Rheumatoid arthritis in adults: management

NICE guideline

Draft for consultation, January 2018

This guideline covers the diagnosis and management of rheumatoid arthritis in adults.

Who is it for?

- Healthcare professionals
- Commissioners and providers of services
- People with rheumatoid arthritis, their families and carers.

This guideline will update and replace NICE guideline CG79 (published February 2009).

We have reviewed the evidence and updated or added new recommendations on investigations following diagnosis, treat-to-target strategy, initial pharmacological management, symptom control and monitoring. You are invited to comment on the new and updated recommendations. These are marked as **[2018].**

You are also invited to comment on recommendations that NICE proposes to delete from the 2009 guideline.

We have not updated recommendations shaded in grey, and cannot accept comments on them. In some cases, we have made minor wording changes for clarification.

See update information for a full explanation of what is being updated.

This version of the guideline contains:

- the draft recommendations
- rationale and impact sections that explain why the committee made the 2018 recommendations and how they might affect practice.
- the guideline context
- recommendations for research.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the evidence reviews, the scope, and details of the committee and any declarations of interest.

Full details of the evidence and the committee's discussion on the 2018 recommendations is in the evidence reviews. Evidence for the 2009 recommendations is in the full version of the 2009 guideline

1

2

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Referral, diagnosis and investigations

Referral from primary care

1.1.1 Refer for specialist opinion any adult with suspected synovitis of undetermined cause. Refer urgently (even with a normal acute-phase response or negative 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 3 months or longer between onset of symptoms and seeking medical advice. **[2009, amended 2018]**

Investigations

These recommendations on investigations are for specialist care.

Investigations for diagnosis

1.1.2 Offer to carry out a blood test for rheumatoid factor in adults with suspected rheumatoid arthritis (RA) who are found to have synovitis on clinical examination. **[2009]**

1.1.3 Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in adults with suspected RA if they are negative for rheumatoid factor~~, and~~

~~there is a need to inform decision-making about starting combination therapy~~. **[2009, amended 2018]**

1.1.4 X-ray the hands and feet ~~early in the course of the disease~~in adults with suspected RA and persistent synovitis~~in these joints~~. **[2009, amended 2018]**

Investigations following diagnosis

1.1.5 As soon as possible after establishing a diagnosis of RA:

- measure anti-CCP antibodies, unless already measured to inform diagnosis
- X-ray the hands and feet to establish whether erosions are present, unless X-rays were performed to inform diagnosis
- measure functional ability using, for example, the Health Assessment Questionnaire (HAQ), to provide a baseline for assessing the functional response to treatment. **[2018]**

1.1.6 If anti-CCP antibodies are present or there are erosions on X-ray:

- tell the person that they have an increased risk of radiological progression but not necessarily an increased risk of poor function, and
- emphasise the importance of monitoring their condition, and seeking rapid access to specialist care if disease worsens or they have a flare. **[2018]**

To find out why the committee made the [2018] recommendations on investigations following diagnosis and how they might affect practice, see rationale and impact.

1.2 Treat-to-target strategy

1.2.1 Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). **[2018]**

1.2.2 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 baselines assessment). **[2018]**

1.2.3 In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly until the target of remission or low disease activity is achieved. **[2018]**

To find out why the committee made the [2018] recommendations on treat-to-target strategy and how they might affect practice, see rationale and impact.

1.3 Communication and education

1.3.1 Explain the risks and benefits of treatment options to adults with RA in ways that can be easily understood. Throughout the course of their disease, offer them the opportunity to talk about and agree all aspects of their care, and respect the decisions they make. **[2009]**

1.3.2 Offer verbal and written information to adults with RA to:

- improve their understanding of the condition and its management, and
- counter any misconceptions they may have. **[2009]**

1.3.3 Adults with RA who wish to know more about their disease and its management should be offered the opportunity to take part in existing educational activities, including self-management programmes. **[2009]**

1.4 Initial pharmacological management

Conventional DMARDs

1.4.1 For adults with newly diagnosed active RA:

- Offer first-line treatment with conventional disease-modifying anti-rheumatic drug (cDMARD) monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.

- Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.
- Escalate dose as tolerated. **[2018]**

1.4.2 Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD. **[2018]**

> To find out why the committee made the [2018] recommendation on short-term bridging treatment with glucocorticoids and how they might affect practice, see rationale and impact.

1.4.3 Offer additional cDMARDs (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. **[2018]**

> To find out why the committee made the [2018] recommendations on cDMARDs and how they might affect practice, see rationale and impact.

1.5 Further pharmacological management

Biological and targeted synthetic DMARDs

NICE has technology appraisal guidance on biological and targeted synthetic synthetic DMARDs for RA. For full details, see our web page on arthritis.

The recommendations below are from NICE technology appraisal guidance 72. The 2009 guideline committee reviewed the evidence on anakinra and incorporated the recommendations into the guideline. The technology appraisal was then withdrawn.

