National Institute for Health and Care Excellence

Final

Rheumatoid arthritis in adults: diagnosis and management

Evidence review D Target for monitoring

NICE guideline NG100

Intervention evidence review

July 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3003-6

Contents

1 Target for monitoring

1.1 Review question: In adults with rheumatoid arthritis, what is the best target to use when monitoring disease activity (remission or low disease activity)?

1.2 Introduction

Current consensus amongst the rheumatology community is that a treat-to-target strategy should be used when treating people with rheumatoid arthritis (RA) with DMARDs. A treat-to-target strategy is a strategy that defines a treatment target (such as remission or low disease activity) and applies tight control (for example, monthly visits and respective treatment adjustment) to reach this target. The treatment strategy often follows a protocol for treatment adaptions depending on the disease activity level and degree of response to treatment.

The 2009 NICE guideline: Rheumatoid arthritis in adults: management[9] suggested a treat-to-target approach in the recommendations that said to measure inflammatory markers and disease activity monthly "until treatment has controlled the disease to a level previously agreed with the person with RA". However, the committee agreed that the evidence for a treat-to-target strategy should be reviewed, to make this recommendation clearer and more direct if supported by the evidence.

The committee also agreed that greater clarity was needed on how frequently people with rheumatoid arthritis should be monitored, as there was currently variation in practice and some uncertainty about how frequent monitoring should be in different groups of people with rheumatoid arthritis with varying degrees of disease activity. However, the frequency of monitoring review excluded an update of the annual review recommended in the previous guideline, as it is an essential and well-established practice and therefore was not included within the scope of this update.

Three interrelated evidence reviews were conducted to answer the following key questions in this area:

1. Is treat-to-target more effective than usual care?
2. If so, should the treatment target be low disease activity or remission?
3. How often should people be monitored, outside of the annual review?

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with RA, with at least moderate disease activity (equivalent to DAS28 ≥ 3.2). Studies in adults with poor prognostic factors will be reviewed separately.
Intervention(s)	Monitoring a composite measure of disease activity with a target of **disease remission** The following composite measures will be considered: • Disease activity score 28 (DAS28). DAS28 < 2.6 = remission

	• Original disease activity score (DAS). DAS < 1.6 = remission • Simplified disease activity index (SDAI). SDAI ≤ 3.3 = remission The different disease activity measures will be pooled in the analysis.
Comparison(s)	Monitoring a composite measure of disease activity with a target of **low disease activity** The following composite measures will be considered: • Disease activity score (DAS28; all versions). DAS28 < 3.2 = low disease activity • Original disease activity score (DAS; all versions). DAS < 2.4 = low disease activity • Simplified disease activity index (SDAI). SDAI ≤ 11.0 = low disease activity The different disease activity measures will be pooled in the analysis.
Outcomes	CRITICAL • Disease Activity Score (continuous) at 12 months • Quality of life (continuous) at 12 months • Function (continuous) at 12 months IMPORTANT • Fatigue (continuous) at 12 months • Pain (continuous) at 12 months • Radiological progression (continuous) at 12 months • Withdrawal/adherence (dichotomous) at longest reported time point
Study design	RCT Systematic review of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[1] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised controlled trials and systematic reviews of randomised controlled trials comparing remission with low disease activity as targets in monitoring RA.

No relevant clinical studies were identified.

See also the study selection flow chart in appendix C.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.5.4 Quality assessment of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

Table 2: UK costs of healthcare professional visits

Type of appointment	Unit cost	Source
GP appointment lasting 9.22 minutes	£36	PSSRU Unit costs 2016[4]
Non-admitted face to face outpatient follow-up attendance, rheumatology (consultant led)	£137	NHS reference costs 2015-2016[5]
Non-admitted face to face outpatient follow-up attendance, rheumatology (non-consultant led)	£87	NHS reference costs 2015-2016[5]
Hospital based nurse, band 6, specialist nurse (per working hour/per hour of patient contact)	£44/£108	PSSRU Unit costs 2016[4]

1.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

No relevant clinical studies were identified.

1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The critical outcomes were agreed to be the Disease Activity Score (DAS), quality of life and function for all 3 reviews.

Pain, radiographic progression, fatigue and the number of people who withdrew from the trial were agreed to be important outcomes for all 3 reviews. The treat-to-target review and the frequency of monitoring review also specified the number of people achieving remission and low disease activity, using DAS thresholds, as important outcomes. The committee agreed that data reported in this format are not as informative as continuous DAS data but still give an indication of symptom relief and disease activity improvement. Disease activity data in this dichotomous format were not considered informative for the review of whether low disease activity or remission was the better target given the question posed by the review.

