant current clinical guidelines for additional eligible systematic reviews and/or randomised controlled trials.
5. To assess the degree of overlap between eligible systematic reviews and to identify the most recent, comprehensive systematic reviews, we drew up a matrix of all of the primary studies included in each eligible systematic review. The matrix of primary studies also ensured that we extracted data from all of the eligible primary studies addressing the evidence summary question.
6. We appraised the validity of all eligible non-Cochrane reviews using the CASP systematic review checklist: https://casp-uk.net/casp-tools-checklists/. The relevant criteria were: the review addressed a focused question (usually presented in PICO format); the review authors looked for the most appropriate studies and study designs (i.e., studies addressed the review's focused question, and RCTs for intervention reviews); all important, relevant studies were included (e.g. by searching multiple databases, with no language restrictions, both unpublished and published literature, and included and excluded studies listed explicitly); the review authors assessed the validity of included studies using appropriate tools (e.g. risk of bias assessment and no scores); if the results of the review were pooled statistically, it was appropriate to do so, and results of individual studies were presented (in enough detail that a reader could replicate the analysis (i.e., for each treatment group in each included trial, summary estimated were reported – means, standard deviation, number of participants for continuous outcomes and number of people with the event and number of participants for dichotomous outcomes). If we judged that the results of the review were valid, or met the five criteria listed above we judged the systematic review as having high validity, or little bias and we extracted and incorporated the data from the non-Cochrane systematic review into the Key Findings, Summary of Findings and evidence tables of the Evidence Summary. If we judged the results of the review to be biased or of limited validity, we stated this in the evidence table and interpreted the results with appropriate caution.
7. In the absence of Cochrane Reviews or high validity non-Cochrane systematic reviews, we searched for randomised controlled trials that meet the PICO criteria of the Evidence Summary. The search was conducted in Ovid MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid) combining standard Cochrane terms for the specific population/disease in question (for example 'rheumatoid arthritis', axial spondyloarthritis" with terms for the intervention of interest (for example, down-titration) using search strategies approved by Cochrane and reported in a living systematic review currently underway *[28]*. The Cochrane highly sensitive search strategy for identifying RCTs was applied to the Ovid Medline search (Higgins 2011: Chapter 6.4.11.1)
8. To identify new trials that may have been published after the search date of existing systematic reviews we conducted a forward search in Ovid MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid). The start date of the forward search would either be determined by the end search date of the most recent, well-conducted systematic review or by the end search date of the systematic review used to inform the most recent clinical guidelines relevant to our question. Data from newly identified eligible studies was extracted and incorporated into the Key Findings, Summary of Findings and evidence tables of the Evidence Summary.
9. To identify any potentially eligible ongoing or planned studies, we also searched clinical trial registries, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/), using search terms for the specific population/disease in question (for example 'rheumatoid arthritis').

Methods for Evidence Synthesis (please see 'Appendices' for Evidence Tables and Supplementary Information for each PICO)

1. For each clinical question, we collected data from systematic reviews, and where applicable, randomised controlled trials, including descriptive information and outcome data.
2. Descriptive information was summarised in evidence tables - this included a description of the methods, population, intervention, comparator and outcomes included in each review and, if applicable, trial.
3. We summarised these key characteristics in comparative summary tables, grouped by clinical question.

Data Synthesis

1. Once we identified all eligible systematic reviews, we set up a matrix of all of the primary studies included in each of the eligible systematic reviews.
2. We then added any additional primary studies identified in the forward search to the matrix. In this way we made sure that we incorporated the data from all eligible primary studies into our analyses and summary of findings tables.
3. If no additional primary studies are identified, we report meta-analyses from existing high-quality systematic reviews.
4. For new trials that have been published after the search date of existing reviews, we will extract the characteristics and outcome data, assess risk of bias, and synthesise the outcomes data from the trials with data from the systematic review using Review Manager (RevMan 2014).
5. For each outcome in each clinical question, we will assess the certainty of the synthesised body of evidence underpinning the outcome using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation). GRADE assesses the body of the evidence according to five factors:
   - the risk of bias
   - the precision of the effect estimates
   - the consistency of the individual study results
   - how directly the evidence answers the question of interest
   - the risk of publication or reporting biases.

