



## PRACTICE

## GUIDELINES

# Diagnosis and management of rheumatoid arthritis in adults: summary of updated NICE guidance

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## What you need to know

- Aim for remission or low disease activity as the target for treatment
- To begin treatment, use one disease modifying anti-rheumatic drug (DMARD) and increase the dose, before adding another DMARD, if needed
- Consider short term bridging therapy with glucocorticoids when starting a new conventional synthetic DMARD
- Consider oral non-steroidal anti-inflammatory drugs (NSAIDs) for uncontrolled pain or stiffness
- Offer the lowest effective dose of NSAID for the shortest possible time, with a proton pump inhibitor and review risk factors for adverse events regularly

Rheumatoid arthritis is a chronic, disabling autoimmune disease characterised by synovitis of small and large joints causing swelling, stiffness, pain, and progressive joint destruction. About 1% of the UK population have rheumatoid arthritis, and approximately 15% of these people have severe disease. It affects roughly three times as many women as men. People tend to develop rheumatoid arthritis between 40 and 60 years of age, although it can arise at any age. The early signs of rheumatoid arthritis are often encountered in primary care, where people present with joint pain and swelling. Fast and accurate referral to rheumatology services is important to achieve early remission and prevent or reduce disability.<sup>1</sup>

This article summarises the update of the National Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of rheumatoid arthritis in adults.<sup>2</sup> The management of rheumatoid arthritis has evolved in the nine years since the previous NICE guideline on rheumatoid arthritis was published, with greater emphasis on a treat-to-target strategy rather than specific drug regimens,<sup>3</sup> and debate about the merit of initiating treatment with combination drug therapy.<sup>4</sup> Technologies such as ultrasound have been increasingly used for diagnosis and monitoring of synovitis where it is unclear

from clinical examination.<sup>5</sup> These aspects of management were investigated by the Guideline Committee, and recommendations have been updated using new evidence, leading to changes to the recommendations for treatment with conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), glucocorticoids for bridging treatment, and choice of treatment for symptom control. Several aspects of the guideline have remained unchanged since its publication in 2009 and update in 2015 and will not be covered here, including the multidisciplinary team, non-pharmacological management, and timing and referral for surgery.

Management of rheumatoid arthritis depends on a multidisciplinary approach and shared care between secondary and primary care. The guideline is relevant to non-specialist health professionals who are involved in the initial assessment of rheumatoid arthritis symptoms and ongoing care of people diagnosed with rheumatoid arthritis. The focus of this summary is the new or updated recommendations relevant to non-specialists, including investigations in primary care, referral to specialist care, and the treatment options for short term symptom control in periods of increased joint inflammation leading to pain and stiffness. Full details of evidence ([www.nice.org.uk/guidance/ng100/evidence](http://www.nice.org.uk/guidance/ng100/evidence)), the recommendations not summarised here ([www.nice.org.uk/guidance/ng100](http://www.nice.org.uk/guidance/ng100)), and the NICE pathway (<https://pathways.nice.org.uk/pathways/rheumatoid-arthritis>) are available via the NICE website.

**What's new in this guidance**

- It is now recommended that investigations for anti-CCP antibodies and radiographic erosions are undertaken at initial diagnosis to inform prognosis as they are associated with a poorer outcome
- Updated recommendations on conventional synthetic DMARDs include recommending initial treatment with monotherapy and then following a step-up approach to treatment if there is an inadequate response
- Updated recommendations emphasise a treat-to-target strategy for management of rheumatoid arthritis with a target of remission or low disease activity
- Updated guidance on pharmacological symptom control with a recommendation for short term bridging treatment with corticosteroids when initiating a new DMARD and updated guidance on which analgesic to use

**Recommendations**

NICE guidelines are based on systematic reviews of the best available evidence. The quality ranged from very low to high. There was explicit consideration of cost effectiveness across all clinical questions within the guideline. All recommendations were made through combining the clinical evidence found with the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in *italic* in square brackets.

**When to refer from primary care**

- Refer for specialist opinion any adult with suspected persistent synovitis of undetermined cause. Refer urgently (even if the person shows a normal acute phase response or tests negative for rheumatoid factor) if any of the following apply:
  - The small joints of the hands or feet are affected
  - More than one joint is affected
  - There has been a delay of three months or longer between onset of symptoms and seeking medical advice. (Updated recommendation 2018)

*[Based on the experience and opinion of the Guideline Committee (GC)]*

**Initial investigations to consider**

If the following investigations are ordered in primary care, do not delay referral for specialist opinion by awaiting results (see recommendation on referral for specialist treatment). Tests such as that for anti-cyclic citrullinated peptide (CCP) antibodies are likely to be interpreted in a specialist clinic, but they could be requested by primary care at referral so that the result is available for the patient at their specialist review.

