Appendix A: Summary of evidence from surveillance

2023 surveillance of Rheumatoid arthritis in adults: management (2018) NICE guideline NG100

Overall surveillance decision

We propose to update the following sections of this guideline.

These sections are:

Section 1.8 Non-pharmacological management

- To consider the role of different exercises/physical activities in improving patient's outcomes.

Sections 1.1 and 1.2 regarding the use of anti-cyclic citrullinated peptide (CCP) antibodies for serological testing will not be updated at this time, as the evidence found at this review broadly supports the current guideline recommendations. Section 1.9 will not be updated at this time as it is largely consistent with current guideline recommendations.

Section 1.5 we will consider incorporating the following technology appraisals into the guideline:

- Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs
- Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
- Tocilizumab for the treatment of rheumatoid arthritis
- Upadacitinib for treating moderate rheumatoid arthritis
- Tofacitinib for moderate to severe rheumatoid arthritis
- Baricitinib for moderate to severe rheumatoid arthritis

- Sarilumab for moderate to severe rheumatoid arthritis
- Filgotinib for treating moderate to severe rheumatoid arthritis
- Upadacitinib for treating severe rheumatoid arthritis
- Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis
- Tofacitinib for treating juvenile idiopathic arthritis

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts was considered alongside the evidence to reach a view on the need to update each section of the guideline.

1.1 Referral, diagnosis and investigations

1.1.1 referral from primary care

Surveillance proposal

These recommendations should not be updated.

Relevant recommendations:

1.1.1 Refer for specialist opinion any adult with suspected persistent synovitis of undetermined cause. Refer urgently (even with a normal acute-phase response, negative anti-CCP antibodies or 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

If the following investigations are ordered in primary care, they should not delay referral for specialist opinion (see recommendation 1.1.1).

For a short explanation of why the committee made the 2018 recommendations and how they might affect practice, see the rationale and impact section on investigations following diagnosis .

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

2012 surveillance review

The 2012 surveillance review found no evidence relating to referrals from primary care.

2015 surveillance review

The 2015 surveillance review found no evidence relating to referrals from primary care.

2020 exceptional review

In the 2020 exceptional surveillance review of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

A cross-sectional survey on general practitioners (GPs) (Scott et al, 2018) that investigated barriers to timely referral for people suspected of having rheumatoid arthritis (RA) from primary care was identified. The surveys were carried out using the RA questionnaire for GPs (RA-QUEST) with 1,388 responses being received. Data was scored using 5-point Likert and 10-point visual analogue scales alongside yes/no questions and free text. Patient history had the greatest impact on referral to secondary care (92% marking a 4 or 5 on Likert scale), however only 26% of GPs would find this sufficient to initiate a referral without additional tests. Those who did request serological testing heavily relied on rheumatoid factor (RF) (95%). Small joint swelling (91%) and patient reported pain (84%) also scored a 4 or 5 on the Likert scale, based on these symptoms GPs were highly likely to refer to secondary care. Serological testing such as anti-CCP (72% rated 4 or 5) and RF (61% rated 4 or 5) had less impact on the decision to refer in a timely manner. The study concludes that in order to achieve faster referral times, GP's may need to consider which symptoms are highest priority for RA referral.

An observational study (Garcia-Montoya et al. 2022) investigated the risk of newly symptomatic Musculoskeletal (MSK) individuals' progression to inflammatory arthritis in primary care was identified. Anti-CCP levels were determined for 6,780 individuals, of which 3% were anti-CCP positive. From the positive cases, 45% progressed to inflammatory arthritis (mostly RA). Higher anti-CCP antibody levels (for the purpose of this study was classified as 3 times the upper normal limit) had a higher association with foot pain (OR 4.10, p=0.003, 95% CI 1.59 to 10.54), hand pain (OR 2.74, p=0.043, 95% CI 1.03 to 7.27) and progression to inflammatory arthritis (OR 9.42, p<0.001, 95% CI 3.13 to 28.30), whereas those with lower antibody levels (any results lower than the 'higher anti-CCP antibody level') and a lack of pain in the hand or foot had a negative predictive value for progression to arthritis of 96%. At the 1 year follow up timepoint, 53 people who were anti-CCP negative at baseline had gone on to develop inflammatory arthritis. Also associated with diagnosis of inflammatory arthritis at 1 year was hand and foot pain. Those with hand or foot pain and low levels of anti-CCP antibody were also at an increased risk of progression. The authors conclude that routinely available tests can be used in primary care to help determine which patients may benefit from a referral to rheumatology.

Intelligence gathering

No new intelligence received from topic experts in this topic area.

Impact statement

A survey of GPs found that patient history was most influential on the decision to refer patients to secondary care, however the majority would not rely on patient history alone without the addition of serological testing. A study of inflammatory arthritis in primary care found that anti-CCP levels could help inform referral decisions. Low anti-CCP levels in combination with hand or foot pain indicated an increased risk of progression to inflammatory arthritis, where as low anti-CCP levels without hand or foot pain did not. High anti-CCP levels had a higher association with hand or foot pain and progression to inflammatory arthritis. This new evidence is consistent with current recommendations, where referral to specialist is recommended for adults with persistent synovitis, and to refer urgently even when anti-CCP is negative if they have hands or feet joint pain, or more than one joint is affected. As such no impact is anticipated at this time.

New evidence is unlikely to change guideline recommendations.

1.1 Referral, diagnosis and investigations

1.1.2-1.1.3 Investigations for diagnosis

Surveillance proposal

These recommendations should not be updated.

Relevant recommendations:

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-CCP antibodies in adults with suspected RA if they are negative for rheumatoid factor. **[2009, amended 2018]**

2012 surveillance review

The 2012 surveillance review found evidence relating to anti-CCP and RF tests were in line with current guideline recommendations, which recommends the use of anti-CCP tests along with RF test and x-rays of the hand and feet. Evidence found for other diagnostic tests such as anti-MCV, MRI and metabolites did not show high sensitivity or specificity in diagnosing RA, however they remained under consideration for future evaluations.

2015 surveillance review

Evidence found at the 2015 surveillance review found beneficial diagnostic accuracy for anti-CCP tests in the diagnosis of RA, which was deemed to be in line with guideline recommendations. Evidence was also found relating to the diagnostic value of antifilaggrin autoantibodies (AFA), however as this was from only one meta-analysis it was deemed insufficient for inclusion at the time. The study authors also highlighted antigens derived from human breast skin was unlikely to be conducive to clinical application.

2020 exceptional review

In the 2020 exceptional surveillance review of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

Inclusion criteria of identified studies:

UK-relevant population, patients were pre-RA/had undifferentiated arthritis (UA), if the population was mixed arthritis there had to be >75% RA or RA subgroup analysis and had a sample size of N>50 (except for MRI or ultrasound studies).

Investigations for diagnosis

Anti-CCP and rheumatoid factor

One case-control study (Ghosh et al, 2021) aimed to assess the diagnostic value of RF and anti-CCP antibodies in patients with RA and undifferentiated polyarthritis in tertiary care was identified. Anti-CCP antibodies were found in 70.7% of patients with RA (n=133) with RF found in 66%, however the reference standard for diagnosis was not disclosed in the abstract, neither were results for the control group (n=67). Results for both anti-CCP and RF are as follows:

	Anti-CCP	RF
Sensitivity	70.76	66.26
Specificity	85.07	90.29
Positive predictive value (PPV)	90	90
NPV	59	45

Anti-CCP was more sensitive (88%) and more specific (98%) than RF when levels were compared across both RA and polyarthritis patients together. The authors suggest that anti-CCP may be highly accurate in the diagnosis of RA. However, the control group and reference standard for this study are unclear or not reported in the abstract. Anti-CCP and RF results appeared to have been retrospectively assigned to diagnosed patients to estimate the test accuracy. These limitations could have biased the accuracies reported.