Evidence Summaries

We report evidence summaries for each of the research questions that include:
- a description of all the included systematic reviews and, where relevant, randomised trials
- the synthesised findings, including meta-analyses and narrative syntheses – we updated effect estimates of outcomes with data from trials, and took into account the entire body of evidence (systematic reviews and RCT's) when assessing the certainty of evidence
- the GRADE assessment
- any outcomes pre-specified as important but for which no evidence was found
- any other identified gaps in the evidence.

Recommendation Development

To guide the development of a recommendation and to help determine the strength of that recommendation, the GRADE methodology that includes the following factors is followed at each guideline development meeting:
- The balance between benefits and harms.
- Confidence in the estimates of effect (certainty of evidence).
- Confidence in values and preferences and their variability (clinical and consumer preferences).
- Resource use (cost and implementation considerations).
- Equity
- Acceptability
- Feasibility

For full details of how GRADE is used for developing clinical recommendations, refer to the GRADE handbook, available at: https://gdt.gradepro.org/app/handbook/handbook.html.

6.1 - Clinical Questions (PICO's)

Preliminary topics and clinical research questions were developed by ANZMUSC and Cochrane Musculoskeletal. Priority questions were validated through a process of stakeholder consultation that involved surveying ARA membership to identify questions of highest importance.

Clinical questions were developed using the framework of population, intervention, comparator and outcome (PICO).

Dose Reduction and Discontinuation Strategies:

PICO 1: In adults with rheumatoid arthritis and low disease activity, what are the benefits and harms of down-titration (dose reduction, disease activity-guided dose reduction or discontinuation) of biological or tsDMARDs on disease activity and remission rates, function, safety, and radiographic damage compared no down-titration of bDMARDs or tsDMARDs?

N.B. PICO 1 was split into 2 sub-questions based on the method of down-titration of DMARD: dose reduction (PICO 1a; included fixed dose reduction and disease activity-guided dose reduction – through either a reduction of dose, keeping the frequency of medication intake the same, or a reduction in the frequency of the medication intake) and discontinuation (PICO 1b).

PICO 2: In adults with psoriatic arthritis and low disease activity, what are the benefits and harms of down-titration (dose reduction, disease activity-guided dose reduction or discontinuation) of biological or tsDMARDs on disease activity and remission rates, function, safety and radiographic damage compared with no down-titration of bDMARDs or tsDMARDs?

N.B. PICO 2 was split into 2 sub-questions based on the method of down-titration of DMARD: dose reduction (PICO 2a; included fixed dose reduction and disease activity-guided dose reduction – through either a reduction of dose, keeping the frequency of medication intake the same, or a reduction in the frequency of the medication intake) and discontinuation (PICO 2b).

PICO 3: In adults with axial spondyloarthritis and low disease activity, what are the benefits and harms of down-titration (dose reduction, disease activity-guided dose reduction or discontinuation) of biological or targeted synthetic DMARDs on disease activity and remission rates, function, safety and radiographic damage compared with no down-titration of bDMARDs or tsDMARDs?

N.B. PICO 3 was split into 2 sub-questions based on the method of down-titration of DMARD: dose reduction (PICO 3a; included fixed dose reduction and disease activity-guided dose reduction – through either a reduction of dose, keeping the frequency of medication intake the same, or a reduction in the frequency of the medication intake) and discontinuation (PICO 3b).

Opioids for Pain Management:

PICO 4: In people with rheumatoid arthritis, is it effective and safe to use opioid analgesics for disease-related pain management?

PICO 5: In people with axial spondyloarthritis, is it effective and safe to use opioid analgesics for disease-related pain management?

PICO 6: In people with psoriatic arthritis, is it effective and safe to use opioid analgesics for disease-related pain management?