1.5.1 On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of RA, except in the context of a controlled, long-term clinical study. **[2009]**

1.5.2 Patients currently receiving anakinra for RA may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. **[2009]**

1.5.3 Do not offer the combination of tumour necrosis factor-α (TNF-α) inhibitor therapy and anakinra for RA. **[2009]**

Glucocorticoids

1.5.4 Offer short-term treatment with glucocorticoids for managing flares in adults with recent-onset or established disease to rapidly decrease inflammation. **[2009]**

1.5.5 In adults with established RA, only continue long-term treatment with glucocorticoids when:

- the long-term complications of glucocorticoid therapy have been fully discussed, and
- all other treatment options (including biological and targeted synthetic DMARDs) have been offered. **[2009]**

1.6 Symptom control

1.6.1 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. **[2018]**

1.6.2 When treating symptoms of RA with oral NSAIDs:

- offer the lowest effective dose for the shortest possible time,
- offer a proton pump inhibitor (PPI), and
- review risk factors for adverse eventsregularly. **[2018]**

1.6.3 If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID

(with a PPI) if pain relief is ineffective or insufficient. **[2009, amended 2018]**

To find out why the committee made the [2018] recommendations on symptom control and how they might affect practice, see rationale and impact.

1.7 The multidisciplinary team

1.7.1 Adults with RA should have ongoing access to a multidisciplinary team. This should provide the opportunity for periodic assessments (see 1.9.1, 1.9.2 and 1.9.3) of the effect of the disease on their lives (such as pain, fatigue, everyday activities, mobility, ability to work or take part in social or leisure activities, quality of life, mood, impact on sexual relationships) and help to manage the condition. **[2009]**

1.7.2 Adults with RA should have access to a named member of the multidisciplinary team (for example, the specialist nurse) who is responsible for coordinating their care. **[2009]**

1.8 Non-pharmacological management

Physiotherapy

1.8.1 Adults with RA should have access to specialist physiotherapy, with periodic review (see 1.9.1, 1.9.2 and 1.9.3), to:

- improve general fitness and encourage regular exercise
- learn exercises for enhancing joint flexibility, muscle strength and managing other functional impairments
- learn about the short-term pain relief provided by methods such as transcutaneous electrical nerve stimulators [TENS] and wax baths. **[2009]**

Occupational therapy

1.8.2 Adults with RA should have access to specialist occupational therapy, with periodic review (see 1.9.1, 1.9.2 and 1.9.3), if they have:

- difficulties with any of their everyday activities, or
- problems with hand function. **[2009]**

Hand exercise programmes

1.8.3 Consider a tailored strengthening and stretching hand exercise programme for adults with RA with pain and dysfunction of the hands or wrists if:

- they are not on a drug regimen for RA, or
- they have been on a stable drug regimen for RA for at least 3 months. **[2015]**

1.8.4 The tailored hand exercise programme for adults with RA should be delivered by a practitioner with training and skills in this area. **[2015]**

Podiatry

1.8.5 All adults with RA and foot problems should have access to a podiatrist for assessment and periodic review of their foot health needs (see 1.9.1, 1.9.2 and 1.9.3). **[2009]**

1.8.6 Functional insoles and therapeutic footwear should be available for all adults with RA if indicated. **[2009]**

Psychological interventions

1.8.7 Offer psychological interventions (for example, relaxation, stress management and cognitive coping skills[1]) to help adults with RA adjust to living with their condition. **[2009]**

NICE has a guideline on depression in adults with a chronic physical health problem.

[1] Such as managing negative thinking.

Diet and complementary therapies

1.8.8 Inform adults with RA who wish to experiment with their diet that there is no strong evidence that their arthritis will benefit. However, they could be encouraged to follow the principles of a Mediterranean diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils). **[2009]**

1.8.9 Inform adults with RA who wish to try complementary therapies that although some may provide short-term symptomatic benefit, there is little or no evidence for their long-term efficacy. **[2009]**

1.8.10 If an adult with RA decides to try complementary therapies, advise them:

- these approaches should not replace conventional treatment
- this should not prejudice the attitudes of members of the multidisciplinary team, or affect the care offered. **[2009]**

1.9 Monitoring

1.9.1 Ensure that all adults with RA have:

- rapid access to specialist care for worsening disease or flares
- information about when and how to access specialist care, and
- ongoing drug monitoring. **[2018]**

1.9.2 Consider a review appointment to take place 6 months after achieving treatment target (remission or low disease activity) to ensure that the target has been maintained. **[2018]**

1.9.3 Offer all adults with RA, including those who have achieved the treatment target, an annual review to:

- assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
- check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression

- assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes
- organise appropriate cross referral within the multidisciplinary team
- assess the need for referral for surgery (see section 1.10)
- assess the effect the disease is having on a person's life. **[2009, amended 2018]**

1.9.4 For adults who have maintained the treatment target (remission or low disease activity) for at least 1 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. **[2018]**

1.9.5 Do not use ultrasound for routine monitoring of disease activity in adults with RA. **[2018]**

To find out why the committee made the [2018] recommendations on monitoring and how they might affect practice, see rationale and impact.