An analysis of prospective cohort studies from Regueiro et al, (2019) aimed to evaluate the combination of 3 serological tests to improve RA classification in early arthritis patients. Data

from 2 prospective cohort studies were used covering 1,057 patients. Both the combination of the 3 serological tests (RF, anti-CCP, and anti-carbamylated protein antibodies) and the 2010 European Alliance of Associations for Rheumatology (EULAR) criteria were assessed in relation to the current gold standard method, the 1987 American College of Rheumatology (ACR) criteria, at baseline and at 2-year follow up. The combined serological tests were predictive for classification of RA (PPV 96.1%, OR 80.9), significantly better than the results obtained when the 2010 EULAR criteria antibody titres were used (PPV 88.8%, OR 26.1). The study used the serological test results to devise a scoring system which had a performance similar to the 2010 EULAR serological scoring system, however the results showed that combining the 3 serological tests with the 2010 EULAR criteria gave the best results for RA classification.

A cohort study (Bettner et al, 2021) aimed to evaluate 3 serological markers in pre- and confirmed RA diagnosis was identified. Anti-CCP3, serum calprotectin (sCP) and RF were tested for in a total of 215 RA cases, all of which had stored blood samples from 3 pre-RA tests and 1 sample available from when RA was clinically confirmed. All 3 markers were raised in pre-RA samples, with sCP and anti-CCP3 being significantly raised compared to RF in the earliest samples. The positive predictive value (PPV) of anti-CCP3 at the 3-year timepoint was 18.7%, however when anti-CCP3 was combined with RF, this significantly increased PPV to 35.6% ($p<0.001$). The PPV for all 3 markers was also higher than anti-CCP3 alone at 53%, however the authors state that this was not significantly higher than when anti-CCP3 and RF were combined ($p=0.248$). The reference standard used was not stated in the abstract, there was also a lack of reporting of the accuracy of anti-CCP compared to RF alone and the combination of anti-CCP + RF. The authors conclude that all 3 serological markers are raised in pre-RA and may provide a useful diagnostic aid.

Intelligence gathering

One topic expert highlighted that there was new evidence on the diagnostic utility of anti-CCP antibodies and as such recommendation 1.1.3 might require an update from “consider” to “offer”. The topic expert also mentioned that the evidence base for anti-CCP being incorporated into early serology for pre-RA and clinically suspect arthralgia (CSA) patients might not yet be sufficient. The topic expert did however highlight that this may be an area of interest in the future, when more substantive evidence is available to guide treatment of patients who are anti-CCP positive, but do not meet the clinical criteria for a diagnosis of RA.

Impact statement

One study suggested that anti-CCP was highly accurate for RA diagnosis in patients with undifferentiated polyarthritis in tertiary care, however this study retrospectively reassigned anti-CCP and RF results to diagnosed patients in order to estimate accuracy, it also did not state which reference standard was used in the abstract, these limitations introduce significant biases on the findings. A second study found that a combination of serological tests was significantly better at predicting RA when compared to the 2010 EULAR serological scoring system. This prediction ability was further increased when the serological tests were combined with the 2010 EULAR criteria for RA classification. However, both

serum calprotectin (sCP) and 2010 EULAR criteria are not routine practice in the UK, and the comparative accuracies of such combination against anti-CCP or RF alone were not reported. A cohort study found anti-CCP + RF had good PPV, however the reference standard used was unclear from the abstract, hence there is uncertainty about the accuracy findings reported. Feedback from topic experts highlighted that anti-CCP was an evolving area of research and as such may result in a major change in serological testing in the future, however the treatment of anti-CCP positive individuals who are not clinically classified as having RA is outside the scope for this guideline. At this time, the new evidence and intelligence found are insufficient to have an impact on current guideline recommendations. However, the utility of anti-CCP in the early stage of the diagnostic pathway should be considered at future reviews when more good quality diagnostic accuracy evidence and cost effectiveness evidence become available.

New evidence is unlikely to change guideline recommendations.

1.1 Referral, diagnosis and investigations

1.1.4 Investigations for diagnosis and 1.1.5-1.1.6 investigations following diagnosis.

Surveillance proposal

These recommendations should not be updated.

Relevant recommendations:

Investigations for diagnosis

1.1.4 X-ray the hands and feet in adults with suspected RA and persistent synovitis. **[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:

- advise 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]**

2012 surveillance review

Evidence from a systematic review explored the use of MRI to aid early diagnosis of RA was identified. However, it was concluded that the data was inadequate to justify widespread use for these purposes. The review did find that MRI bone oedema may be predictive of RA in certain populations. MRI was also found to be a sensitive method for detecting axial skeleton involvement in RA for better disease outcomes in a second study. No evidence was found at the 2012 review for investigations following diagnosis.

2015 surveillance review

No evidence was found relating to the use of MRI for diagnosis of RA. Clinical feedback indicated new evidence may be available regarding imaging for diagnosis of RA, however none of the studies stated met the inclusion criteria for the 2015 review. The topic of imaging was noted to be raised at the next surveillance review.

The 2015 review found evidence regarding the use of ultrasound following diagnosis of RA which suggested it may be beneficial for detecting synovitis and predicting progression, however one study in this area stated that further validation was required. Ultrasound was included in the scope of the guideline 2018 update.

2020 exceptional review

In the 2020 exceptional surveillance review of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

Investigations for diagnosis - MRI

A longitudinal study (Boer et al, 2017) examined 2 cohorts of patients at risk for developing RA (clinically suspect arthralgia and undifferentiated arthritis) using MRI of hand and foot with a comparison group of symptom free volunteers. Both the clinically suspect arthralgia group (n=225) and undifferentiated arthritis group (n=201) underwent MRI of metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP) joints at baseline and for a follow up period of 1 year on progression to arthritis. A positive MRI prediction was seen if 1 joint showed inflammation, or if 1 joint had inflammation that was not seen in the healthy volunteers of the same age. When using the data from healthy volunteers, the authors report an increase in inflammation specificity from 22% to 56% in the arthralgia group and 10% to 36% in the undifferentiated arthritis group, without significantly affecting sensitivity (88% to 85% in the arthralgia group, 93% at both points in the undifferentiated arthralgia group). An increase in diagnostic accuracy was seen across both groups (32% to 60% arthralgia, 22% to 44% undifferentiated arthritis groups) indicating that a substantial reduction in false positives was seen when a population of healthy volunteers were used as a reference population for

MRI of pre-arthritis patients. However, the study was lacking a robust design, so the results are difficult to interpret.

A secondary analysis of a cohort study (Boer et al, 2018) aimed to assess the additional value of MRI detected synovitis and number of involved joints when the 2010 ACR/EULAR criteria for RA was used. A cohort of 277 patients were enrolled and had 1.5-T MRI of the MCP, wrist and MTP joints, with number of joints involved assessed with and without MRI detected synovitis. Baseline assessments found 143 patients met the criteria for RA, however a further 14 met the criteria when MRI detected synovitis was considered. Sensitivity changed from 62% to 67%, specificity from 90% to 84% and AUC from 0.76 to 0.75 when the number of joints involved, as determined by MRI detected synovitis was included. The authors concluded that they found no scientific support to suggest that MRI detected synovitis is of additional benefit for the performance of the 2010 classification criteria.

