2023 surveillance of rheumatoid arthritis in adults: management

(NICE guideline NG100)

Surveillance proposal

We will update section 1.8 non-pharmacological management of the guideline on Rheumatoid arthritis in adults: management, with the focus on exercise/physical activity for people with rheumatoid arthritis.

We will not update other sections of the guideline.

Reasons for the proposal

Evidence was found regarding a variety of exercise methods for people with rheumatoid arthritis (RA). Aerobic exercise, resistance training and water-based exercise were found to improve fatigue, anxiety, grip strength and aerobic capacity, whilst reducing C-reactive protein (CRP) levels. Low intensity exercise (such as yoga) was found to improve anxiety, depression and sleep quality whilst being safe and feasible for people with RA. This was also echoed by topic experts and patient groups who felt that physical activity was an area of interest for this guideline. An external guideline, the European Alliance of Associations for Rheumatology (EULAR) 2021 guideline also provided a combination of evidence-based and consensus-based recommendations relating to exercise. Currently NG100 does not have any specific recommendations regarding exercise or physical activity for the improvement of symptoms related to RA. As such this may require a change to section 1.8 on non-pharmacological management.

For further details and a summary of all evidence identified in surveillance, see the summary of evidence from surveillance.

Overview of 2023 surveillance methods

NICE's surveillance team checked whether recommendations in rheumatoid arthritis in adults: management (NICE guideline NG100) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- Feedback from patient groups via a questionnaire.
- A search for new or updated Cochrane reviews and national policy.
- Consideration of evidence from previous surveillance.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders.

For further details about the process and the possible update proposals that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to specific parts of the guideline. Following feedback from topic experts, patient groups and a NICE clinical adviser, we searched for new evidence in the following areas:

- Anti-CCP serological testing
- CBT for fatigue
- Exercise
- MRI for diagnosis/monitoring

We found 41 studies in a search for all study types published between 01 October 2017 and 11 September 2023. Inclusion criteria were based on the original 'clinical methodological introduction' sections from the full guideline. Review questions from the 2018 update were also used however these did not cover all sections in this review (such as non-pharmacological management). This information guided study type selection, number of participants, requirement for a UK based population and a minimum percentage of 75% RA in mixed arthritis population. Outcomes of interest taken from the full guideline included efficacy, joint damage, function, quality of life, clinical features for prognosis, diagnostic tests and health economic evaluations.

We also included:

- 3 relevant studies from a total of 9 identified by topic experts via questionnaire.

From all sources, we considered 44 studies to be relevant to the guideline.

See the summary of evidence from surveillance for details of all evidence considered, and references.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 2 studies were assessed as having the potential to change recommendations. Therefore, we plan to regularly check whether these studies have published results and evaluate the impact of the results against current recommendations as soon as they are published. These ongoing studies are:

- ISRCTN - ISRCTN14277030: The Gait Rehabilitation in Early Arthritis Trial
- ISRCTN - ISRCTN16170070: Comparing the effectiveness of our tailor-made management approach for rheumatoid arthritis with routine care from a clinical, patient, as well as economic point of view.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We received 5 questionnaire responses from topic experts, including consultant rheumatologists, professor of MSK medicine with special interest in rheumatology, associate professor in clinical pharmacy with special interest in pain management and a consultant radiologist with special interest in MSK.

Three topic experts felt that an update of NICE guideline NG100 was required, whilst 2 did not agree. The experts that felt no update was required commented that the guideline recommendations are balanced and appropriate, and whilst there are emerging areas of interest such as anti-CCP antibody serology, this is likely to be consistent with current recommendations. They also highlighted that pharmacological management was sufficiently described by existing technology appraisals. The 3 topic experts who felt an update was required suggested the following areas of interest: diagnostic utility of anti-CCP antibodies, the use of MRI in diagnosis and monitoring, and pharmacological management with biologics, synthetic DMARDS and pain medication. However as pharmacological management is covered extensively by NICE technology appraisals, this area was not selected as a search area for this review. The issues raised regarding anti-CCP antibodies and MRI helped form the search strategy for this review.

Views of patient groups

We received 2 responses from a questionnaire sent out to 3 patient groups. Both respondents felt that the guideline required updating.

The following areas for potential update were highlighted: holistic review of the impact of RA, person centred approach, signposting to national charities, support for fatigue, new pharmacological medications such as Janus Kinase

(JAK) inhibitors, physical activity, smoking cessation, and the frequency of monitoring when in remission. Following NICE clinical adviser input we added physical activity/exercise and CBT for fatigue to our search strategy. As above, it was felt that pharmacological management was covered sufficiently with guidance from technology appraisals.