In the treat-to-target review, no data were available for the outcome of fatigue. For the frequency of monitoring review, no data were available for any of the disease activity outcomes, quality of life or fatigue.

No studies were identified for the review of remission compared with low disease activity as a treatment target.

1.9.1.2 The quality of the evidence

Treat-to-target versus usual care

Five studies were included in the review of treat-to-target versus usual care. The quality of the evidence was varied, ranging from moderate to very low quality, with the majority of the outcomes graded either low or very low quality. A lack of blinding was a source of risk of bias in all of the included studies. Some studies also poorly reported aspects of their design such as how they randomised participants, concealed allocation, and dealt with missing data, which affected the quality rating. For those outcomes where the data was reported by only 1 or 2 trials, the confidence intervals tended to be wide which meant there was some uncertainty about whether the treat-to-target strategy was more effective than usual care.

Importantly, there was substantial inconsistency in the magnitude of the benefit of treat-to-target across the studies and between different treat-to-target arms within studies, which also affected the quality of the evidence for most outcomes (DAS, HAQ, remission, low disease activity, pain, and study discontinuation). It was not possible to conduct formal subgroup analysis to see if this explained the heterogeneity, as there were too few studies in each subgroup category. However, the committee discussed the possible reasons for these differing results. The committee noted the great variation in the design of the studies, particularly around the disease duration of participants (which ranged from less than 1 year in 1 study, to a median of 6-7 years in another study), the nature of the target used in the intervention arm (whether a DAS-based target was used), and whether or not either or both study arms used a protocol-driven treatment strategy (some studies did not use a protocol in either arm, other studies used a protocol in both arms and some studies compared a protocol in the intervention arm to usual care without a protocol).

The committee agreed that it was not possible to establish definitively which of these factors (if any) might explain the differences in the magnitude of the effect between the studies. However, the committee noted that while there was some inconsistency in the magnitude of the benefit of treat-to-target in improving disease activity, function and pain, in general the majority of evidence across outcomes favoured treat-to-target over usual care. The few

results that did suggest a benefit of usual care were generally from the non- DAS-based target arms of 2 studies (which used targets of zero swollen joint count and matrix metalloproteinase 3 levels).The results of the DAS-based target arms of those studies favoured the intervention arm, consistent with the other study results.

Remission or low disease activity as the target

No evidence was identified comparing the targets of remission or low disease activity. Recommendations were therefore informed by GC consensus opinion.

Frequency of monitoring

One study was included in the review of different monitoring frequencies. This study compared patient-initiated rapid access with traditionally scheduled reviews every 3 to 6 months. All of the evidence was assessed to be very low quality. Lack of blinding, along with relatively high rates of missing data and limited information about how this was dealt with in the analysis contributed to the risk of bias. It was also unclear what was measured at each review and whether the minimum requirements as specified in the review protocol were satisfied (assessment of the joints for swelling and measurement of inflammatory markers), which further weakened the evidence. The evidence was also assessed to be indirect to that specified in the protocol due to the variation in the frequency of reviews in the control group, and the population being a mix of people with stable and unstable disease.

No studies were found comparing any other frequencies of monitoring.

People at risk of poor outcomes

People with a poor prognosis were pre-specified as a separate stratum in the protocols for the review of remission versus low disease activity as a target and the review of frequency of monitoring. People with a poor prognosis were considered to be those with one or more of the key prognostic factors identified in a separate review, which were anti-CCP positive status and the presence of erosions at baseline. No evidence was found in this subgroup of people for either question.

1.9.1.3 Benefits and harms

Treat-to-target versus usual care

The committee agreed that the evidence for the treat-to-target versus usual care review suggested that a treat-to-target approach was more effective than usual care. The committee acknowledged the limitations of the evidence base described above, but were persuaded by the consistency of the overall findings of a clinically important benefit in favour of treat-to-target across almost all of the outcomes. The committee acknowledged that the more frequent appointments usually required with treat-to-target management could, for some people, be difficult to combine with full time work, although this would depend on the individual. The committee were reassured by the evidence that not only did treat-to-target appear to be more clinically effective than usual care, study discontinuation rates tended to be lower in people receiving treat-to-target care, even though the frequency of monitoring in the treat-to-target groups was often higher and so the burden on people attending the appointments greater.