A longitudinal cohort study (Dakkak et al, 2019) investigated whether progression from undifferentiated arthritis to clinical RA diagnosis could be improved by adding foot MRI to the researchers' usual practice of hand MRI. Patients (n=125) and symptom free controls (n=193) underwent 1.5-T contrast enhanced MRI of the hand and foot, with results taken for bone marrow oedema, synovitis and tenosynovitis. Patients were then followed for 1 year to observe whether progression to clinical RA (defined as meeting the requirements for treatment because of the expert opinion of RA) occurred, of which 52% went on to develop RA. Both foot (OR 2.55, 95% CI 1.01 to 6.43) and hand (OR 3.99, 95% CI 1.64 to 9.69) tenosynovitis were predictive of progression to RA, however when both foot and hand tenosynovitis results were used together (sensitivity 73%, specificity 54%, AUC 0.64) there was no improvement in predictive accuracy compared to hand MRI alone (sensitivity 72%, specificity 59%, AUC 0.66).

A systematic review (de Pablo et al, 2022) investigated the accuracy of MRI or ultrasound for predicting progression to RA in patients with unclassified arthritis. Of 19 included studies, 13 assessed MRI (n=1,143) and 6 assessed ultrasound (n=531). Three studies found MRI detected synovitis in 1 or more joint to have a sensitivity of 93% (95% CI 88% to 96%) and a specificity of 25% (95% CI 13% to 41%), however the authors state that due to heterogeneity, study design, inclusion of patients with RA at baseline, differential verification, lack of blinding, differing diagnostic thresholds and a lack of consensus in grading, further meta-analysis was not possible. Ultrasound results were not available in the study abstract due to difficulties in synthesis due to differing standards within studies. Due to the lack of consistency within the included studies and the limitations of these studies, further work is required in this area, specifically with consistent RA definitions, to investigate whether MRI or ultrasound are more accurate in predicting progression of UA to RA.

A prospective study (den Hollander et al, 2022) aimed to assess the predictive value of MRI hand and foot for progression to a clinical RA diagnosis in patients with unclassified arthritis was identified. Two cohorts of patients were included in the study, the criteria-based group (n=405) consisted of people with current UA who didn't meet either the 1987 or 2010 EULAR criteria for a clinical RA diagnosis, and the expert opinion group (n=564) who had a clinical diagnosis of RA from a rheumatologist. Both groups had hand and foot contrast

enhanced MRI at baseline and were followed up for RA development over a 1-year period. In the criteria-based group, 21% of UA patients developed clinically diagnosed RA. Both MRI detected synovitis and tenosynovitis were predictive of progression to RA, while tenosynovitis was independently associated with RA progression (OR 2.79, 95% CI 1.40 to 5.58). This particularly applied to those UA patients who were anti-citrullinated protein antibodies (ACPA) negative (OR 2.91, 95% CI 1.42 to 5.96). Further analysis was undertaken to observe prior risks of RA development, using mono, oligo and polyarthritis as subgroups for UA patients. The subgroup analysis found the biggest prediction in progression to RA was seen in the oligoarthritis group of UA patients, with a PPV of 27% and negative predictive value of 93%, with similar results found when the expert opinion group's results were analysed. The authors conclude that MRI has the most value in UA patients who are ACPA negative and present with oligoarthritis and suggest a negative MRI result could prevent overprescribing.

A cohort study (Matthijssen et al, 2019) aimed to improve the identification of RA specific features in people with CSA using MRI of the MCP and MTP joints. The study used MRI to identify which combinations of features went on to predict clinical RA diagnosis. MRIs consisted of contrast enhanced 1.5 T MRI scans of the metatarsophalangeal (MTP) and metacarpophalangeal wrist joints (MCP). These were examined for bone marrow oedema, synovitis and tenosynovitis, recording numbers of joints inflamed, severity of inflammation and combinations of inflamed joints. In the cohort of 225 CSA patients, 15% went on to be clinically diagnosed with RA within one year. The number of locations with subclinical inflammation was found to be a predictor of RA (1-2 locations HR 2.54, range 1.11 to 5.82, ≥3 locations HR 3.75, range 1.49 to 9.48). Presence of MCP-extensor peritendonitis (HR 4.38, range 2.07 to 9.25) was also found to be predictive of progression to clinical RA, however the severity of inflammation and combinations of inflammatory lesions was not determined to be predictive of clinical RA progression. The authors conclude that MCP-extensor peritendonitis (tenosynovitis) is an early predictor of clinal RA diagnosis in CSA patients, combining this finding on MRI with the number of areas of subclinical inflammation seen improved the PPV to 63-67%.

Investigations following diagnosis

MRI

A cross-sectional study (Boeters et al, 2018) investigated whether MRI detected erosions were specific to RA and if they could be distinguished from physical erosions. Patients with RA (n=238), other forms of arthritis (n=351) and symptom free controls (n=193) had contrast enhanced 1.5 T MRI of unilateral metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints. Participants were divided into 3 age groups (<40 years, 40-59 years and ≥60 years) with results scored using total erosion score, location, number and severity of erosions and MRI detected inflammation (bone marrow oedema and/or synovitis). MTP1 erosions were specific to RA patients aged less than 40 years when compared to healthy controls and those with other forms of arthritis. Grade ≥ 2 erosions and MTP5 erosions were also specific to RA when compared to both groups (specificity 98 to 100%), with total erosion scores being statistically significantly higher for the RA group when compared to the control group.

However, the authors state that when examined at a person level, individual scores largely overlapped and highlighted caution for estimating the value of MRI in the RA diagnostic process, despite RA specific erosion characteristics being identified.

A diagnostic test accuracy study (Tang et al, 2020) aimed to evaluate and compare MRI and ultrasound (US) imaging of RA patients for bone erosion to try and improve the efficiency of diagnosis. Data was extracted from 26 articles, with subgroup analysis to evaluate performance, including scanning position and type of machine used. For MRI, the collated sensitivity and specificity was 0.77 (95% CI 0.63 to 0.87) and 0.89 (95% CI 0.80 to 0.95) respectively. For US imaging, sensitivity and specificity were 0.61 (95% CI 0.43 to 0.77) and 0.95 (95% CI 0.88 to 0.98) respectively. The authors concluded that neither MRI or US gave a satisfactory diagnostic test accuracy for bone erosion detection in patients with RA. Also, the study sample is relatively small (N=26 articles).

Anti-CCP

A cohort study (Murata et al, 2020) retrospectively reviewed data from the ANSWER cohort, to determine whether family history of RA and/or positive anti-CCP antibody test was predictive of poor outcome. Patient data was viewed at baseline, 1- and 2-years post diagnosis for 260 newly diagnosed RA patients, 11.9% of which had a family history of RA. When comparing data for those with and without a family history of RA, there was no significant difference in age of onset, time to first visit, sex, RF results or anti-CCP results. Patients who were anti-CCP positive with a family history of RA did however have significantly lower levels of C-reactive protein (CRP) and ESR. The authors conclude that family history of RA in anti-CCP positive patients is not predictive of poor outcome at 1- or 2- years post onset of RA.