**Investigations for diagnosis**

- Offer to carry out a blood test for rheumatoid factor in adults with suspected rheumatoid arthritis who are found to have synovitis on clinical examination.
- Consider measuring anti-CCP antibodies in adults with suspected rheumatoid arthritis if they are negative for rheumatoid factor and there is a need to inform decision making about starting combination therapy. (Updated recommendation 2018)
- X ray the hands and feet early in the course of the disease in adults with suspected rheumatoid arthritis and persistent synovitis in these joints.

*[Based on the experience and opinion of the GC]*

**Investigations to inform prognosis**

- If anti-CCP antibodies are present or there are erosions visible on x ray:
  - Advise the person that they have an increased risk of radiological progression but not necessarily an increased risk of poor function
  - Emphasise the importance of monitoring their condition and seeking rapid access to specialist care if disease worsens or they have a flare. (Updated recommendation 2018)

*[Based on seven prospective cohort studies with very low to moderate quality evidence and the experience and opinion of the GC]*

**Treat-to-target strategy**

Disease activity can be measured by various tools, such as the DAS28, which is based on a clinical assessment of the number of tender joints, swollen joints, global pain, and a biomarker for inflammation (either erythrocyte sedimentation rate (ESR) or C reactive protein (CRP)). Definitions of remission or low disease activity will vary according to the measure used. For example, with the DAS28, remission is a score of <2.6 and low disease activity is  $\leq 3.2$ .

- Treat active rheumatoid arthritis in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). (Updated recommendation 2018)
- Consider making the target remission rather than low disease activity for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on x ray at baseline assessment). (Updated recommendation 2018)
- In adults with active rheumatoid arthritis, measure CRP and disease activity (using a composite score such as DAS28) monthly until the target of remission or low disease activity is achieved. (Updated recommendation 2018)

*[Based on five randomised controlled trials with very low to moderate quality evidence and the experience and opinion of the GC]*

**Initial pharmacological management after a new diagnosis**

Initial pharmacological management is led by specialists. These recommendations are included for information as they are fundamental to ongoing management. Conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) are differentiated from targeted synthetic DMARDs (such as Janus kinase inhibitors) and biologic DMARDs, which were not within the scope of this guideline.

- For adults with newly diagnosed active rheumatoid arthritis:
  - Offer first line treatment with conventional synthetic DMARD monotherapy using oral methotrexate, leflunomide, or sulfasalazine as soon as possible and ideally within three months of onset of persistent symptoms
  - Consider hydroxychloroquine for first line treatment as an alternative for mild or palindromic disease
  - Escalate dose as tolerated.

*[Based on 21 randomised controlled trials with very low to high quality evidence and the experience and opinion of the GC]*

- Offer additional conventional synthetic DMARDs (oral methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. (Updated recommendation 2018) *[Based on four randomised controlled trials with very low to moderate quality evidence and the experience and opinion of the GC]*
- Consider short term bridging treatment with glucocorticoids (oral, intramuscular, or intra-articular) when starting a new conventional synthetic DMARD. *[Based on five randomised controlled trials with very low to low quality evidence and the experience and opinion of the GC]*
- For adults who have maintained the treatment target (remission or low disease activity) for at least a year without glucocorticoids, consider cautiously reducing drug doses or stopping drugs in a step-down strategy. Return promptly to the previous DMARD regimen if the treatment target is no longer met. *[Based on moderate to very low quality evidence from one randomised controlled trial and the experience and opinion of the GC].*

## Symptom control

To be considered in both primary and secondary care. Although control of synovitis with conventional synthetic DMARDs and corticosteroids improves symptoms, some patients require additional analgesia. The committee found very limited evidence for paracetamol, opioids, and tricyclic antidepressants for symptom control in rheumatoid arthritis, so the recommendation for “other analgesics” was removed from the update of this guideline and replaced with a recommendation for NSAIDs alone.

- Consider oral non-steroidal anti-inflammatory drugs (NSAIDs), including traditional NSAIDs and cox II selective inhibitors, when control of pain or stiffness is inadequate. Take account of potential gastrointestinal, liver, and cardio-renal toxicity, and the person’s risk factors, including age and pregnancy. (Updated recommendation 2018) *[Based on 48 randomised controlled trials with very low to moderate quality evidence and the experience and opinion of the GC]*
- When treating symptoms of rheumatoid arthritis with oral NSAIDs:
  - Offer the lowest effective dose for the shortest possible time
  - Offer a proton pump inhibitor (PPI)
  - Review risk factors for adverse events regularly.*[Based on the experience and opinion of the GC]*

## Monitoring

- Ensure that all adults with rheumatoid arthritis have:
  - Rapid access to specialist care for flares
  - Information about when and how to access specialist care
  - Ongoing drug monitoring.*[Based on the experience and opinion of the GC]*
- Consider a review appointment for six months after achieving treatment target (remission or low disease

activity) to ensure that the target has been maintained. *[Based on the experience and opinion of the GC]*

- Do not use ultrasonography for routine monitoring of disease activity in adults with rheumatoid arthritis. *[Based on evidence from one randomised controlled trial and five prospective cohort studies with very low to moderate quality evidence]*

## Implementation

People with rheumatoid arthritis who are currently receiving treatment should not change or stop any treatment as a result of this guideline without consultation with their rheumatologist.