1.10 Timing and referral for surgery

1.10.1 Offer to refer adults with RA for an early specialist surgical opinion if any of the following do not respond to optimal non-surgical management:

- persistent pain due to joint damage or other identifiable soft tissue cause
- worsening joint function
- progressive deformity
- persistent localised synovitis. **[2009]**

1.10.2 Offer to refer adults with any of the following complications for a specialist surgical opinion before damage or deformity becomes irreversible:

- imminent or actual tendon rupture
- nerve compression (for example, carpal tunnel syndrome)
- stress fracture. **[2009]**

1.10.3 When surgery is offered to adults with RA, explain that the main[2] expected benefits are:

- pain relief,
- improvement, or prevention of further deterioration, of joint function, and
- prevention of deformity. **[2009]**

1.10.4 Offer urgent combined medical and surgical management to adults with RA who have suspected or proven septic arthritis (especially in a prosthetic joint). **[2009]**

1.10.5 If an adult with RA develops any symptoms or signs that suggest cervical myelopathy[3]:

- request an urgent MRI scan, and
- refer for a specialist surgical opinion. **[2009]**

1.10.6 Do not let concerns about the long-term durability of prosthetic joints influence decisions to offer joint replacements to younger adults with RA. **[2009]**

Terms used in this guideline

Bridging treatment

Glucocorticoids used for a short period of time when a person is starting a new DMARD, intended to improve symptoms while waiting for the new DMARD to take effect (which can take 2 to 3 months).

Conventional disease-modifying anti-rheumatic drug (cDMARD)

Conventional disease-modifying anti-rheumatic drugs are synthetic drugs that modify disease rather than just alleviating symptoms. They include methotrexate, sulfasalazine, leflunomide and hydroxychloroquine, but do not include biological DMARDs and targeted synthetic DMARDs.

[2] Cosmetic improvements should not be the dominant concern.
[3] For example, paraesthesia, weakness, unsteadiness, reduced power, extensor plantars.

Palindromic

Palindromic rheumatism is an inflammatory arthritis that causes attacks of joint pain and swelling similar to RA. Between attacks the joints return to normal.

Rapid access to specialist care

Direct access to specialist care without the need of a GP referral.

Step-up strategy

Additional DMARDs are added to DMARD monotherapy when disease is not adequately controlled.

Step-down strategy

During treatment with 2 or more DMARDs, tapering and stopping at least 1 drug once disease is adequately controlled.

Synovitis

Soft tissue joint swelling.

Treat-to-target

A treat-to-target strategy is a strategy that defines a treatment target (such as remission or low disease activity) and applies tight control (for example, monthly visits and respective treatment adjustment) to reach this target. The treatment strategy often follows a protocol for treatment adaptations depending on the disease activity level and degree of response to treatment.

Recommendations for research

The guideline committee has made the following high-priority recommendations for research**.**

1 Analgesics

What is the clinical and cost effectiveness of analgesic drugs other than non-steroidal anti-inflammatory drugs (NSAIDs) in adults with rheumatoid arthritis (RA) whose pain or stiffness control is not adequate?

Why this is important

Analgesics (including NSAIDs, paracetamol, opioids and compound analgesics) are sometimes used with disease-modifying treatments to relieve pain and stiffness when symptom control is inadequate. Current practice regarding the choice of analgesic in RA is variable. The evidence is limited for many of the analgesic drugs other than NSAIDs, and their relative effectiveness is unknown. Further research in this area may inform future guidance on the use of analgesic drugs other than NSAIDs for controlling symptoms.

2 Short-term bridging treatment with glucocorticoids

What is the clinical and cost effectiveness of short-term bridging treatment with glucocorticoids for adults with RA starting a new disease-modifying anti-rheumatic drug (DMARD), including the most effective dosing strategy and mode of administration?

Why this is important

All DMARDs have a slow onset of action. In some cases, response may not be seen for 2 to 3 months. In contrast, glucocorticoids have an immediate effect on joint pain and swelling. In clinical practice, several different regimens are prescribed to ‘bridge’ the time between the initial prescription of DMARDs and the clinical response. However, good quality evidence from randomised controlled trials (RCTs) demonstrating the effectiveness of glucocorticoids as bridging treatment is limited and inconclusive. Further research is needed to inform recommendations for practice regarding whether bridging treatment with steroids should be used until the new DMARD begins to take effect.

The optimal dosing strategy and mode of administration for bridging glucocorticoids also needs to be established. Although the anti-inflammatory response is dose dependent, side effects of glucocorticoids vary according to both the dose and the duration of treatment.

3 Ultrasound in monitoring

What is the clinical and cost effectiveness of using ultrasound to monitor disease in adults with RA when clinical examination is inconclusive or inconsistent with other signs of disease activity?

Why this is important

RA is a chronic inflammatory condition that needs regular review to enable adjustments in management to achieve a target of remission or low disease activity.

Although ultrasound is able to show subclinical inflammation or erosions in some people in clinical remission, evidence from RCTs does not support using ultrasound for routine monitoring. However, ultrasound may be useful for assessing disease activity in some people with RA; specifically, when clinical examination is inconclusive or is inconsistent with other signs of disease activity (for example, pain or markers of inflammation). There is no reliable evidence on the added value of ultrasound as part of a monitoring strategy in these subgroups.

In addition, when there is inconsistency between clinical examination and disease activity, it may be unclear if the person has subclinical inflammatory synovitis or more of a widespread pain syndrome, which is not inflammatory. These need very different treatments, so it is important to define them accurately.