A single centre, observational cohort study (Ahmad et al, 2018) aimed to assess the relationship between anti-CCP2 antibodies, disease activity and bone mineral density (BMD) in established RA patients. Patients were assigned to subgroups based on the anti-CCP2 status, 1 group for negative (n=47) and 3 groups of increasing antibody concentrations for positive (n=102). Mean disease duration was greater in the anti-CCP2 positive groups compared to the anti-CCP2 negative group, with BMD being lower in the positive groups compared to the negative group. Disease activity was less likely to be low in the low BMD groups. The study concludes that anti-CCP2 positive patients were more likely to have low BMD scores and less likely to have low disease activity than those who were anti-CCP negative, suggesting that anti-CCP2 has a role in disease monitoring of patients with established RA.

A cohort study (Ziegelasch et al, 2020) aimed to determine if anti-CCP is predictive of RA disease activity in cohorts from 1996-1999 (TIRA-1 (a Swedish acronym for early interventions in rheumatoid arthritis ‘tidiga insatser vid reumatoid artrit’), n=239) and 2006-2009 (TIRA-2, n=444). Two confirmation cohorts were also included, TRAM-1 (Swedish acronym for early rheumatoid arthritis reception ‘tidig reumatoid artrit mottagning’) 1996-2000 (n=249) and TRAM-2 2006-2011 (n=528). Baseline anti-CCP data was collected, along with clinical, ongoing treatment, and radiographic data for up to 3 years. Anti-CCP positive

patients had higher DAS 289 score, CRP level, ESR and swollen joint care in the TIRA-1 cohort compared to anti-CCP negative patients, however this was not seen in the TIRA-2 cohort. The TIRA-2 cohort did however find a significant association between baseline anti-CCP positivity and higher radiographic joint damage over 3 years (p=0.039). No data from TRAM-1 was described in the abstract, however for TRAM-2 was able to predict radiographic damage in anti-CCP positive patients (p=0.027) with no significant difference in DAS 28 score. The authors conclude that close radiographic monitoring is required in early arthritis patients who are anti-CCP positive.

Intelligence gathering

No new intelligence received from topic experts in this topic area.

Impact statement

Investigations for diagnosis - MRI

All the identified studies on MRI are of predictive nature of progression to clinical RA from UA, these studies do not provide the diagnostic accuracy of MRI in diagnosis RA against a specific reference standard. The reference standards used for the final confirmatory diagnosis in these studies is either unclear or not reported. None of the studies compared the diagnostic accuracy of RF or anti-CCP in diagnosing RA. As such, the new evidence on MRI has no significant impact on current recommendations.

Investigations following diagnosis

MRI

New evidence on the use of MRI or US to detect bone erosions following diagnosis is inconclusive, with a number of methodological limitations. None of the identified studies compared the accuracy and cost effectiveness of MRI to detect bone erosions with current practice, which is erosions on X-ray or presence of anti-CCP antibodies. As such, new evidence is insufficient to have a significant impact on current recommendations.

Anti-CCP

A cohort study found family history of RA in patients with anti-CCP antibodies is not a predictor of poor outcomes at 1- or 2-years post diagnosis. A second cohort study found that anti-CCP2 positive patients had lower BMD scores and were less likely to have low disease activity compared to people with negative anti-CCP results, however this study shows a low quality association, and the results should be interpreted with caution. A third cohort study found radiographic monitoring to be important in patients who are anti-CCP positive, as anti-CCP positivity was associated with higher radiographic joint damage. The guideline already recommends to advise the person that they have an increased risk of radiological progression if anti-CCP antibodies are present. The recommendations currently do not include information on family history or associations between anti-CCP and BMD, as such further evidence would be required in these areas before an impact on the recommendations could be identified.

New evidence is unlikely to change guideline recommendations.

1.2 Treat-to-target strategy

Surveillance proposal

These recommendations should not be updated.

Relevant recommendations:

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). Achieving the target may involve trying multiple conventional disease-modifying anti-rheumatic drugs (cDMARDs) and biological DMARDs with different mechanisms of action, one after the other. [2018, amended 2020]

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 baseline 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 in specialist care until the target of remission or low disease activity is achieved. [2018]

2012 & 2015 surveillance reviews

Treat-to-target recommendations were added following the 2018 update of the guideline, as such were not an area included in the 2012 and 2015 reviews.

2020 exceptional review

In the 2020 exceptional surveillance review of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

An RCT (Moller-Bisgaard et al, 2019) aimed to determine whether outcomes in RA patients in clinical remission could be improved using an MRI based treat-to-target strategy compared to a conventional clinical approach led treat-to-target strategy. Patients (n=200) were recruited across 9 hospitals in Denmark if they were in clinical remission from RA, defined as a DAS28-CRP score of less than 3.2. Patients were randomised 1:1 to either the MRI guided or clinical guided groups, with results available for 76 and 95 patients respectively. The primary end point of clinical remission (DAS28-CRP <2.6) was achieved by 85% patients in the MRI guided group and 88% in the clinically guided group, with the primary radiographic end point (absence of bone marrow oedema) being reached in 66% and 62% respectively. Serious adverse events were noted in 17% of the MRI guided group and 6% of the clinically guided group. The authors conclude that an MRI based treat-to-target strategy does not improve

disease activity rates or radiographic progression and as such clinical judgement should be used.

Intelligence gathering

No new intelligence received from topic experts in this topic area.

Impact statement

An RCT found an MRI based treat-to-target strategy did not improve disease activity rates or radiographic progression when compared to clinical examination. The evidence found in this section is largely consistent with current guideline recommendations, as such no impact is anticipated.

New evidence is unlikely to change guideline recommendations.

Section 1.8 Non-pharmacological management

Surveillance proposal

Section 1.8 of the guideline should be updated.

Relevant recommendations:

1.8 Non-pharmacological management

Physiotherapy

1.8.1 Adults with RA should have access to specialist physiotherapy, with periodic review (see 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 1.9.2 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]**

2012 surveillance review

The 2012 review found aerobic and strength based exercise to be beneficial to people with RA, provided a tailored approach was taken.

2015 surveillance review

Evidence was found relating to access to physiotherapy and improving general fitness such as muscle strengthening and joint flexibility exercises. No impact was anticipated as the evidence was consistent with the guideline recommendations.

2020 exceptional review

In the 2020 exceptional surveillance review of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

General exercise/physical activity

An RCT (Azeez et al, 2020) aimed to investigate the effects of an exercise programme on multiple outcomes for patients (n=66) with RA. Primary outcomes included aerobic capacity, body composition, cognition and muscle strength. Patients were randomised to usual care or a personalised exercise programme. The exercise group saw significant improvements in CRP level (p=0.025), fatigue scores (p=0.047), truncal fat (p=0.004), aerobic capacity (p=0.002) and grip strength (right p=0.025, left p=0.005). Improvements in cognitive function were seen in the exercise group at 3 months post intervention with median Montreal Cognitive Assessment scores improving from 25.5 to 28.0 (p=0.01). Median waist circumference was significantly decreased in the exercise group compared to the usual care group (p<0.0001). The authors conclude that a significant and positive impact is seen on cognitive function in RA patients when exercise is increased, and also state that physical activity is safe for people with inflammatory joint disease, however no data for safety was presented in the abstract.

An RCT (Katz et al 2018) aimed to increase physical activity and decrease fatigue with a pedometer based intervention in people with RA. Participants (n=96) were randomised to a control group (education only) or one of 2 intervention groups, consisting of pedometer and step monitoring with (PED+ group) or without (PED group) daily step targets. Assessments were undertaken at baseline, 10 and 21 weeks, with baseline and week 21 also including a

week of activity monitoring. The control group saw a reduction in steps, however both the PED and PED+ group saw significant improvements in step count (p=0.004 and p=0.001 respectively). All 3 groups saw a significant improvement in mean fatigue scores from baseline to week 21, with the PED and PED+ groups also reporting an improvement in function and self-reported disease activity. The authors conclude that activity levels can be improved by provision of pedometers with and without daily step goals.