In further support of treat-to-target despite the differences in the included studies, the committee agreed that one included study most closely reflected the treat-to-target and usual care approaches used in clinical practice in England, whereas some of the other included studies used more unusual designs. This study was the only study that utilised more frequent monitoring and a protocol-driven treatment strategy in the intervention group, compared with less frequent visits and treatment at the discretion of treating doctor in the usual care group. The committee noted that this trial found consistent and substantial benefits of treat-to-target approach over usual care, which further reinforced their view that treat-to-target was more

effective than usual care. In addition, the committee noted that many of the included studies in the separate evidence review of DMARD treatment, which reported positive outcomes for people with rheumatoid arthritis, were strategy trials that employed a treat-to-target approach. This provided further indirect evidence of the importance of treating-to-target to achieve good outcomes for people with rheumatoid arthritis.

The committee unanimously agreed that a treat-to-target approach to managing rheumatoid arthritis was essential to achieving rapid and sustained disease control and was the cornerstone of modern rheumatology practice. The lay members of the committee strongly emphasised the difference made to the lives of people with rheumatoid arthritis when a treat-to-target approach is implemented. Without a treat-to-target approach, people with rheumatoid arthritis risk being left in a moderate disease activity state, and these disease levels will have a significant impact on their daily life. If implemented appropriately, a treat-to-target approach should also avoid many people with rheumatoid arthritis having high disease activity levels warranting biologic DMARD treatment in the future. Although the quality of evidence from this review was not of high quality, the GC agreed that the importance of this recommendation in clinical practice, combined with this evidence and the indirect evidence from other reviews where the strategy was employed, all supported a strong recommendation for all people with rheumatoid arthritis.

Remission or low disease activity as the target

Having agreed that a treat-to-target approach is beneficial, the committee discussed what the disease activity target should be. The committee discussed the existing recommendation, which did not specify a target, and agreed that although no evidence was identified for this review, it was important to specify a target to ensure that people were fully treated and achieved the best possible outcomes and understood the goal of the treatment.

In the absence of available evidence the committee discussed which of the 2 targets was most appropriate based on their experience and expertise. The committee agreed that the aim should always be to control disease activity to the lowest possible level, but that this would depend on the individual as in some people, treatment will not be able to achieve very low targets. The committee decided by consensus that remission (for example, DAS28 less than 2.6) is the ideal target for most people with rheumatoid arthritis, but for people who were unable to achieve this target despite a treat-to-target approach with appropriate escalation, low disease activity (for example, DAS28 less than 3.2) would be acceptable as this is more achievable for some people and agreed as a good outcome if remission can’t be achieved. The committee noted that remission and low disease activity can be measured using various composite scoring measures. The committee were of the view that the most appropriate measures were validated scoring systems that incorporated inflammatory markers and a swollen joint count. Such measures include DAS, DAS28 and SDAI.

In order to treat-to-target using a target of remission or low disease activity, it is essential that a disease activity score such as the DAS28 is measured at each visit. The committee acknowledged that the DAS28 can be calculated using either ESR or CRP (both inflammatory markers), but agreed that current consensus is that CRP is subject to less variability as it is a direct measure of inflammatory protein. Hence, CRP is generally the preferred measure for people treated with conventional DMARDs. Therefore, the committee agreed to maintain the previous recommendation to measure CRP and disease activity using a composite score such as DAS28.

Frequency of monitoring

The committee discussed how frequently people should be monitored (a) while their disease is active as part of a treat-to-target approach, (b) after they have achieved the treatment target, and (c) once they have maintained disease activity below the treatment target for a period of time and their disease is considered well-controlled.

No evidence was identified specifically looking at how often people with active disease should be monitored. The committee noted that the previous guideline recommended monthly monitoring for people with active disease. The committee also considered the monitoring regimens in the studies included in the treat-to-target review. These varied between studies, however, the study considered to be the most applicable evidence (discussed above) employed monthly monitoring in the treat-to-target arm, compared with three monthly in the usual care arm. The committee agreed by consensus that monthly review of people with active disease remained the most appropriate monitoring frequency as part of the treat-to-target approach. Monthly monitoring in active disease was considered necessary in order to escalate DMARD doses, to consider the need for short-term glucocorticoids while waiting for DMARDs to take effect, to establish whether people were tolerating the drug and assess side effects, and to provide support and encourage adherence. Any more frequent was considered to be unnecessary from both an effectiveness and resource impact perspective, and would increase the burden for people with RA.

The committee discussed how frequently people should be monitored once their disease was below the target activity level of remission or low disease activity. The committee discussed the previous guideline recommendation, which was to provide appointments at a frequency and location suitable to [the person's] needs. The committee agreed that this should be more specific if possible, to improve consistency and avoid under or over monitoring of this group of people. It was agreed by consensus that a review appointment should be considered 6 months after a person achieves the treatment target, to assess whether the disease control has been maintained.