4 Ultrasound in diagnosis

What is the clinical and cost effectiveness of using ultrasound in addition to clinical assessment when there is uncertainty about the diagnosis in adults with suspected RA?

Why this is important

Early diagnosis of RA is essential to reduce the impact of the disease on multiple systems in the body. The course of RA and the initial presentation can be highly variable; most people with RA have definite synovitis on clinical assessment, but sometimes this is not obvious, leading to uncertainty about the diagnosis. Ultrasound is a non-invasive and relatively inexpensive imaging modality that can detect subclinical synovitis and early erosive disease. It might help determine an early diagnosis of RA when the diagnosis would otherwise be uncertain. Early diagnosis enables earlier treatment providing an opportunity to improve the longer term outcomes for people with RA. The use of ultrasound may also allow healthcare professionals to be more confident about ruling out a diagnosis of RA.

5 Management of poor prognosis

What is the clinical and cost effectiveness of managing RA with a poor prognosis (identified as presence of anti-CCP antibodies or evidence of erosions on X-ray at diagnosis) with a different strategy from that used for standard management of RA?

Why this is important

Current recommendations suggest all people with RA should be offered the same management; however clinical experience suggests that the condition responds less well in some people and some suffer progressive radiographic damage and impaired function despite standard management. Several factors have been identified in the literature that, if present and identified early in the course of the disease, may predict a poor prognosis (greater radiographic progression). These include anti-CCP antibody positivity and the presence of radiographic erosions at baseline. At present it is unclear whether people with poor prognostic markers should have different management early in the disease, and whether this would improve radiographic and functional (HAQ) outcomes in this group.

6 Subcutaneous methotrexate

What is the clinical and cost effectiveness of subcutaneous methotrexate compared with oral methotrexate for adults with early onset RA starting a new DMARD?

Why this is important

Methotrexate is an important drug in the treatment of RA. Subcutaneous administration is an alternative option for people who have side effects with oral treatment. Evidence on the effectiveness of subcutaneous methotrexate is lacking, but its effects may be superior, due to increased bioavailability, and side effects fewer than with oral drugs. Research on subcutaneous methotrexate will inform future guideline recommendations.

Rationale and impact

Investigations following diagnosis

Why the committee made recommendations 1.1.5 and 1.1.6

Evidence showed that anti-cyclic citrullinated peptide (CCP) antibodies and radiographic damage at baseline were both important prognostic factors for subsequent radiographic progression. Anti-CCP antibodies are usually measured and X-rays often taken as part of diagnosis. When this has not been done, the committee agreed that the tests should be performed as soon as possible. The results will inform discussions with the patient about how their rheumatoid arthritis (RA) might progress and reinforce the importance of active monitoring and rapidly seeking specialist care if the disease worsens.

There was limited evidence on poor function, as measured by the Health Assessment Questionnaire (HAQ), as a prognostic factor. However, the committee agreed that functional ability (measured, for example, by HAQ) should be determined at diagnosis to provide a baseline for assessing response to treatment at the annual review.

Evidence suggests that all people with RA should be offered the same management strategy; however, in the committee's experience some people may respond less well and have more progressive radiographic damage and impaired function. Because the evidence was limited as to whether people with poor prognostic markers should follow a different management strategy to improve radiographic and functional (HAQ) outcomes, the committee agreed to make a research recommendation.

How the recommendations might affect practice

Anti-CCP antibodies are usually measured so there should be no change in current practice. X-raying the hands and feet and measuring functional ability at baseline reflects current best practice, but not everyone with RA currently has these investigations. There may be an increase in the number of X-rays, especially in units without early inflammatory arthritis clinics, but this is unlikely to have a substantial resource impact.

Measuring functional ability at baseline will involve a change of practice for some providers, but the cost is low and so it this is not expected to have a substantial resource impact.

Full details of the evidence and the committee's discussion are in evidence review B: Risk factors.

Investigations (ultrasound in diagnosis)

Why the committee made the research recommendation on ultrasound in diagnosis

Ultrasound is not used widely in diagnosing RA, but use is increasing and depends on the clinic and the rheumatologist. Evidence was inconsistent and too limited for the committee to make any recommendation for or against its use in diagnosis. The committee noted that the studies generally included only people with clinically definite synovitis and agreed that ultrasound may be more useful when there is uncertainty about the diagnosis after clinical assessment. They decided to make a research recommendation to inform future guidance on who (if anyone) should have ultrasound to aid diagnosis.

Full details of the evidence and the committee's discussion are in evidence review A: Ultrasound for diagnosis.

Treat-to-target strategy

Why the committee made recommendations 1.2.1 to 1.2.3

Strategy and treatment target

Evidence showed that a treat-to-target strategy was more effective than usual care for managing RA and improved outcomes at no additional cost. The committee agreed that this approach was more likely to achieve rapid and sustained disease control .

No evidence was identified to indicate whether a target of remission or low disease activity was more effective. However, the committee agreed that remission (for example, a DAS28 score of less than 2.6) is the most appropriate target for most people, but for some who are unable to achieve remission despite a treat-to-target approach with appropriate escalation, low disease activity (for example, a DAS28 score of less than 3.2) is acceptable. It was agreed that for those identified as being at risk of poor prognosis, a target of remission may be more appropriate.