An RCT (Lange et al, 2019) investigated the effect of a 20 week moderate to high intensity gym based exercise program (n=36) compared to home based, light intensity exercise (n=38) in older adults (ages 65-75) with RA. The primary outcome of difference in the Health Assessment Questionnaire disability index (HAQ-DI) was assessed at baseline, 20 weeks and 12 months, no significant between group differences were seen. However, from baseline to 12 months a significant improvement in HAQ-DI was seen in the gym based exercise group (p=0.022). Significant between group differences in favour of the gym based group were seen for the secondary outcomes of aerobic capacity (p<0.001) and endurance and strength (p<0.05), patient rated health scores were also higher in the gym based group (74%) compared to the home based group (24%). The authors conclude that aerobic and resistance based moderate to high intensity exercise improved physical fitness of older RA patients.

Water-based exercise

A systematic review (Medrado et al, 2022) aimed to investigate the effect of aquatic based exercise on inflammatory arthritis (IA). Studies were included if the primary intervention was aquatic exercise for people with IA, compared to any other intervention or usual care. Nine studies with 604 participants were included in the analysis. Aquatic exercise was superior to home based exercise for the outcome of pain, in 2 studies. Aquatic exercise significantly improved disease activity in 1 study compared to both a control group and a land based exercise group. Improvements in physical function were seen in 2 studies that used therapy containing aquatic exercise. The results of the 4 remaining included studies were not reported in the abstract. The systematic review suggests that aquatic exercise may be beneficial for patients with IA, however the authors state that further research is required to determine superiority to land based exercise.

Resistance exercise

A systematic review and meta-analysis (Dos Santos et al, 2021) investigated the impact of low intensity resistance training combined with blood flow restriction in patients with RA and osteoarthritis, as high and medium intensity resistance exercise may present challenges to patients. Five RCTs were included in the review, however no improvements were seen for low intensity resistance exercise with blood flow restriction when compared to high or medium intensity resistance exercise. Results were measured using muscle strength, assessed by quadricep function (p=0.96), functionality, assessed by walking pattern tests (p=0.82), and comparisons in muscle mass between the low intensity and high intensity exercise (similar gain reported). The knee extension test was used to assess muscle strength in 1 group where low intensity resistance exercise was compared with and without blood flow restriction, reporting that the blood flow restriction group was generally higher. Although the results for

certain aspects of this review seem positive, there is a lack of data in the abstract to support these claims. It is also not possible to determine which patients had RA in these groups.

A meta-analysis (Wen & Chai, 2021) of 17 RCTs examined the effect of resistance exercise (n=512) on RA patient outcomes compared to a control group (n=498). Disease activity score (DAS28 was significantly reduced in the resistance exercise group (SMD -0.69, 95% CI -1.26 to -0.11), as was erythrocyte sedimentation rate (SMD -0.86, 95% CI -1.65 to -0.07) and time taken to walk 50 ft (SMD -0.61, 95% CI -1.49 to -0.27). However, no significant improvement was seen in visual analogue scale or health assessment questionnaires. The results suggest that resistance exercise may be beneficial for RA patients, however the authors state that larger RCTs are required in this area.

Aerobic exercise

A meta-analysis (Kelley et al, 2018) of 9 RCTs (n=298) used the minimal important difference (MID) approach to investigate if there was an association between land based aerobic exercise and self-reported fatigue in RA patients. Statistically significant reductions in self-reported fatigue were seen (MID -0.34, 95% CI -0.58 to -0.10, p=0.006) when results were pooled using a random effects model. Results remained significant when 1 effect size represented each study (MID -0.39, 95% CI -0.76 to -0.03, p=0.04). However, the authors conclude that it may not be possible for patients with RA to achieve clinically relevant fatigue reductions across a substantial number of patients.

A systematic review and meta-analysis (Kelley et al, 2018) examined the effects of aerobic and/or strength training on anxiety in adults with RA, osteoarthritis, or fibromyalgia. RCTs (n=14) were included where the exercise intervention lasted a minimum of 4 weeks and included adults aged 18 and over. Average exercise duration per session across all trials was 28.8 (+/- 14.3) minutes, 3.3 (+/-1.3) times per week, lasting an average of 15.8 (+/-6.7) weeks. Anxiety was significantly reduced (p=0.0004, 95% CI -0.65 to -0.15) in the exercise groups (n=539) compared to the control groups (n=387). The authors conclude that further RCTs are needed in this area. Despite improvements in anxiety being seen, the abstract does not provide detailed information on the number of adults with RA seeing an improvement in their anxiety, as such making it difficult to extrapolate the results for this population.

A systematic review and meta-analysis (Ye et al 2022) aimed to evaluate the safety and effectiveness of aerobic activity in RA patients for the primary outcome of improving RA symptoms. The meta-analysis (13 RCTs, 967 patients) found aerobic exercise to significantly improve aerobic capacity (MD = 2.41, 95% CI 1.36 to 3.45, P < 0.00001), functional ability (MD - 0.25, 95% CI - 0.38 to - 0.11, P = 0.0002) and relieve pain (SMD = - 0.46, 95% CI - 0.90 to - 0.01, P = 0.04) in RA patients. The sit to stand test also saw significant improvements (MD = 1.60, 95% CI 0.07 to 3.13, P = 0.04). The authors conclude that aerobic exercise appears to be both safe and effective for patients with RA, however state that further high-quality studies should be conducted to verify the results.

Hand exercises

An RCT (Ellegaard et al, 2019) aimed to examine whether a compensatory intervention (CIP) with additional hand exercises (intervention group) improved daily living activities compared to CIP alone (control group) in women (n=55) with hand related RA. The CIP process involved alternative ways of performing daily tasks, assistive devices and joint protection. Assessments took place at baseline and at 8 weeks, with results showing no significant differences between the control and the intervention group (95% CI -0.16 to 0.25). Both groups did however see significant improvements from baseline (Intervention 95% CI 0.09 to 0.39, control 95% CI 0.05 to 0.35), with 13 and 12 participants from each group respectively achieving clinically relevant improvements in motor ability. The study concludes that no additional benefit was seen when hand exercises were added to the CIP intervention.

A Cochrane review (Williams et al, 2018) aimed to assess the benefits and harms of hand exercises in adults with RA. Seven studies (n=841 20-94 year olds) met the inclusion criteria with most using appropriate validated diagnostic criteria. Two studies were classed as having high-quality evidence, 1 found little or no improvement on mean grip strength with exercise compared to usual care (95% CI -0.27 to 3.07), while the other found no effect of exercise on pinch strength (95% CI -0.14 to 0.74). Three studies had moderate quality evidence. One found exercise 'probably slightly improves hand function' in the medium (3- 11 months, 95% CI 1.58-7.42) and long term (12 months +, 95% CI 0.86-7.74) compared to usual care. One study found little to no difference on pain in the medium (95% CI -6.96 to 1.36) or long term (95% CI -8.1 to 0.7) between the exercise and control groups. The third study noted that exercise + adherence strategies probably helped adherence compared to no adherence strategies in the medium term. Other studies assessed as having low or very low quality evidence found exercise slightly improves short-term (less than 3 months) hand function compared to usual care (95% CI 1.58 to 7.42) in 1 study, pain improvement was uncertain between the exercise and no treatment groups in 2 studies (95% CI -48.93 to -7.03), 1 study found uncertainty between groups for pinch strength. The authors note that no study used the American College of Rheumatology 50 criteria. Only 1 study reported on adverse events (none found). The mixed evidence suggests uncertainty on the impact of exercise on hand function/pain in patients with RA.