The committee discussed whether people with sustained disease levels below the treatment target required regular monitoring between annual reviews in the absence of worsening symptoms or deterioration (annual reviews were not updated in this guideline). The committee considered the study included in the frequency of monitoring review to be somewhat applicable to this situation, as it enrolled participants with long term, established disease. The evidence suggested that patient-initiated rapid access (median 8 reviews over 6 years) was no less effective than traditionally scheduled medical review every 3-6 months (median 13 reviews over 6 years) in this group of people with rheumatoid arthritis. The committee acknowledged the limitations of this evidence (discussed above), but agreed it reflected their experience that regular scheduled appointments (over and above an annual review) were not necessary in people with well-controlled disease.

Overall, the committee agreed that once people with rheumatoid arthritis had achieved the treatment target, and this was sustained at a 6 month follow-up appointment, there was no need for additional routine appointments to be scheduled other than the annual review. However, the committee emphasised the importance of all people with rheumatoid arthritis having rapid access to specialist care for disease flares, and the need for ongoing drug monitoring. The committee agreed this was addressed by the existing recommendations on rapid access, which had not been reviewed in the update, with some amendments to the wording to improve clarity.

People at risk of poor outcomes

The committee agreed that there was no evidence suggesting people with a poor prognosis should be managed any differently to the general rheumatoid arthritis population, in terms of the treatment target or the frequency of monitoring. The committee agreed that the standard recommendations regarding treatment-to-target with monthly monitoring should ensure that people with a poor prognosis receive effective treatment of their disease.

1.9.2 Cost effectiveness and resource use

For the treat-to-target review, 2 economic evaluations were identified, comparing a treat-to-target approach to usual care (Nair 2015, Grigor 2004). Nair 2015 was a cost–utility analysis

based on a cohort of people with early RA. This evaluation used clinical effectiveness data from the CAMERA trial, which was also included in the clinical review for treat-to-target. Analysis within this study identified treat-to-target to be cost effective, and in fact cost saving compared to usual practice (being less costly and more effective). The treat-to-target strategy resulted in less medical consumption and improved quality of life due to better DAS28/HAQ; however, drug costs were higher. The committee noted the relatively short time horizon of the study and questioned the ability of the study to capture the long-term cost benefits associated with the treat-to-target approach. The second analysis (Grigor 2004) was a cost–consequences analysis based on the TICORA RCT (same paper) which was also included in the clinical review. This analysis also found that treat-to-target was less costly and more effective than usual care. No analysis of uncertainty was conducted however; confidence intervals indicate that there is some uncertainty in both the costs and outcomes. The committee considered these confidence intervals and concluded that at a minimum treat-to-target was likely to be cost neutral.

Based on the clinical and economic evidence reviewed, the committee concluded that treat-to-target appeared to improve outcomes at no additional cost. As treat-to-target is already considered current practice and was recommended in the previous guideline, it is not anticipated that this recommendation will have a substantial resource impact.

No health economic studies were identified regarding the frequency of monitoring or the target for monitoring. Unit costs were provided for rheumatologist consultations to aid the consideration of cost effectiveness. The committee considered the potential economic impact of increasing frequency of monitoring from monthly to fortnightly and agreed that this would have a substantial impact on NHS resources and that there was no clinical evidence to support it. The committee agreed to keep the previous recommendation of monthly monitoring based on the clinical evidence reviewed. The committee noted that monthly visits may not have been implemented nationwide and this is reflected in a survey of the 2009 guideline implementation in the Midlands (25–62% receiving monthly monitoring). If this is reflective of practice across the country, this recommendation will likely involve a change in practice in many clinics around the country and may have a resource impact. Although there was no direct health economic evidence for the frequency of monitoring, the Grigor 2004 and Nair 2015 treat-to-target economic analyses suggested that even with more frequent visits (monthly versus every 3 months), a treat-to-target approach was cost saving. Finally, the committee noted that these monthly visits are often conducted by a nurse specialist rather than a consultant. The unit costs of different healthcare professionals were presented to the committee and it was noted that the cost of a nurse consultation would be less expensive than that of a consultant.

Regarding the target, aiming for low disease activity or remission is considered unlikely to have a resource impact. With either target, the individual will require ongoing monitoring and treatment adjustment, both of which have cost implications that are unlikely to differ depending on the target.

The committee made a recommendation to consider a review appointment within 6 months of stabilising. This recommendation was made based on expert opinion and consensus. The committee considered that this recommendation might reduce unwarranted variation in follow-up across the country as the prior recommendation may have led to unnecessary consultations for some or others receiving no follow-up.