Frequency of monitoring for active disease

No studies were identified that compared different frequencies of monitoring specifically in people with active disease. The committee noted that the 2009 guideline recommended monthly monitoring and that this was used in some of the studies of a treat-to-target strategy. The committee agreed that monthly monitoring of C-reactive protein (CRP) and disease activity was most appropriate for active disease. This allows dose escalation of disease-modifying anti-rheumatic drugs (DMARDs), checking the need for short-term bridging treatment with glucocorticoids and whether people are tolerating the drug regimen, assessing side effects, providing support and encouraging adherence.

People at risk of poor outcomes

There was no evidence that people with a poor prognosis should have different management in terms of the treatment target or the frequency of monitoring. However, in the committee's experience RA often responds less well to standard management in this group. The committee agreed that the recommendations on treat-to-target with monthly monitoring should ensure that people with a poor

prognosis receive effective treatment, but they decided to make a research recommendation to inform future guidance for managing RA in this group.

How the recommendations might affect practice

A treat-to-target strategy is current best practice in most NHS settings. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis indicated that healthcare professionals set a treatment target for about 90% of their patients. Although the 2018 recommendation specifies a target of remission or low disease activity, rather than a disease level previously agreed with the person, the committee agreed that these are the targets commonly used and so this is unlikely to involve a significant change in practice.

Monthly monitoring was recommended in the 2009 guideline, but the committee acknowledged that many clinics do not monitor active disease this often. A regional survey (Tugnet 2013) reported that about two-thirds of people with RA received monthly CRP monitoring but only a quarter had monthly monitoring of disease activity (with about 40% in dedicated early arthritis clinics) until disease control was achieved. The committee were unsure whether these rates reflected practice across England and noted that practice had improved since the survey was conducted in 2011. However, the committee agreed that monthly monitoring would likely involve a change in practice in some clinics.

Full details of the evidence and the committee's discussion are in evidence review C: Treat-to target.

DMARDs

Why the committee made recommendations 1.4.1, and 1.4.3

First-line treatment

Evidence showed that starting treatment with more than 1 conventional DMARD (cDMARD) was no more effective than starting with a single cDMARD. The committee agreed that cDMARD monotherapy might have fewer side effects and recommended cDMARD monotherapy as first-line treatment. This differed from the 2009 guideline which recommended combination therapy. The difference is largely a

result of inclusion of different evidence and a different approach to analysing that evidence.

Many of the studies included in the 2009 guideline used cDMARDs that are no longer commonly used in UK practice (for example, ciclosporin), and these studies were excluded from the evidence for the 2018 update. In addition, the 2018 update included new evidence published after the 2009 guideline. Further, a different approach to analysing the evidence was taken, with the 2018 update aiming to identify the most effective cDMARD strategy (monotherapy, sequential monotherapy, step-up therapy, step-down therapy or parallel combination therapy) as well as which cDMARD should be used. The 2009 guideline compared treatment strategies only, regardless of the particular cDMARDs, and combined evidence according to treatment strategy.

The evidence included in the 2018 update was therefore different to that included in 2009 and supported cDMARD monotherapy as first-line treatment.

Evidence from randomised controlled trials in people who had never had a DMARD showed no consistent differences in the effectiveness of methotrexate, leflunomide and sulfasalazine as monotherapies. The drugs also had similar costs. The committee agreed that any of these drugs can be used as first-line treatment.

Hydroxychloroquine was less effective, but fewer people stopped treatment because of side effects. The committee agreed that hydroxychloroquine could be considered for people with mild or palindromic disease.

People at risk of poor outcomes

Evidence for different first-line treatment in people with a poor prognosis was limited so the committee decided not to make a separate recommendation for this group. They agreed that the recommendation for dose increases and treating to target (with the aim of keeping disease activity low) should ensure adequate treatment for these people. Given the limited evidence in this area, the committee also decided that the possible benefit of managing RA with a poor prognosis with a different strategy was a priority for future research.

Further treatment

Evidence supported adding another cDMARD when needed (step-up strategy) rather than replacing the cDMARD with another (sequential monotherapy). The committee acknowledged that more side effects were possible with a step-up strategy, but in their experience these could be managed by drug monitoring and were outweighed by the clinical benefit of combination treatment when monotherapy was inadequate. A published cost analysis supported a step-up approach rather than sequential monotherapy.

Subcutaneous methotrexate

No evidence was found for subcutaneous methotrexate, but the committee agreed that the effects may be superior and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the committee was not able to recommend this without evidence of clinical benefit and cost effectiveness relative to oral cDMARDs. The committee decided to make a research recommendation to inform future guidance.

How the recommendations might affect practice

The 2009 guideline recommended a combination of cDMARDs (including methotrexate and at least 1 other cDMARD) for newly diagnosed RA and emphasised the importance of starting effective cDMARD therapy as soon as possible.

The 2009 recommendation to start with combination therapy was not widely adopted. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that only 46% of people with RA received combination cDMARDs at any time. Currently there is variation in practice regarding the choice of cDMARD(s) and treatment strategy, with many healthcare professionals preferring to start with monotherapy and only use combination therapy when response is inadequate.