A secondary analysis of the SARAH trial (Boniface et al, 2022) investigated the effect of 'prescribed dose' of hand strengthening exercise for RA patients (n=490), using 3 different analyses. Analysis 1 assessed therapist background and grade, participants baseline physical and psychological state and prescribed dose of hand strengthening exercise. Being prescribed a lower dose of hand strengthening exercise was associated with a higher number of swollen wrist/hand joints, patients feeling downhearted, joint deformity and being treated by an occupational therapist. While being prescribed a higher dose of hand strengthening exercise was associated with greater participant confidence, higher baseline grip strength, confidence in exercising and being treated by a grade 6 therapist. Analysis 2 and 3 compared prescribed hand exercise dose with overall hand function and grip strength, finding significant improvements for both (95% CI 0.001 to 0.010 and 95% CI 0.000 to 0.025 respectively) at 4

months post intervention. The study concludes that higher prescribed doses of hand exercises were associated with better clinical outcomes.

Yoga & Tai Chi

An RCT (Gautam et al, 2019) aimed to investigate the effects of a yoga based mind body intervention on RA inflammatory markers. Patients (n=72) were randomised to either the yoga intervention group (yoga + DMARDs) or control group (DMARDs) alone. Blood samples were collected at baseline and at 8 weeks to measure systemic biomarkers. Systemic inflammatory markers were significantly reduced in the yoga group, as was the DAS 28 ESR score ($p<0.0001$) and HAQ-DI ($p=0.001$) compared to the control group. A significant time dependent step wise decline in depressive symptoms was also seen in the yoga based group compared to the control group over the 8 week period ($p<0.0001$). The authors concluded that the yoga mind body intervention aided remission and depression in patients with RA.

An RCT (Puksic et al, 2021) aimed to explore the effectiveness and feasibility of yoga on HRQoL in RA patients. The yoga intervention group involved 90 minute yoga sessions twice a week for 12 weeks, while the control group received 60 minutes of educational lectures on RA topics once a week. No significant impact on RA disease activity was seen in the yoga group compared to the control group, however improvements in fatigue (95% CI 1.29 to 8.86, $p=0.009$) and mood (anxiety 95% CI -3.34 to - 0.23, $p = 0.025$ and depression 95% CI -2.38 to -0.36), $p = 0.008$) were significant, and were maintained at post intervention follow up (24 weeks). Patient adherence and retention was high with no serious adverse events reported. The study concludes that yoga programs may compliment RA treatment, and is both feasible and safe for patients in this population.

A systematic review and meta-analysis (de Orleans et al, 2022) investigated the effect of yoga in patients with chronic fatigue syndrome, fibromyalgia, osteoarthritis and RA for the primary outcomes of anxiety, depression, overall mood and sleep quality. Of 27 included studies, 18 were included in the meta-analysis, however the authors state that a high or uncertain risk of bias was seen in the majority of included studies. Yoga was found to significantly improve anxiety (SMD-0.51; 95% CI = -0.81 to -0.20), depressive symptoms (SMD -0.88, 95% CI -1.42 to -0.34) and sleep quality (SMD = -0.96; 95% CI = -1.36 to -0.56) in this population, however when yoga was compared to other exercise methods, no significant differences were seen ($p<0.01$). As the study population included patients other than those with RA, it is difficult to ascertain if yoga is effective for the above outcomes for RA patients.

A systematic review and meta-analysis (Ye et al, 2020) aimed to investigate the efficacy of yoga for RA patients. Ten RCTs (n=840 patients) were included, with an age range of 30-70 years old. Statistically significant effects were seen for yoga interventions for disease activity (SMD -0.38, 95% CI -0.71 to -0.06, $P = 0.02$), grip strength (SMD 1.30, 95% CI 0.47-2.13, $P = 0.002$) and physical function (SMD -0.32, 95% CI -0.58 to -0.05, $P = 0.02$). Inflammatory cytokines were investigated (CRP, ESR, IL-6, TNF-alpha) however no significant effect was seen. Similar no significant effects were seen for pain, swollen or tender joints. The results

indicate a positive effect of yoga for RA patients however the study authors suggest caution in interpreting these results due to methodological limitations and small sample sizes.

A Cochrane review (Mudano et al, 2019) that assessed the impact of Tai Chi for RA was updated, adding 3 further studies (156 patients), now totalling 7 trials (345 patients). Studies with any duration of Tai Chi intervention (range 8-12 weeks) were included if they had a control group, in RA patients aged 16 and over, from centres in China, South Korea and the USA. The results state uncertainty as to whether Tai Chi programmes improved pain in a clinically significant way compared to no therapy or alternative therapy, assessed using the visual analogue scale with scores ranging from a decrease in pain (0.51) to an increase (1.6) at the 12 week timepoint. The majority of studies included had very low quality evidence, which was downgraded due to lack of blinding and attrition bias. One study found a slight improvement with Tai Chi compared to a control group for disease activity, however it had a small sample size and problems with bias. Results from the remaining studies were inconclusive, however patients in Tai Chi groups did see a lower drop out rate compared to control groups. Not all studies reported on short-term adverse events such as muscle pain, joint pain and cramps, with no reporting of long term adverse events. The authors conclude there has been minimal change from the previous review, and as such state there is uncertainty as to whether Tai Chi impacts on RA-related pain.

Intelligence gathering

An NIHR study (Williamson et al., 2020) was highlighted during intelligence gathering, and also through the search for new evidence. As such it has been summarised above in the 2023 surveillance summary.

A review (Gwinnutt et al, 2022) of the 2021 EULAR recommendation on lifestyle behaviours for rheumatic and musculoskeletal disease (RMD) was undertaken to assess 6 lifestyle exposures for 7 RMDs. The review resulted in 5 principles and 18 recommendations, focusing on the importance of a healthy lifestyle for RMD patients, particularly highlighting the importance of exercise on disability and pain, a healthy balanced diet, support to quit smoking and encouraging work participation. The review found small amounts of alcohol were unlikely to have an impact on the RMDs, with the exception of moderate amounts of alcohol in RA and gout patients. The findings of this review are largely in line with the recommendations in NICE guideline NG100, however greater emphasis on exercise could be applied to NG100.

A patient group highlighted that exercise should be an important pillar of non-pharmacological treatment for people with RA, particularly resistance and high intensity aerobic exercise. They also mentioned that suitable online programmes are available which are aimed at people with arthritis.

Impact statement

General exercise/physical activity

An RCT found improved CRP with increased exercise in people with RA, alongside improvements in fatigue, grip strength aerobic capacity and cognitive function. A second RCT found the use of a pedometer increased exercise in RA patients and led to improved fatigue scores and reduced disease activity. Moderate to high intensity gym based exercise were evaluated by a third RCT, improvements in aerobic capacity and endurance were found in older people with RA, however the abstract does not detail whether these factors are important measures for people with RA. Overall, increased physical activity improved cognitive issues and disease activity scores in people with RA. There are currently no recommendations regarding general exercise for people with RA, as such the new evidence in this area is likely to impact guideline recommendations.

Water-based exercise

A systematic review found water-based exercise was more beneficial for inflammatory arthritis patients compared to home based exercises, however it did not specify the results for RA patients alone. There are currently no recommendations regarding exercise for people with RA, as such this systematic review might have an impact on current guideline recommendations.