7 - Guideline Panel - Membership and Terms of Reference

Members of the Living Guideline Development Panel *(as at 3 September, 2020)*

Name	Affiliation	Area of Expertise
Rachelle Buchbinder (Chair)	Monash University (Vic)	Rheumatology
Simon Bell	Monash University (Vic)	Pharmacy
Rachel Black	Royal Adelaide Hospital; Queen Elizabeth Hospital / SA Health (SA)	Rheumatology
Linda Bradbury	Gold Coast University Hospital (Qld)	Rheumatology Nursing
Chris Fong	Eastern Health (Vic)	Rheumatology
Pravin Hissaria	SA Pathology; Royal Adelaide Hospital (SA)	Clinical Immunology
Ben Horgan	University of Western Australia (WA)	Health Advocacy / Consumer Representation
Lyn March	Northern Sydney Local health District / NSW Health (NSW)	Rheumatology
Suzie Edward May	Giving Voice (WA)	Health Advocacy / Consumer Representation
Peter Nash	Private Practice; University of Queensland (Qld)	Rheumatology
Sean O'Neill	University of Sydney; Royal North Shore Hospital (NSW)	Rheumatology
Huai Leng (Jess) Pisaniello	PhD Candidate, University of Manchester (UK); Basil Hetzel Institute (SA)	Rheumatology
Philip Robinson	Metro North Hospital and Health Service (Qld)	Rheumatology
Amee Sonigra	Princess Alexandra Hospital; Logan Hospital / Queensland Health (Qld)	Rheumatology
Lyndal Trevena	University of Sydney (NSW)	General Practitioner
Glen Whittaker	La Trobe University (Vic)	Podiatry
Sam Whittle	Queen Elizabeth Hospital / SA Health (SA)	Rheumatology
Anita Wluka	Monash University (Vic)	Rheumatology

A copy of the Terms of Reference for membership of the Living Guideline Development Panel can be found **HERE**

8 - Conflict of Interests

The policy for management of conflicts of interest, the conflict of interest 'risk matrix', and the template used for collecting the declarations of interest will be published on our website: mskguidelines.org

Conflict of Interest Policy - please click **HERE**

Conflict of Interest Assessment 'Risk Matrix' - please click **HERE**

Declaration of Interests Template - please click **HERE**

9 - Glossary, Abbreviations and Acronyms

Table of Acronyms

bDMARD	biologic DMARD
CI	Confidence Interval
csDMARD	Conventional synthetic DMARD
DAS28	Disease Activity Score in 28 joints
DMARD	Disease-modifying anti-rheumatic drug
MD	Mean difference
mSvdH	modified Sharp van der Heijde
NNTB	Number needed to treat for an additional beneficial outcome
NNTH	Number needed to treat for an additioanl harmful outcome
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomised controlled trial
RR	Risk ratio
TNF	Tumour necrosis factor
tsDMARD	Targeted synthetic DMARD

10 - Appendices - Figures, Tables and Supplementary Information

Evidence Tables and Systematic Search-related Criteria and Results

Dose Reduction & Discontinuation Strategies:
PICO 1: Dose Reduction or Discontinuation of b/ts DMARDs for RA - please click **HERE**
PICO 2: Dose Reduction or Discontinuation of bDMARDs for AxSpA - please click **HERE**
PICO 3: Dose Reduction or Discontinuation of b/ts DMARDs for PsA - please click **HERE**

Opioids for Pain Management:
PICO 4: Opioids for Pain in RA - please click **HERE**
PICO 5: Opioids for Pain in AxSpA - please click **HERE**
PICO 6: Opioids for Pain in PsA - please click **HERE**

Supplementary Figures and Tables (includes Forest plots)

Dose Reduction & Discontinuation Strategies:
PICO 1: Dose Reduction or Discontinuation of b/ts DMARDs for RA - please click **HERE**
PICO 2: Dose Reduction or Discontinuation of bDMARDs for AxSpA - please click **HERE**
PICO 3: Dose Reduction or Discontinuation of b/ts DMARDs for PsA - please click **HERE**

Opioids for Pain Management:
PICO 4: Opioids for Pain in RA - please click **HERE**
PICO 5: Opioids for Pain in AxSpA - please click **HERE**
PICO 6: Opioids for Pain in PsA - N/A

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