The 2018 recommendations to start with monotherapy and add drugs when the response is inadequate are unlikely to have a substantial impact on practice or resources, as they align with the current approach taken by many healthcare professionals. However, the recommendations should result in a more consistent

treatment strategy and reduce the number of people prescribed combination therapy on diagnosis.

The 2009 guideline recommended methotrexate as one of the first drugs used in combination therapy. The 2018 recommendations do not specify which cDMARD should be used at any stage of treatment. Again, this will be unlikely to have a significant impact on practice, and methotrexate is likely to remain one of the most commonly prescribed drugs.

The recommendations on dose escalation and reduction have not changed substantially from the 2009 guideline and reflect current clinical practice. The committee clarified that dose reduction and the use of a step-down strategy should only be considered after a person has maintained the treatment target for at least 1 year without the use of glucocorticoids.

Full details of the evidence and the committee's discussion are in evidence review F: DMARDs.

Short-term bridging treatment with glucocorticoids

Why the committee made recommendation 1.4.3

Evidence from randomised controlled trials on the use of short-term bridging treatment with glucocorticoids to relieve symptoms while people are waiting for a new DMARD to take effect was limited. There was some evidence that fewer people withdrew from the studies due to inefficacy or adverse events when they were taking glucocorticoids, although there was no evidence that glucocorticoids were effective in terms of disease activity score, quality of life or function, as studies did not report these outcomes. In the committee's experience people with active arthritis may benefit from the anti-inflammatory effects of glucocorticoids. However, for others with less active disease this additional treatment may not be needed. The committee agreed that short-term glucocorticoids could be considered on a case-by-case basis.

Because of the lack of good quality evidence, the committee decided to make a research recommendation to determine the effectiveness of short-term glucocorticoids for adults taking a new DMARD, including the most effective regimen.

How the recommendations might affect practice

Most healthcare professionals offer short-term bridging treatment with glucocorticoids to adults starting a new DMARD. They can continue to offer this but the recommendation encourages them to consider whether this additional treatment is always needed. Therefore this is unlikely to result in additional spending for the NHS.

Full details of the evidence and the committee's discussion are in evidence review H: Glucocorticoids.

Symptom control

Why the committee made recommendations 1.6.1 and 1.6.2

Evidence suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may offer a small benefit in relieving symptoms for adults with RA (including pain and stiffness). The committee agreed that this was likely to outweigh the increase in gastrointestinal adverse events associated with NSAIDs. To minimise adverse events, the committee agreed that NSAIDs should be used at the lowest doses and for the shortest possible time, with a proton pump inhibitor, and that risk factors for adverse events should be reviewed regularly. The recommendations for analgesic treatment in this guideline replace those in the 2009 guideline.

There was limited evidence on paracetamol, opioids and tricyclic antidepressants and no evidence for nefopam, gabapentinoids or selective serotonin reuptake inhibitor (SSRI) and SSNRI antidepressants. The committee acknowledged that the 2009 guideline had recommended analgesics other than NSAIDs for pain control. However, the 2009 guideline indicated that the evidence on analgesia other than NSAIDs was 'sparse'. No further evidence on these drugs was identified since the publication of the 2009 guideline. The committee for the 2018 guideline decided to make a research recommendation rather than a practice recommendation on non-NSAID analgesics.

How the recommendations might affect practice

Current practice regarding the choice of analgesic is variable, with paracetamol, compound analgesics and NSAIDs all commonly used to control symptoms. Choice

of analgesic tends to be based on individual effectiveness as well as the person's risk profile, tolerance, and side effects. In particular, there are some groups of people for whom NSAIDs are unsuitable because of contraindications, comorbidities or tolerability, and other people who are currently benefiting from analgesic drugs other than NSAIDs. The current approach is likely to continue but there may be an increase in prescribing of NSAIDs instead of other analgesic drugs for people with newly diagnosed RA.

Full details of the evidence and the committee's discussion are in evidence review G: Analgesics.

Monitoring

Why the committee made recommendations 1.9.1, 1.9.2, 1.9.4 and 1.9.5

Frequency of monitoring when treatment target has been achieved

No evidence was identified on monitoring frequency once the treatment target has been achieved. However, the committee agreed that once people with RA had achieved the treatment target, and this was sustained at a 6-month follow-up appointment, there was no need for additional routine appointments to be scheduled other than the annual reivew. All people with RA should have an annual review.

In people with established RA (RA for at least 2 years), the evidence suggested that patient-initiated rapid access and scheduled medical review every 3 to 6 months were similarly effective. The committee agreed that all adults with RA should have rapid access to specialist care for worsening disease or disease flares, and ongoing drug monitoring.

Ultrasound in monitoring

Randomised controlled evidence did not support using ultrasound for routine monitoring of RA. However, in the committee's experience ultrasound can be useful for monitoring when clinical examination is inconclusive or is inconsistent with other signs of disease activity (for example, pain or markers of inflammation). The committee decided to make a research recommendation to inform future guidance about using ultrasound in these situations.

How the recommendations might affect practice

The frequency of monitoring and review appointments for people who have reached the treatment target vary around the country, with some people being seen more often than needed and others not receiving adequate follow-up. The 2018 recommendations are likely to reduce unwarranted variation.

Most people with RA currently have rapid access to specialist care when they have a flare. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that 92% of people had access to urgent advice, with 97% of providers running a telephone advice line. Therefore the recommendation will not affect current practice.