References

1. Barlow JH, Barefoot J. Group education for people with arthritis. Patient Education and Counseling. 1996; 27(3):257-267

2. Bykerk VP, Keystone EC, Kuriya B, Larche M, Thorne JC, Haraoui B. Achieving remission in clinical practice: lessons from clinical trial data. Clinical and Experimental Rheumatology. 2013; 31(4):621-32

3. Cardiel MH. Treat to target strategy in rheumatoid arthritis: real benefits. Reumatologia Clinica. 2013; 9(2):101-5

4. Curtis L, Burns A. Unit costs of health and social care 2016. Canterbury. Personal Social Services Research Unit University of Kent, 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/

5. Department of Health. NHS reference costs 2015-16. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016 Last accessed: 06/10/2017.

6. Edmonds J. Objectives study in RA (OSRA): A RCT defining the best clinical target control in RA. American College of Rheumatology: Annual Scientific Meeting. 2007; Nov(2151)

7. Hodkinson B, Musenge E, Tikly M. Tight control of rheumatoid arthritis in a resource-constrained setting: a randomized controlled study comparing the clinical disease activity index and simplified disease activity index. Rheumatology. 2015; 54(6):1033-8

8. Jurgens MS, Welsing PM, Jacobs JW. Overview and analysis of treat-to-target trials in rheumatoid arthritis reporting on remission. Clinical and Experimental Rheumatology. 2012; 30(4 Suppl 73):S56-63

9. National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. NICE clinical guideline 79. London. Royal College of Physicians, 2009. Available from: http://guidance.nice.org.uk/CG79

10. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

11. Pincus T, Castrejon I. Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. Bulletin of the Hospital for Joint Disease 2013; 71 (Suppl 1):S33-40

12. Pope JE, Haraoui B, Rampakakis E, Psaradellis E, Thorne C, Sampalis JS et al. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor inhibitor: results from a real-world cluster-randomized adalimumab trial. Arthritis Care & Research. 2013; 65(9):1401-9

13. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. Arthritis Research & Therapy. 2014; 16:R56

14. Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Annals of the Rheumatic Diseases. 2010; 69(4):638-43

15. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Annals of the Rheumatic Diseases. 2016; 75(1):3-15

16. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Annals of the Rheumatic Diseases. 2016; 75(1):16-22

17. van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Annals of the Rheumatic Diseases. 2008; 67(11):1574-7

18. Wells G, Boers M, Tugwell P, M. D. A. Working Group. Low disease activity state in rheumatoid arthritis: concepts and derivation of minimal disease activity. Clinical and Experimental Rheumatology. 2006; 24(6 Suppl 43):S-52-9

Appendices

Appendix A: Review protocols

Table 3: Review protocol: Which target to monitor in rheumatoid arthritis?

Field	Content
Review questions	In adults with rheumatoid arthritis, what is the best target to use when monitoring disease activity (remission or low disease activity)? In adults with poor prognosis rheumatoid arthritis, what is the best target to use when monitoring disease activity (remission or low disease activity)?
Type of review question	Intervention
Objective of the review	A treat-to-target approach to managing rheumatoid arthritis requires monitoring of disease activity against a specified target. Composite measures are usually used to assess disease activity but the best target threshold is not known. The aim of this review is to identify whether low disease activity or remission is a better target for monitoring disease activity. The focus of this review will be on monitoring of disease activity in patients between each annual review. The annual review of patients with rheumatoid arthritis is an established and comprehensive monitoring practice recommended in the current guideline and was not prioritised for update.
Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis according to validated classification criteria, with at least moderate disease activity (equivalent to DAS28 ≥ 3.2). This might also be described as active disease, persistent disease or refractory disease. Studies in adults with poor prognostic factors will be analysed and reported separately.
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Monitoring a composite measure of disease activity with a target of disease remission The following composite measures will be considered: Disease activity score 28 (DAS28). DAS28 < 2.6 = remission Original disease activity score (DAS). DAS < 1.6 = remission Simplified disease activity index (SDAI). SDAI ≤ 3.3 = remission The different disease activity measures will be pooled in the analysis.
Eligibility criteria – comparator(s) / control or reference (gold) standard	Monitoring a composite measure of disease activity with a target of low disease activity The following composite measures will be considered: Disease activity score (DAS28; all versions). DAS28 < 3.2 = low disease activity