Implementation of the guideline

One patient group highlighted that more has been done to address referral times and reducing time to treatment, however they also mention that the National Early Inflammatory Arthritis audit may have influenced practice. They also highlight concerns that not all people with RA are receiving annual reviews or general practitioners (GP) based RA health checks (where factors such as cardiovascular disease and osteoporosis are measured).

Two topic experts also highlighted that RA treatment, both pharmacological and non-pharmacological can be a 'postcode lottery' with access to high-cost drugs, podiatry services and occupational therapy services being an ongoing issue.

Information considered in this surveillance review

The following studies were considered to have met the inclusion criteria for this surveillance review.

Referral from primary care (recommendation 1.1.1)

Two studies relating to referral from primary care met the inclusion criteria for this review. A cross-sectional survey (1,388 responses) of GP's found patient history to be the most influential factor when deciding whether to refer to secondary care, however this was mostly used in conjunction with serological testing such as anti-CCP and rheumatoid factor (RF). Another observational study (n=6,780) found that anti-CCP levels could help inform the decision to refer to secondary care in patients presenting with inflammatory arthritis in primary care. There was an association between low anti-CCP levels and hand or foot pain with progression to inflammatory arthritis as well as a high

association with hand or foot pain and progression when high anti-CCP levels were seen.

Impact statement

Using anti-CCP serology when a patient presents to primary care with a history of joint pain is consistent with the current guideline recommendations. Urgent specialist referral is also recommended for those presenting to primary care with persistent synovitis, hand and/or foot pain, or more than one affected joint regardless of anti-CCP serology results. The new evidence found supports current guideline recommendations.

Investigations for diagnosis- recommendations 1.1.2-1.1.3

Three studies met the inclusion criteria for investigations for diagnosis. Anti-CCP serology was found to be highly accurate for RA diagnosis in a case-control study (n=133) for patients presenting with undifferentiated polyarthritis in tertiary care. However, a limitation of this study was that accuracy was estimated by retrospectively reassigned anti-CCP and RF results to patients. A prospective cohort study (data from 2 cohorts totalling 1,057 patients) found a combination of serological tests was significantly better at predicting progression to a clinical RA diagnosis from pre-RA when compared to the 2010 EULAR serological scoring system, however combining the serological tests with the 2010 EULAR system further increased the ability to predict progression to a clinical RA diagnosis. Another cohort study (n=215) also found anti-CCP together with RF had significantly increased positive predictive value (PPV) when analysing 3 serological markers for RA diagnosis.

Impact statement

Anti-CCP serology was found to be accurate for RA diagnosis. The accuracy and PPV were significantly improved across the studies when anti-CCP results were used in conjunction with RF results. This is consistent with feedback from topic experts who raised that anti-CCP serology is an emerging area for RA diagnosis with advances in the utility of anti-CCP serology likely to continue in the future. However, the evidence found at present is insufficient

to have an impact on the current weak 'consider' recommendation for the use of anti-CCP in RA diagnosis. This topic area will be monitored for future review.

Investigations for, and following diagnosis – recommendations 1.1.4-1.1.6

Eleven studies met the inclusion criteria for the above recommendations. Six studies investigated the use of MRI to predict progression to clinical RA diagnosis from undifferentiated arthritis (UA). These are indirect studies as they explored predictive accuracy of disease progression rather than diagnostic accuracy at certain timepoint. None of the studies compared the diagnostic accuracy of RF or anti-CCP for diagnosing RA, and there were several studies where the reference standards used were not clear or not reported.

For investigations following diagnosis, 2 studies were found relating to the use of MRI or ultrasound to detect bone erosions on patients with a clinical RA diagnosis, however this evidence had methodological limitations and was largely inconclusive. There was also a lack of data on cost-effectiveness and accuracy for using MRI to detect bone erosions.

Three cohort studies investigated the use of anti-CCP. One study found anti-CCP positive results alongside a family history of RA did not predict poor outcomes. The second study found bone marrow density (BMD) and disease activity were lower in people who were anti-CCP2 positive, with the third study finding radiographic monitoring was important in those who were anti-CCP positive, as there was an association with higher joint damage.

Impact statement

The studies found for investigations for diagnosis using MRI were indirect and lacking data on its diagnostic accuracy, and the reference standards used in the studies were not clear. As such the new evidence found has no significant impact on recommendation 1.1.4.

For investigations following diagnosis, the new evidence found was insufficient to have an impact on recommendations 1.1.5 and 1.1.6. This was largely due to methodological limitations, quality issues with identified studies, a lack of data for the impact of family history of RA, and the association between anti-CCP positivity and BMD. No impact on these recommendations is anticipated at this time.