Use and availability of ultrasound varies widely across the country and even between healthcare professionals in the same department. Some healthcare professionals use it routinely whereas others use it on a case-by-case basis. The recommendation should reduce the overall use of ultrasound while still allowing its use for selected subgroups.

Full details of the evidence and the committee's discussion are in evidence review E: Frequency of monitoring.

Putting this guideline into practice

[This section will be finalised after consultation]

NICE has produced tools and resources [link to tools and resources tab] to help you put this guideline into practice.

[Optional paragraph if issues raised] Some issues were highlighted that might need specific thought when implementing the recommendations. These were raised during the development of this guideline. They are:

- [add any issues specific to guideline here]
- [Use 'Bullet left 1 last' style for the final item in this list.]

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

[Clinical topics only] Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. **Raise awareness** through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.

2. **Identify a lead** with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.

3. **Carry out a baseline assessment** against the recommendations to find out whether there are gaps in current service provision.

4. **Think about what data you need to measure improvement** and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.

5. **Develop an action plan**, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.

6. **For very big changes** include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.

7. **Implement the action plan** with oversight from the lead and the project group. Big projects may also need project management support.

8. **Review and monitor** how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See our into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Context

Rheumatoid arthritis (RA) is an inflammatory disease largely affecting synovial joints. It typically affects the small joints of the hands and the feet, and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and so can affect the whole body, including the heart, lungs and eyes.

The incidence of the condition is low, with around 1.5 men and 3.6 women developing RA per 10,000 people per year. The overall occurrence of RA is 2 to 4 times greater in women than men. The peak age of incidence in the UK for both genders is the 70s, but people of all ages can develop the disease.

Drug management aims to relieve symptoms, as pain relief is the priority for people with RA, and to modify the disease process. Disease modification slows or stops radiological progression, which is closely correlated with progressive functional impairment.

RA can result in a wide range of complications for people with the disease, their carers, the NHS and society in general. The economic impact of this disease includes:

- direct costs to the NHS and associated healthcare support services
- indirect costs to the economy, including the effects of early mortality and lost productivity
- the personal impact of RA and subsequent complications for people with RA and their families.

Approximately one-third of people stop work because of the disease within 2 years of onset, and this increases thereafter. Clearly this disease is costly to the UK economy and to individuals.

More information

[The following sentence is for post-consultation versions only – editor to update hyperlink with guideline number]You can also see this guideline in the NICE pathway on [pathway title]. [Note: this should link to the specific topic pathway, not to the overarching one.]

To find out what NICE has said on topics related to this guideline, see our web page on [developer to add and link topic page title or titles; editors can advise if needed].

[The following sentence is for post-consultation versions only – editor to update hyperlink with guideline number]

For full details of the evidence and the committee's discussions, see the evidence reviews. [link to evidence tab]You can also find information about how the guideline was developed, [link to documents tab] including details of the

committee.

Update information

This guideline is an update of NICE guideline 79 (published February 2009) and will replace it.

New recommendations have been added on investigations following diagnosis, treat-to-target strategy, initial pharmacological management, symptom control and monitoring.

Recommendations are marked as **[2018]** if the recommendation is new or the evidence has been reviewed.

NICE proposes to delete some recommendations from the 2009 guideline, because either the evidence has been reviewed and the recommendations have been updated, or NICE has updated other relevant guidance and has replaced the original recommendations. Recommendations that have been deleted or changed sets out these recommendations and includes details of replacement recommendations. Where there is no replacement recommendation, an explanation for the proposed deletion is given.

Where recommendations are shaded in grey and end **[2009]**, the evidence has not been reviewed since the original guideline.

Where recommendations are shaded in grey and end **[2009, amended 2018]**, the evidence has not been reviewed but changes have been made to the recommendation. These may be:

- changes to the meaning of the recommendation (for example, because of equalities duties or a change in the availability of medicines, or incorporated guidance has been updated)
- editorial changes to the original wording to clarify the action to be taken.

These changes are marked with yellow shading, and explanations of the reasons for the changes are given in 'Recommendations that have been deleted or changed' for information.

See also the original NICE guideline and supporting documents.

Recommendations that have been deleted or changed

Recommendations to be deleted

Recommendation in 2009 guideline	Comment
In people with recent-onset active RA, measure CRP and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA. [2009] (1.5.1.2)	Replaced by: Treat active RA in adults with the aim of achieving a target of remission or low disease activity (1.2.1)
Measure CRP and key components of disease activity (using a composite score such as DAS28) regularly in people with RA to inform decision-making about: - increasing treatment to control disease - cautiously decreasing treatment when disease is controlled. [2009] (1.5.1.1)	Replaced by: In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly until the target of remission or low disease activity is achieved. (1.2.2)