Field	Content
	Original disease activity score (DAS; all versions). DAS < 2.4 = low disease activity Simplified disease activity index (SDAI). SDAI ≤ 11.0 = low disease activity The different disease activity measures will be pooled in the analysis.
Outcomes and prioritisation	CRITICAL Disease Activity Score (continuous) at 12 months Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument; continuous) at 12 months Function (for example, Health Assessment Questionnaire, activities of daily living; continuous) at 12 months IMPORTANT Fatigue (for example, fatigue severity scale, FACIT, BRAF; continuous) at 12 months Pain (for example, visual analogue scale; continuous) at 12 months Radiological progression (continuous) at 12 months Withdrawal/adherence (dichotomous) at longest reported time point For outcomes other than those below, data must be least 6 months. If multiple time points, take closest time point to 12 months. For radiological progression, data must be at least 12 months. If multiple time points, take the longest time point. For withdrawal and adherence, take the longest reported time point.
Eligibility criteria – study design	RCTs Systematic review of RCTs
Other inclusion / exclusion criteria	Studies in mixed inflammatory arthritis populations will be excluded, unless the results are presented separately for people with RA. Studies in people with RA as well as another rheumatic disease (e.g. lupus) will be excluded.
Proposed sensitivity / subgroup analysis, or meta-regression	In the case of heterogeneity, the following subgroup analyses will be considered: Disease activity of patients enrolled in trial (active versus moderate versus mixed) Disease duration (≤ 2 years versus > 2 years) Frequency of monitoring (monthly versus less than monthly)
Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists will be double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus cannot be reached, for more information please see the separate Methods report for this guideline.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).

Field	Content
	GRADEpro will be used to assess the quality of evidence for each outcome. Endnote will be used for bibliography, citations, sifting and reference management
Information sources – databases and dates	Clinical search databases: The databases to be searched are Medline, Embase and the Cochrane Library. Date limits for search: None Language: English Health economics search databases: Medline, Embase, NHSEED and HTA Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[9] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-

Field	Content
	effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 4: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[10] Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in

Review question	All questions – health economic evidence
	discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017. https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 09 October 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (Ovid)	1974 – 09 October 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 10 of 12 CENTRAL to 2017 Issue 9 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	(tight* adj control*).ti,ab.
30.	t2t.ti,ab.
31.	((mission or aiming or aim or aimed or aims or achiev* or sustain* or reach*) adj2 remission).ti,ab.

32.	((treat* or therap*) adj2 (target* or goal*)).ti,ab.
33.	(symptom* adj2 (reduc* or improv* or control*)).ti,ab.
34.	low disease activity.ti,ab.
35.	(abrogat* adj2 inflammat*).ti,ab.
36.	optimi*.ti,ab.
37.	or/29-36
38.	28 and 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ti,ab.
42.	placebo.ab.
43.	drug therapy.fs.
44.	randomly.ti,ab.
45.	trial.ab.
46.	groups.ab.
47.	or/39-46
48.	Clinical Trials as topic.sh.
49.	trial.ti.
50.	or/39-42,44,48-49
51.	Meta-Analysis/
52.	Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	38 and (50 or 61)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/

11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	(tight* adj control*).ti,ab.
28.	t2t.ti,ab.
29.	((mission or aiming or aim or aimed or aims or achiev* or sustain* or reach*) adj2 remission).ti,ab.
30.	((treat* or therap*) adj2 (target* or goal*)).ti,ab.
31.	(symptom* adj2 (reduc* or improv* or control*)).ti,ab.
32.	low disease activity.ti,ab.
33.	(abrogat* adj2 inflammat*).ti,ab.
34.	optimi*.ti,ab.
35.	or/27-34
36.	26 and 35
37.	random*.ti,ab.
38.	factorial*.ti,ab.
39.	(crossover* or cross over*).ti,ab.
40.	((doubl* or singl*) adj blind*).ti,ab.
41.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
42.	crossover procedure/
43.	single blind procedure/
44.	randomized controlled trial/
45.	double blind procedure/
46.	or/37-45
47.	systematic review/
48.	meta-analysis/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.

54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	36 and (46 or 57)

Cochrane Library (Wiley) search terms

#1.	[mh "Arthritis, Rheumatoid"]
#2.	(rheumatoid near/2 (arthritis or arthrosis)):ti,ab
#3.	(caplan* near/2 syndrome):ti,ab
#4.	(felty* near/2 syndrome):ti,ab
#5.	(rheumatoid near/2 factor):ti,ab
#6.	((inflammatory or idiopathic) near/2 arthritis):ti,ab
#7.	inflammatory polyarthritis:ti,ab
#8.	(or #1-#7)
#9.	(tight* next control*):ti,ab
#10.	t2t:ti,ab
#11.	((mission or aiming or aim or aimed or aims or achiev* or sustain* or reach*) near/2 remission):ti,ab
#12.	((treat* or therap*) near/2 (target* or goal*)):ti,ab
#13.	(symptom* near/2 (reduc* or improv* or control*)):ti,ab
#14.	low disease activity:ti,ab
#15.	(abrogat* near/2 inflammat*):ti,ab
#16.	optimi*:ti,ab
#17.	(or #9-#16)
#18.	#8 and #17

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to rheumatoid arthritis population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 06 October 2017	Exclusions Health economics studies
Embase	2014– 06 October 2017	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2001 – 06 October 2017 NHSEED - 2001 – 31 March 2015	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.