Resistance exercise

A systematic review and meta-analysis found no improvement for RA and osteoarthritis patients when low intensity exercise with additional blood flow restriction was compared to medium and high intensity exercise. A meta-analysis found resistance exercise improved ESR, disease activity and walk time but not visual analogue scale or health assessment questionnaires in RA patients. The evidence found for resistance exercise is mixed, however as there are currently no recommendations on exercise, there may be an impact on the guideline recommendations.

Aerobic exercise

A meta-analysis found fatigue was reduced with land based aerobic exercise in RA patients, while a systematic review and meta-analysis also found anxiety was reduced by aerobic exercise in RA, osteoarthritis and fibromyalgia patients. However, this review did not give the results for RA patients alone. A second systematic review and meta-analysis found exercise was both safe and effective for patients with RA, as the study noted this is often a concern for patients in this population. Overall aerobic exercise was safe and effective for reducing fatigue and anxiety in RA patients, as such the new evidence found may have an impact on guideline recommendations.

Hand exercises

An RCT found no significant differences when hand exercises were added to a compensatory intervention for RA patients. A Cochrane review found mixed evidence on hand exercises for

the outcomes of grip strength, hand function, pain and pinch strength. Whereas an analysis found higher prescribed doses of hand exercises led to improved clinical outcomes for RA patients. The current guideline recommendations state to consider a tailored approach to hand exercises in people with RA, and as such the evidence found does not suggest a change at this time.

Yoga & Tai Chi

An RCT found yoga based interventions improved depressive symptoms and aided RA remission, with a second RCT finding yoga interventions to be both safe and feasible for RA patients. A systematic review and meta-analysis found yoga improved anxiety, depression and sleep quality at least as well as other exercise interventions, however this was a mixed population where subgroup effects for RA cannot be explored at abstract level. A second systematic review and meta-analysis found yoga improved disease activity, grip strength and physical fitness but not joint pain in RA patients.

A meta-analysis found yoga improves knee-based arthritis however it did not specify how much improvement was seen in RA patients compared to osteoarthritis patients. An updated Cochrane review found that uncertainty remains over the usefulness of Tai Chi based interventions for patients with RA. Yoga and Tai Chi are not currently included within the guideline recommendations, as there are no recommendations on exercise in general. As such the evidence found here may have an impact on the guideline recommendations.

Other external guidelines on exercise

The 2021 EULAR guidelines highlight the importance of exercise on disability and pain in RA patients. These recommendations are largely evidence-based with consensus reached by a broad range of health professionals, scientists and people with RA. There are 7 exercise specific exposure recommendations:

- Exercise 1: Exercise is beneficial for many health outcomes, including but not limited to RMD symptoms and progression
- Exercise 2: People with rheumatic and musculoskeletal diseases (RMDs) should exercise because of the benefits on pain, function and quality of life
- Exercise 3: People with RMDs should avoid physical inactivity; they should engage in regular exercise according to their abilities
- Exercise 4: People with RMDs should perform both aerobic and strengthening exercises aiming for at least moderate intensity
- Exercise 5: People with RMDs should be advised that exercise is safe and that it is never too late to start exercising
- Exercise 6: Exercise can be performed in different settings, alone or in groups. There is a slight benefit favouring group exercises over exercises performed alone

- Exercise 7: People with osteoarthritis and axial spondyloarthritis should be especially encouraged to exercise as it is particularly beneficial for disease related outcomes

Final summary of impact

Exercise/physical activity has a positive impact on a variety of health metrics for patients with RA, with yoga, aerobic exercise and resistance exercise appearing to be particularly beneficial. The 2021 EULAR guidelines actively promote exercise for this patient group. Currently there is a gap in NICE guideline NG100 where physical activity is concerned, with section 1.8 (non-pharmacological management) being focused on specific areas such as hand exercises. There is not currently a suitable NICE guideline that covers the same aspects of physical activity for this population. Patient groups also felt strongly that the inclusion of recommendations on physical activity would benefit people with RA and currently represents a lack of consistency with EULAR recommendations was also raised. There is high volume of evidence identified in this surveillance review that exercise and physical activity are beneficial to people with RA. This is a gap in current guideline that addition of recommendations may be required.

New evidence identified that may change current recommendations.

1.8 Cognitive behavioural therapy for fatigue

Surveillance proposal

These recommendations should not be updated.

Relevant recommendations

Psychological interventions

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

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

2012 surveillance review

The 2012 review found psychological treatment to be beneficial to many people with RA, including self-regulation interventions. No impact was anticipated as this was found to be consistent with existing guideline recommendations.

2015 surveillance review

No evidence was found at this surveillance review.

2020 exceptional review

In previous surveillance of this guideline, no studies relevant to this section of the guideline were identified.

2023 surveillance summary

A systematic review (DiRenzo et al, 2018) of 5 RCT's and 1 post hoc analysis (n=399) investigated the efficacy of mindfulness-based interventions on RA. Both patient and clinician reported outcomes were considered. Clinical RA outcomes were evaluated in 3 studies, with 1 study showing an improvement in disease activity, however a meta-analysis found no statistically significant difference. Improvements in depressive symptoms, psychological distress and self-efficacy were seen when evaluating psychological outcomes in 4 of the studies. The authors conclude that mindfulness-based interventions may be useful in improving psychological distress in RA patients.

A systematic review and meta-analysis (Shen et al 2020) of 6 RCT's examined the effects of cognitive behavioural therapy (CBT) on both the physiological and psychological health of RA patients. Standard mean difference and 95% confidence intervals were used for analysis. CBT significantly reduced fatigue in RA patients ($p=0.006$). Anxiety ($p=0.005$) and depression ($p<0.00001$) were also reduced significantly with the use of CBT. However, no detail of the stage of patients RA was given in the abstract, neither were details of the type of CBT used. The authors conclude that further studies in this area are required, such as large scale RCTs.

A systematic review of reviews (Prothero et al 2018) aimed to assess the impact of psychological interventions on biopsychosocial outcomes for adults with RA. Eight studies met the review inclusion criteria; RCT's of psychological interventions, adult RA patients and reported at least 1 of the primary outcomes (disease activity, fatigue, functional disability, pain and psychological status). Aims of the review included: determining the effectiveness of psychological outcomes, assessing the intensity of psychological interventions on outcomes and assessing the impact of usual care in the comparator group on outcomes. The results state that only a small post intervention improvement was seen for the outcome of fatigue, however the psychological interventions examined in this review were not limited strictly to CBT. Other psychological techniques were included such as supportive counselling, psychotherapy and self-regulation techniques, all of which were used alongside existing medication. Other examined outcomes such as self-efficacy, coping and physical activity saw greater improvements which were maintained for longer, particularly when the intervention was delivered of a longer period. The results also state that some small improvements were seen in the usual care group, however the abstract does not specify which outcomes these improvements were for. Authors conclude that these results indicate areas for future research regarding the use of CBT in patients with RA.