Some rheumatologists who have not adopted a treat-to-target strategy may need a change in practice. This will require revision of local protocols in order that step-up protocols may be implemented rather than initial combination therapy. The recommendation to especially target patients with poor prognostic markers will need to be included in new protocols. In addition, there may be challenges to health professionals in primary and secondary care when explaining risk factors for progression to some patients. Ultrasound scanning of joints is increasing, and the recommendation not to use ultrasound routinely may need to be reflected in the revision in local protocols.

Some people with rheumatoid arthritis take analgesics routinely without necessarily addressing the symptomatic benefit from treatment. The concept of NSAIDs being the only symptom control medication recommended in the new guideline could be challenging to some people, but the merits of analgesia will need to be addressed on an individual basis.

## Future research

The current evidence suggests that all people with rheumatoid arthritis should be offered the same management strategy. However, it is unclear whether people with baseline factors indicating risk of poor prognosis, identified in this update, should follow a different management strategy and whether such a strategy would improve radiographic and functional outcomes in this group. A high priority research recommendation has been included to answer this question.

Although the evidence did not support using ultrasonography for routine monitoring of rheumatoid arthritis, the Guideline Committee thought ultrasound could be useful for monitoring when clinical examination is inconclusive or is inconsistent with other signs of disease activity (such as pain or markers of inflammation). The committee decided to make a research recommendation to inform future guidance about using ultrasound in these situations.

A further high priority research recommendation was made to investigate the effectiveness of subcutaneous methotrexate compared with oral methotrexate. Oral methotrexate is known to be an effective DMARD treatment, but subcutaneous methotrexate is thought to have fewer side effects and might be similarly effective. Further research is required to confirm this.

**Guidelines into practice**

- Do laboratory investigations alone inform the need for referral to a specialist? What other factors might influence this decision?
- How often do you document the number of tender and swollen joints or inflammatory markers when monitoring someone with rheumatoid arthritis?
- How might you interpret the presence of anti-CCP antibodies or radiographic evidence of erosions in a person with rheumatoid arthritis, and how might this affect their management?

**How patients were involved in the creation of this article**

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

**Further information on the guidance****Methods**

This guidance was developed by the National Guideline Centre (NGC) in accordance with NICE guideline development methods ([www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf](http://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf)).

A multidisciplinary guideline committee of health professionals and researchers as well as lay members was recruited by the National Guideline Centre (NGC). The NGC undertook evidence reviews and the committee combined this evidence with their experience and expertise in rheumatoid arthritis to formulate the guideline recommendations. This was undertaken with a view to the quality of the evidence which was assessed in the NGC reviews using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for intervention reviews and QUIPS checklist for prognostic reviews and Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) for diagnostic reviews. Health economic evidence was sought relating to the key clinical issues being addressed in the guideline and systematic reviews of the published economic literature were undertaken.

The scope and draft of the guideline went through public consultation in which stakeholder organisations were invited to comment on both the scope and the draft. The committee took all comments into consideration in the final version of the guideline.

All versions of the guideline are available from the NICE website ([www.nice.org.uk/ng100](http://www.nice.org.uk/ng100)).

Members of the guideline committee were: Stephen Ward, chair, Brighton and Sussex University Hospitals NHS Trust; Frank McKenna, clinical lead, Trafford

Hospitals, Manchester University NHS Foundation Trust; Ailsa Bosworth, lay member; Victoria Chamberlain, Trafford Hospitals, Manchester University NHS Foundation Trust; Jennie Jones, lay member; Bruce Kirkham, Guy's & St Thomas' NHS Foundation Trust; Anupama Nandagudi, Basildon and Thurrock University Hospital NHS Trust; Benjamin Parker, Manchester Royal Infirmary, Manchester University NHS Foundation Trust; Heidi Siddle, Leeds Teaching Hospitals NHS Trust and University of Leeds; Louise Warburton, Telford Musculoskeletal Service; Ann Bevan, GP (retired); Hilary McKee, Northern Health and Social Care Trust; Amanda Isaac, topic expert member, Guy's & St Thomas' NHS Foundation Trust.

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Competing interests: We declare the following interests based on NICE's policy on conflicts of interests (available at [www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/code-of-practice-for-declaring-and-managing-conflicts-of-interest.pdf](http://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/code-of-practice-for-declaring-and-managing-conflicts-of-interest.pdf)): FM has received honoraria from Sanofi for attending an advisory board relating to a new biosimilar for rheumatoid arthritis, and Janssen for speaking at a satellite symposia relating to depression in rheumatoid arthritis.

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