44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/

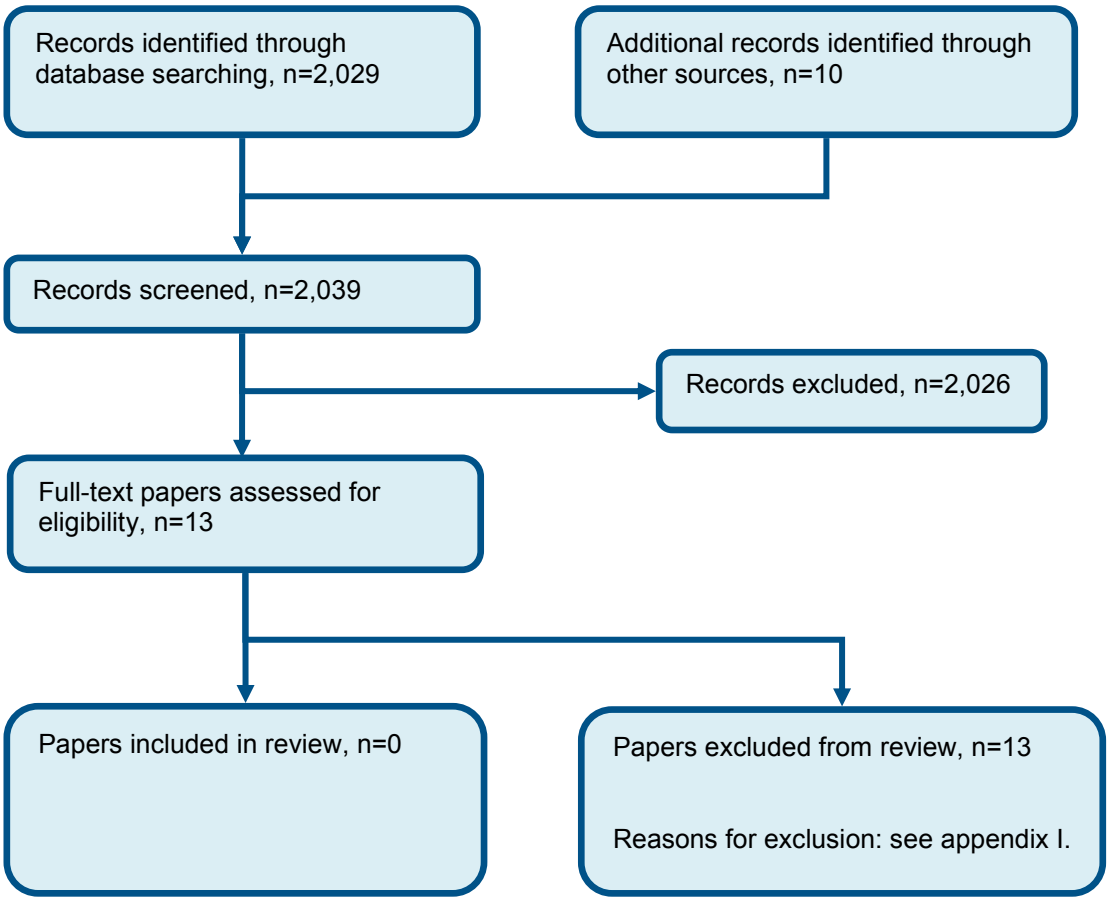
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))
#5.	((rheumatoid adj2 factor))
#6.	(((inflammatory or idiopathic) adj2 arthritis))
#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of 'Which target to monitor in rheumatoid arthritis?'



Appendix D: Clinical evidence tables

No relevant clinical studies were identified.