The RAFT RCT (Hewlett et al 2019) investigated whether group CBT + usual care reduced fatigue impact in RA patients compared to usual care alone. Adult patients were enrolled from multiple centres if they had a fatigue severity >6/10 and no recent changes to their prescribed medication. The group CBT course consisted of 7 sessions delivered by pairs of

rheumatology occupational therapists or nurses. Usual care involved following the Arthritis Research UK fatigue booklet. Outcomes were measured using the Bristol RA Fatigue Effect Numerical Rating Scale (BRAF-NRS 0-10), with baseline scores adjusted for using intention to treat regression analysis. A total of 308 patients completed the initial 26-week study period (156 CBT + usual care group, 152 usual care alone). At 26 weeks, improvements in BRAF-NRS effect (-0.59, CI -1.11 to -0.06), BRAF multidimensional questionnaire (MDQ) (-3.42, CI -6.44 to -0.39), living with fatigue (-1.19, CI -2.17 to -0.21) and emotional fatigue (-0.91, CI -1.58 to -0.23) were seen in the group CBT + usual care group, compared to the usual care alone group. These significant improvements were maintained for all outcomes at 2 years post intervention. The CBT + usual care group achieved a patient satisfaction score of 89% in 8/10 participants, which was significantly higher ($p<0.0001$) than in the usual care alone group where this was only achieved by 54% of participants. The authors conclude that multiple fatigue outcomes in RA patients can be improved for a period of at least 2 years by the use of group CBT delivered by rheumatology teams.

A single arm, open label study (Blaney et al 2021) investigated the effect of a non-therapist assisted, online mental health intervention which targets anxiety in RA patients. Participants (n=34) were enrolled if they had raised anxiety symptoms and confirmed RA. The online mental health intervention consisted of an internet based CBT program which had been validated and shown to be effective in the general population. Outcomes were reported at baseline, post intervention and at 3 month follow up, using self-reported measures covering a variety of symptoms including: anxiety, depression, fatigue and pain. Fatigue symptoms were significantly improved from baseline to 3 months follow up, confirmed by post-hoc analysis (effect size 0.39 to 0.81, however this also included results for anxiety and depression). As this study did not include a comparison group it is difficult to establish whether the internet led CBT program was more effective than usual care for fatigue in patients with RA.

A clinical trial (Yousefi et al 2022) compared 2 treatment options for patients with RA to usual care. Fifty-seven patients were randomly assigned to either Mindfulness-Based Stress Reduction (MBSR), CBT, or care as usual (control group). Results were scored at 3 timepoints, baseline, post treatment and follow up using the following scales: Activity Disease (DAS-28), Chalder Fatigue Scale, Pittsburgh sleep quality and Tower of London test. Chronic fatigue and sleep quality were significantly improved at the post treatment and follow up stages in both the MBSR and CBT groups compared to the usual care group ($p<0.01$). However, the abstract did not state what the MBSR intervention consisted of, nor the approach to CBT taken.

Intelligence gathering

An NIHR study was highlighted during intelligence gathering which added further analysis to the RAFT study above by Hewlett et al. The NIHR study abstract describes the clinical effectiveness results as above, however it adds a cost-effective analysis. This was explored during the intervention by assessing RA-related health and social care costs which allowed QALYs to be calculated with the EQ-5 D-5 L. The study found no significant difference in costs when the intervention group (group CBT) was compared to usual care alone, however no significant difference was seen in QALYs gained between groups. The authors state the

probability of RAFT being cost-effective at the NICE thresholds of £20,000-£30,000 was 28-35%. Data was missing for a small number of patients (n=25) and the EQ-5 D-5 L may not have captured change in fatigue. The authors conclude that RAFT is effective at improving fatigue, sustained over a 2-year period. They also note patient satisfaction was high and no harms were reported. However, despite the NHS costs being similar for each group, the RAFT programme had a low likelihood of being cost-effective, suggesting that further work could be undertaken in this area.

Impact statement

Results from all 6 studies found improvements in fatigue from various psychological interventions, including CBT, internet based CBT, group CBT and mindfulness interventions. These results were significant in 4 of the studies. However, no study used the same scale for outcome results, and 4 of the studies did not detail what the psychological intervention involved (type, duration, method of delivery). One study did not have a control group, making it difficult to interpret the value of the findings. The cost-effective analysis of the RAFT RCT, despite finding little difference in NHS costs between groups, had only a 28-35% chance of being cost-effective. Where significant improvements were seen, these were maintained at varying timepoints depending on the study endpoints, with the RAFT RCT maintaining improvements in fatigue at 2 years post intervention.

Recommendation 1.8.7 currently states to offer psychological interventions such as cognitive coping skills to help RA patients adjust to living with their condition. Fatigue is mentioned in recommendation 1.7.1 which calls for MDT access for RA patients to help manage conditions affecting their daily lives, such as fatigue, however there are no recommendations currently linking CBT to manage fatigue.

The evidence found at this review is currently mixed and spread across multiple applications of CBT, while also finding it unlikely to be cost-effective. At this time there is not enough evidence to suggest a change to the current guideline recommendations, however this topic should be noted on the guideline issue log for the next surveillance review.

New evidence is unlikely to change guideline recommendations.

1.9 Monitoring

Surveillance proposal

These recommendations should not be updated.

Recommendations

1.9.1 Ensure that all adults with RA have:

- rapid access to specialist care for 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.

  Follow recommendation 1.2.1 if the target is not maintained. **[2009, amended 2020]**

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]**

2012 surveillance review

No evidence identified at this review.

2015 surveillance review

Evidence was found relating to gait analysis for lower limb assessment in RA patients, however the study authors concluded that further work was needed in this area. The review also found evidence relating to monitoring disease activity using DAS, DAS28, CRP and joint count assessment, these were deemed to be in line with current guideline recommendations. There was no clinical feedback in this area at the 2015 surveillance review.

2020 exceptional review

No evidence identified at this review.

2023 surveillance summary

Zhang et al, 2018 aimed to investigate the value of MRI for the diagnosis of subclinical inflammation in predicting radiographic progression in people with early RA. patients (n=76) were included if they were in remission for at least 1 year from early RA and had MRI imaging from baseline and 12 months available. The MRI showed some inflammation for the included patients at the 1-year time point (43.4% synovitis, 39.5% bone marrow oedema, and 9.2% tenosynovitis) with bone erosion progression noted in 25 patients (32.9%). The results for increase in bone marrow oedema and bone erosion progression were statistically significant ($p=0.01$, $p<0.001$ respectively). The authors conclude that although the observed patients were in clinical remission, sustained inflammation could be detected via MRI and may be a strong predictor of bone erosion progression in the future.

Intelligence gathering

A study highlighted by a topic expert on the European society of skeletal radiology (ESSR), with its recommendations on use of MRI (2015) which states that MRI is currently considered the best non-invasive imaging modality to evaluate inflammation in the joints, tendons and bone marrow. Indications for MRI in rheumatic disease classification includes early diagnosis of inflammation, disease follow up including therapeutic monitoring, assessment of peripheral joint inflammation and confirmation of clinically active joint changes. It gives very detailed information regarding the wide variety of uses for MRI in RA patients from initial diagnosis through to monitoring of other joints in the body for complications.

Impact statement

There is new evidence which suggests MRI may play a role in monitoring disease progression as sustained inflammation could be detected on MRI for patients in clinical remission. However, this is a small study and it is unclear whether MRI monitoring predicts clinical progression or whether it is cost-effective, and as such further evidence is needed in this area. Imaging checks are not currently recommended at either the 6 month or annual review for people in remission. Currently, only a 'do not use' recommendation is given in section 1.9 regarding the use of imaging for monitoring, which is for ultrasound rather than MRI. The use of MRI for monitoring of people with RA who are in remission should be monitored closely at the next review as it is an emerging area of interest, as highlighted by the ESSR recommendations, however as more evidence is required, no impact is anticipated at this time.

New evidence is unlikely to change guideline recommendations.

Research recommendations

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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified

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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

5 Management of poor prognosis

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

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.