Treat-to-target strategy – recommendations 1.2.1-1.2.3

One RCT (n=200) was found to meet the inclusion criteria for this review. The RCT aimed to explore whether outcomes for RA patients in clinical remission could be improved with the use of an MRI based treat-to-target strategy. At the end of the study a clinical DAS28-CRP score of <2.6 was achieved by 85% of patients in the MRI guided group and 88% of patients in the clinical decision guided group. The study concluded that an MRI based treat-to-target strategy does not improve disease activity rates or radiographic progression beyond the standard clinical judgement.

Impact statement

No significant improvements were seen when an MRI based treat-to-target strategy was used compared to standard clinical judgement. The recommendations in this section currently state the target of treatment should be remission, or if this is not possible, low disease activity. The new evidence found does not contradict the recommendations in this section, as such no impact is anticipated.

Non-pharmacological management – section 1.8 recommendations 1.8.1-1.8.4

Exercise/physical activity

An RCT (n=66) found CRP levels, fatigue, grip strength, aerobic capacity and cognitive function improved when exercise was increased in people with RA. Pedometer use also increased exercise in a second RCT (n=96), which led to improved fatigue scores and reduced disease activity in people with RA. A third RCT (n=74) found moderate to high intensity gym-based exercise

improved aerobic capacity and endurance in older people with RA, however the abstract does not detail whether these are important aspects of health to people in this group. A systematic review (9 studies, n=604 participants) found water-based exercise was beneficial compared to home-based exercise for people with inflammatory arthritis, however results were not available for specific subgroups of the study such as those with RA.

Resistance exercise was found to improve erythrocyte sedimentation rate (ESR), disease activity and walk time in a meta-analysis (n=512), however when low intensity exercise with additional blood flow restriction was compared to medium and high intensity exercise in a systematic review (5 RCTs), no improvements were seen. Aerobic exercise in RA patients was found to decrease fatigue levels in a meta-analysis (n=298), with a systematic review (14 RCTs) also finding anxiety was reduced with increased aerobic exercise. A second systematic review (13 RCTs, 967 patients) found aerobic exercise was safe for people with RA, which the study noted is often a concern when considering exercise for patients in this population. Aerobic activity also significantly improved aerobic capacity, functional ability and relieved pain in people with RA.

Impact statement

Overall, increased levels of physical activity, including exercises, were found to improve cognitive abilities and disease activity scores in people with RA. Water-based exercise was beneficial compared to home-based exercise, however the population used for the study included all types of inflammatory arthritis and results specific to the RA population were not provided in the abstract, further assessment of the full paper is warranted. The new evidence found for resistance exercise was mixed across 2 studies with one finding no difference and the other showing improvements in a variety of health metrics. Aerobic exercise was found to be safe and effective for people with RA, with reduced fatigue and reduced anxiety. However, one systematic review had a mixed population (RA, fibromyalgia and osteoarthritis) and did not clarify the numbers of people with RA who saw improvements in their anxiety. There are currently no specific recommendations regarding general exercise or physical

activity for people with RA in section 1.8. This gap was also highlighted through topic expert and patient group feedback. The 2021 EULAR guidelines identified in this review also include a range of evidence and consensus-based recommendations highlighting the importance of exercise/physical activity in people with RA. The new evidence found suggests that this is an area of increasing importance for people with RA and has the potential to improve symptom management. As such the evidence found is likely to have an impact on the current guideline recommendations.

Hand exercises

An RCT (n=55) found no significant differences were seen when hand exercises were added to an intervention for RA patients. A Cochrane review (7 studies, n=841) also found mixed evidence for the outcomes of grip strength, hand function and pinch strength. However, a secondary analysis of the SARAH trial (n=490) found increasing the prescribed dose of hand exercises led to improved clinical outcomes for RA patients.

Impact statement

The new evidence found for hand exercises was mixed across the 3 included studies. The guideline currently recommends a tailored approach to hand exercises, which is broadly consistent with the new evidence found. As such no change to this area is anticipated.

Yoga & Tai-Chi

Five studies were found relating to the use of yoga for symptom management for people with RA. Yoga interventions were found to significantly improve depressive symptoms, anxiety and sleep quality, aid RA remission, increase grip strength and physical fitness in RA patients. However significant improvements in joint pain were not seen. Uncertainty remains over the usefulness of Tai-Chi when evidence from an updated Cochrane review was examined.

Impact statement

Improvements in a number of areas were seen with the use of yoga based interventions for people with RA, however the populations in 2 of the studies

found were mixed with results not specified for RA alone. Neither yoga nor Tai-Chi are included at present in section 1.8. Further evidence on yoga based interventions for RA populations is required, as such an impact on the guideline recommendations is unlikely at this time.

Overall impact for recommendations 1.8.1-1.8.4

NICE guideline NG100 currently does not have specific recommendations regarding exercise or physical activity, with only hand exercises covered in section 1.8 (non-pharmacological management). There is a high volume of evidence identified at this surveillance review indicating that exercise and physical activity may be beneficial to people with RA. This is a gap in the current guideline where the addition of recommendations may be useful for people with RA.

Cognitive behavioural therapy for fatigue – recommendation 1.8.7

Six studies were found for the use of CBT for fatigue for people with RA that met the inclusion criteria for this review. Improvements in fatigue were seen across all 6 studies from a variety of psychological interventions such as CBT, internet-based CBT, group CBT and mindfulness interventions. These improvements were significant in 4 of the 6 studies, however the detailed components of the interventions used were not stated in the majority of the studies, including type of intervention, duration and mode of delivery. Several of the studies had low numbers of participants, with none of the 6 studies using the same scale for results, making it difficult to compare outcomes. The RAFT RCT maintained improvements in fatigue at 2 years post intervention however had a low probability of being cost-effective.

Impact statement

Although improvements in fatigue were seen with the use of CBT, this presents mixed evidence spread across multiple applications of CBT with inconsistent measurement scales used. Recommendation 1.8.7 is permissive of the use of psychological interventions to ‘help RA patients adjust to living

with their condition'. Recommendation 1.7.1 mentions access to multi disciplinary teams for RA patients to help manage conditions affecting their daily lives such as fatigue. Currently there is insufficient evidence to suggest a change to these recommendations, as such no impact is anticipated at this time. However, the issue should be monitored and considered at the next surveillance review.

Monitoring – section 1.9

One study met the inclusion criteria for this surveillance review, finding that MRI imaging may predict bone erosion progression for patients with RA who are in clinical remission. Inflammation was seen on MRI whilst in remission at the 1-year time point (43.4% synovitis, 39.5% bone marrow oedema, and 9.2% tenosynovitis), with a statistically significant increase in bone marrow oedema and bone erosion progression ($p=0.01$, $p<0.001$ respectively). The study however had a relatively small population (n=76).

Impact statement

Sustained inflammation was seen on MRI in people who had achieved clinical remission from RA, suggesting that MRI based monitoring may provide information on disease progression. The European society of skeletal radiology recommendations on the use of MRI were highlighted during intelligence gathering, which state that MRI is currently considered to be the best non-invasive imaging modality for inflammation of the bone marrow, joints and tendons. Currently the recommendations for the 6 month or annual RA reviews do not cover the use of MRI monitoring. However, this is a small study and it is unclear whether MRI monitoring predicts clinical progression or whether it is cost-effective; as such there is insufficient evidence at this time to indicate an impact. However, this area should be considered at future reviews.

Information considered when developing the 2018 update of the guideline

The 2018 update found no evidence relating to referral from primary care or investigations for diagnosis (section 1.1). For investigations following diagnosis, the update found that baseline anti-CCP, ESR and CRP were not

independently associated with the modified health assessment questionnaire (mHAQ) at the 2-year timepoint. Evidence also suggested baseline anti-CCP having an independent association with radiographic progression after 12 months. These form the basis of the 2018 updated recommendations.

The 2018 update found treat-to-target strategies (section 1.2) had a clinically important benefit in terms of disease activity, quality of life, remission, pain, radiological progression and fewer trial withdrawals compared to usual care. No clinical difference was found when treat-to-target was compared to usual care for the outcomes of function, low disease activity or work limitations. Health economic evaluation found treat-to-target is less costly than usual care. The clinical and economic evidence led the committee to conclude that treat-to-target strategies appeared to improve outcomes with no additional cost, and stated it was already considered current clinical practice.

No evidence was found in the 2018 update regarding frequency of monitoring in RA patients. The committee agreed that once people with RA had achieved their treatment target and sustained this at the 6-month review, there was no need for additional routine monitoring appointments, with the exception of their annual review. The committee also highlighted that ongoing drug monitoring may be required and amended the recommendations around rapid access to include this. Evidence was also identified in the 2018 update on the use of ultrasound in monitoring people with RA, however the evidence did not support its use in routine care.

Non-pharmacological management was not in the scope of the 2018 update.

Equalities

One patient group highlighted geographical variations with biological treatment availability due to some clinical commissioning groups restricting access to such treatments. One patient group highlighted that health inequalities continue to exist for people from areas of social deprivation and for people from ethnic minorities. However, the patient group did not provide further details on their experiences.

One topic expert mentioned that people with moderate RA are a subgroup that is not currently addressed in the guideline. The other 4 topic experts did not raise any equalities issues.

No equality issues were noted during intelligence gathering or evidence searches.

An equalities and health inequalities assessment was completed during this surveillance review. See Appendix B for details.

Overall proposal

After considering all evidence and other intelligence and the impact on current recommendations, we decided that an update to section 1.8 – non-pharmacological management is necessary. This will focus on evidence relating to exercise/physical activity for managing symptoms of RA.