Appendix E: Forest plots

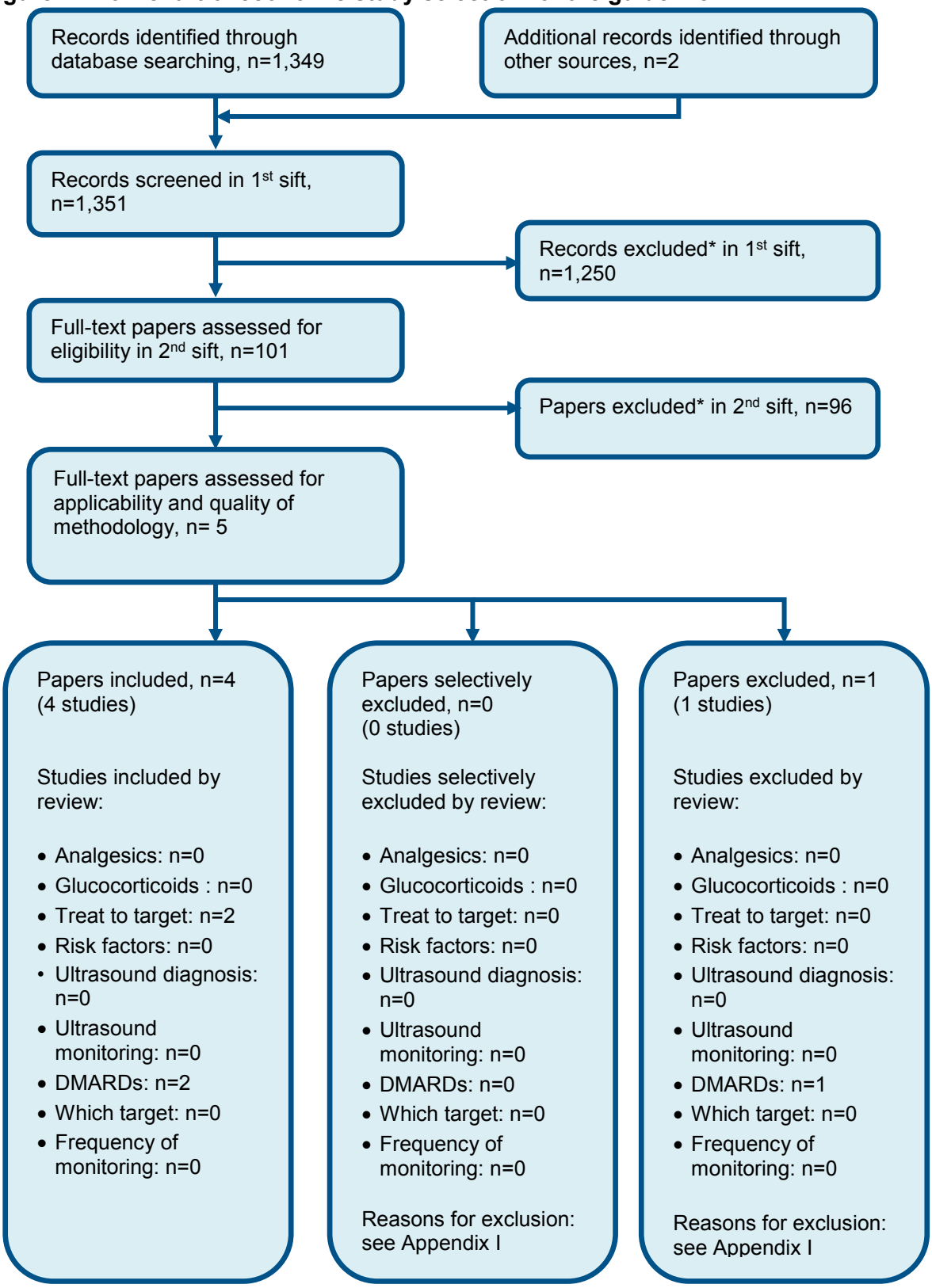
No relevant clinical studies were identified.

Appendix F:GRADE tables

No relevant clinical studies were identified.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of economic study selection for the guideline



** Non-relevant population, intervention, comparison, design or setting; non-English language*

Appendix H: Health economic evidence tables

No relevant economic studies were identified.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Study	Exclusion reason
Bykerk 2013[2]	Systematic review: methods are not adequate/unclear
Cardiel 2013[3]	Systematic review: methods are not adequate/unclear
Edmonds 2007[6]	Inappropriate comparison. conference abstract
Hodkinson 2015[7]	Incorrect interventions. Inappropriate comparison
Jurgens 2012[8]	Systematic review: methods are not adequate/unclear
Pincus 2013[11]	Systematic review: literature search not sufficiently rigorous
Pope 2013[12]	Inappropriate comparison
Radner 2014[13]	Incorrect study design
Schoels 2010[14]	Systematic review: methods are not adequate/unclear
Smolen 2016[15]	Systematic review: methods are not adequate/unclear
Stoffer 2016[16]	Systematic review: methods are not adequate/unclear
van Tuyl 2008[17]	Inappropriate comparison
Wells 2006[18]	Incorrect study design. Inappropriate comparison

I.2 Excluded health economic studies

Table 8: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None