In people with newly diagnosed active RA, offer a combination of DMARDs (including methotrexate) and at least one other DMARD, plus short-term glugogorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms (1.4.1.1) In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate[2], start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. (1.4.1.4)	Replaced by: For adults with newly diagnosed active RA: - Offer first-line treatment with conventional disease-modifying anti-rheumatic drug (cDMARD) monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms. - Escalate dose as tolerated (1.4.1) For adults with newly diagnosed mild or palindromic disease, consider hydroxychloroquine for first-line treatment as an alternative to monotherapy with oral methotrexate, leflunomide or sulfasalazine (1.4.2) Offer additional cDMARDs (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. (1.4.4)
Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed RA if they are not already receiving glucocorticoids as part of DMARD combination therapy. (1.4.1.2)	Replaced by: Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD. (1.4.3)
In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. (1.4.1.3) In people with established RA whose disease is stable, cautiously reduce dosages of disease-modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. (1.4.1.5)	Replaced by: For adults who have maintained the treatment target (remission or low disease activity) for at least 1 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. (1.10.7)

When introducing new drugs to improve disease control into the treatment regimen of a person with established RA, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. (1.4.1.6)	
In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. (1.4.1.7)	Replaced by: Ensure that all adults with RA have: - rapid access to specialist care for worsening disease or flares - information about when and how to access specialist care, and - ongoing drug monitoring. (1.9.1) Consider a review appointment to take place 6 months after achieving treatment target (remission or low disease activity) to ensure that the target has been maintained. (1.9.2)
Offer analgesics (for example, paracetamol, codeine or compound analgesics) to people with RA whose pain control is not adequate, to potentially reduce their need for long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2) inhibitors. (1.4.4.1) All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. (1.4.4.4)	Replaced by: Consider oral non-steroidal anti-inflammatory drugs (NSAIDs), including 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. (1.6.1)
Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. (1.4.4.2) When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a	Replaced by: When treating symptoms of RA with oral NSAIDs: - offer the lowest effective dose for the shortest possible time, and - review risk factors and the need for gastroprotective treatment regularly. (1.6.2)

COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost. (1.4.4.3)	
If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen. (1.4.4.6)	Deleted as new recommendations to follow a 'treat-to-target' strategy mean that this should apply throughout management when symptom control is not adequate and therefore this specific recommendation is no longer required.
Offer people with satisfactorily controlled established RA review appointments at a frequency and location suitable to their needs. In addition, make sure they: - have access to additional visits for disease flares, - know when and how to get rapid access to specialist care, and - have ongoing drug monitoring. (1.5.1.3)	Replaced by: Ensure that all adults with RA have: - rapid access to specialist care for worsening disease or flares - information about when and how to access specialist care, and - ongoing drug monitoring. (1.9.1)
In people with recent-onset active RA, measure CRP and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA. [2009] (1.5.1.2)	Replaced by: Treat active RA in adults with the aim of achieving a target of remission or low disease activity (treat-to-target). (1.2.1) In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly until the target of remission or low disease activity is achieved. (1.2.2)

1

2 **Amended recommendation wording (change to meaning)**

Recommendation in 2009 guideline	Recommendation in current guideline	Reason for change
Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently 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 3 months or longer between onset of	Refer for specialist opinion any adult with suspected synovitis of undetermined cause. Refer urgently (even with a normal acute-phase response or negative 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	Recommendations 1.1.1.1 and 1.1.1.2 from 2009 have been merged to clarify the intension and reduce any ambiguity regarding when to refer urgently.

symptoms and seeking medical advice. (1.1.1.1) Refer urgently any person with suspected persistent synovitis of undetermined cause, even if their blood tests show a normal acute-phase response or negative rheumatoid factor. (1.1.1.2)	3 months or longer between onset of symptoms and seeking medical advice. (1.1.1)	
Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in people with suspected RA if: - they are negative for rheumatoid factor, and - there is a need to inform decision-making about starting combination therapy. (1.1.2.2)	Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in adults with suspected RA if they are negative for rheumatoid factor. (1.1.3)	Combination therapy is no longer recommended as the first line treatement option, therefore this recommendation has been edited for consistency with the updated DMARD recommendations.
X-ray the hands and feet early in the course of the disease in people with persistent synovitis in these joints. (1.1.2.3)	X-ray the hands and feet in adults with suspected RA and persistent synovitis. (1.1.4)	This now falls under a sub-heading of 'investigations for diagnosis'. It has been updated to clarify that this applies to adults with suspected RA as there is a separate recommendation for those with diagnosed RA.
If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient. (1.4.4.5)	If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient. (1.6.3)	Edited to reflect that aspirin is no longer used as an analgesic, and non-NSAID analgesics are no longer recommended within the guidance, therefore other treatments for RA should be considered instead of NSAIDs.
Offer people with RA an annual review to: - assess disease activity and damage, and measure functional ability (using, for example, the Health	Offer all adults with RA, including those who have achieved the treatment target, an annual review to: - assess disease activity and damage, and measure functional ability	Edited to clarify that this applies to all adults with RA, even if they have reached their treatment target.

Assessment Questionnaire [HAQ]) - check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression - assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes - organise appropriate cross referral within the multidisciplinary team - assess the need for referral for surgery (see section 1.6) - assess the effect the disease is having on a person's life. (1.5.1.4)	(using, for example, the Health Assessment Questionnaire [HAQ]) - check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression - assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes - organise appropriate cross referral within the multidisciplinary team - assess the need for referral for surgery (see section 1.10) - assess the effect the disease is having on a person's life. (1.9.3)	

1

2 ISBN: