National Institute for Health and Care Excellence

Final

Rheumatoid arthritis in adults: diagnosis and management

Evidence review E Frequency of 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, where appropriate, their carer or guardian.

Local commissioners and 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 All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-3003-6

Contents

1 Frequency of monitoring in rheumatoid arthritis 6
1.1 Review questions: 6
In adults with rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)? 6
In adults with poor prognosis rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)? 6
1.2 Introduction 6
1.3 PICO table 6
1.4 Methods and process 7
1.5 Clinical evidence 7
1.5.1 Included studies 7
1.5.2 Excluded studies 8
1.5.3 Summary of clinical studies included in the evidence review 8
1.5.4 Quality assessment of clinical studies included in the evidence review 10
1.6 Economic evidence 12
1.6.1 Included studies 12
1.6.2 Excluded studies 12
1.6.3 Unit costs 12
1.7 Resource costs 12
1.8 Evidence statements 12
1.8.1 Clinical evidence statements 12
1.8.2 Health economic evidence statements 12
1.9 The committee's discussion of the evidence 13
1.9.1 Interpreting the evidence 13
1.9.2 Cost effectiveness and resource use 17
References 19

Appendices 21
Appendix A: Review protocols 21
Appendix B: Literature search strategies 25
B.1 Clinical search literature search strategy 25
B.2 Health Economics literature search strategy 29
Appendix C: Clinical evidence selection 33
Appendix D: Clinical evidence tables 34
Appendix E: Forest plots 38
Appendix F: GRADE tables 39
Appendix G: Health economic evidence selection 40
Appendix H: Health economic evidence tables 42
Appendix I: Excluded studies 43

I.1 Excluded clinical studies 43
I.2 Excluded health economic studies 43

1 Frequency of monitoring in rheumatoid arthritis

1.1 Review questions:

In adults with rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)?

In adults with poor prognosis rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)?

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. The population will be split into strata: 1. Adults with active RA – people who are newly diagnosed and starting their first DMARD, or people who are changing treatment strategy (new drug, dose or regimen; will include most people with moderate or active disease activity). 2. Adults with active RA with poor prognostic factors 3. Adults with controlled RA – people whose treatment is not being changed (including people in remission or low disease activity) 4. Adults with controlled RA with poor prognostic factors
Intervention	Monitoring at any of the below frequencies: • monthly • 3–4 monthly • 6 monthly • annually • rapid access/review on request Monitoring must include (at a minimum) an examination of the joints (including recognition of whether swollen) and the measurement of inflammatory markers (either ESR or CRP).
Comparison	All of the above frequencies compared with each other.
Outcomes	CRITICAL • Disease Activity Score (continuous) at 12 months • Quality of life at 12 months • Function at 12 months IMPORTANT • Remission (dichotomous) at 12 months • Low disease activity (dichotomous) at 12 months • Fatigue at 12 months • Pain at 12 months • Radiological progression (continuous) at 12 months • Withdrawal from trial/adherence to strategy (dichotomous) at longest reported time point
Study design	Randomised controlled trials (RCTs) 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 different frequencies of monitoring disease activity in people with rheumatoid arthritis with each other. One study (3 papers) was included in the

review;[6-8] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

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

Table 2: Summary of randomised controlled trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Hewlett 2000[7], Kirwan 2003[8], Hewlett 2005[6]	Patient-initiated rapid access (n=105) versus traditional routinely scheduled medical reviews (n=104) Reviews in intervention group were accessed by person with rheumatoid arthritis or their GP through nurse-led telephone helpline with a maximum wait of 10 working days to be seen in rheumatology clinic. In the control group, medical reviews were ordered every 3-6 months.	People with established RA (disease duration more than 2 years) who fulfilled 1987 ACR criteria Age (mean): 58	• Health assessment Questionnaire at 6 years • Pain at 6 years • Radiological progression (Larsen index – change from baseline) at 6 years • Withdrawal from trial (declined to complete) over the course of 6 years	Patients were invited to take part in a 2 year RCT initially but were afterwards invited to continue the study for a further 4 years. Comparison is indirect as the frequency of medical reviews in the control group varied from 3 to 6 months. Population indirect as it is mixed: active and controlled RA. It is unclear what exactly was examined at each review but every 2 years (baseline, 2, 4 and 6 years) plasma viscosity, C reactive protein, haemoglobin concentration, grip strength, range of movement, and hand x-rays were assessed. Patient-initiated rapid access participants received 38% fewer hospital reviews over 6 years. Median of 8 reviews versus 13 routinely scheduled medical reviews

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Patient-initiated versus regular planned (3–6 monthly) review

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular planned review	Risk difference with Patient-initiated (95% CI)
Disease activity score (continuous) at 12 months - not reported	-	-	-	-	-
Quality of life (continuous) at 12 months – not reported	-	-	-	-	-
Health Assessment Questionnaire (HAQ – change from baseline) Scale from 0 to 3.	119 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness		The HAQ change from baseline (median (IQR)) in the control group was 0.25 (0 to 0.75)	The HAQ change from baseline (median (IQR)) in the intervention group was 0.19 (-0.125 to 0.75) (median difference: 0.06 lower in intervention group)
Pain (Change in VAS from baseline) Scale from 0 to 10.	120 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness		The Pain VAS change from baseline (median (IQR)) in the control group was 1.1 (-1.00 to 3.60)	The Pain VAS change from baseline (median (IQR)) in the intervention group was 1.25 (-0.40 to 3.25) (median difference: 0.15 higher in intervention group)
Radiological progression (Final Larsen index) Scale from 0 to 190.	182 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness		The mean radiological progression in the control groups was 50.1	The mean radiological progression in the intervention groups was 1.7 lower (8.73 lower to 5.33 higher)
Withdrawal from trial (declined to complete)	209 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, indirectness,	RR 0.53 (0.3 to 0.96)	250 per 1,000	118 fewer per 1,000 (from 10 fewer to 175 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Regular planned review	Risk difference with Patient-initiated (95% CI)
		imprecision			

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence was based on indirect comparisons and indirect population
[3] Cannot assess imprecision using median (IQR)
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

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 4: UK costs of healthcare professional visits

Type of appointment	Unit cost	Source
GP appointment lasting 9.22 minutes	£36	PSSRU Unit costs 2016[3]
Non-admitted face to face outpatient follow-up attendance, rheumatology (consultant led)	£137	NHS reference costs 2015-2016[4]
Non-admitted face to face outpatient follow-up attendance, rheumatology (non-consultant led)	£87	NHS reference costs 2015-2016[4]
Hospital based nurse, band 6, specialist nurse (per working hour/per hour of patient contact)	£44/£108	PSSRU Unit costs 2016[3]

1.7 Resource costs

The recommendations made in this review are likely to have a substantial impact on resources.

Additional costs are likely to be incurred for the following reasons: although monthly monitoring was recommended in the previous guideline, monthly monitoring does not appear to have been implemented nationwide and so there may be a change in practice and therefore some resource impact. Further work is being carried out to quantify the potential resource impact in this area.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- Patient-initiated versus regular planned (3–6 monthly) review

Evidence from 1 study (very low quality; n=209) showed no clinically important difference between patient-initiated versus regular planned (3–6 monthly) reviews in terms of function and pain at 6 years or radiological progression at 2 years. There was a clinically important benefit for patient-initiated reviews in terms of fewer withdrawals from the trial at 6 years. No evidence was available for disease activity or quality of life.

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 and the committee agreed that DAS provides a useful measure for a treat to taget approach.

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 committee 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 people leaving the study 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. The variation in frequency of monitoring in the intervention group and population mix across the study meant that direct reccomendations of the frequencies of monitoring utilised in the study were not appropriate though the results were included in the committee's dicussions.

No studies were found comparing any other frequencies of monitoring.

<u>People at risk of poor outcomes</u>

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 committee 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 3 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. The annual review recommendation from NICE guideline: Rheumatoid arthritis in adults: management published in 2009 was 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, and made amendments to the original wording to improve clarity.

People at risk of poor outcomesThe 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 recommendations on treat-to-target with monthly monitoring should ensure that people with a poor prognosis receive effective treatment, but

they decided to make a research recommendation to inform future guidance for management of RA in this group.

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. Barrett EM. A shared care system of hospital follow up reduced pain and use of healthcare resources and increased satisfaction in patients with rheumatoid arthritis... commentary on Hewlett S, Mitchell K, Haynes J, et al Patient-initiated hospital follow-up for rheumatoid arthritis. Rheumatology 2000 Sep;39:990-7. Evidence-Based Nursing. 2001; 4(2):51

3. 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/

4. 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.

5. Goodwin VA, Paudyal P, Perry MG, Day N, Hawton A, Gericke C et al. Implementing a patient-initiated review system for people with rheumatoid arthritis: a prospective, comparative service evaluation. Journal of Evaluation in Clinical Practice. 2016; 22(3):439-445

6. Hewlett S, Kirwan J, Pollock J, Mitchell K, Hehir M, Blair PS et al. Patient initiated outpatient follow up in rheumatoid arthritis: six year randomised controlled trial. BMJ. 2005; 330(7484):171

7. Hewlett S, Mitchell K, Haynes J, Paine T, Korendowych E, Kirwan JR. Patient-initiated hospital follow-up for rheumatoid arthritis. Rheumatology. 2000; 39(9):990-997

8. Kirwan JR, Mitchell K, Hewlett S, Hehir M, Pollock J, Memel D et al. Clinical and psychological outcome from a randomized controlled trial of patient-initiated direct-access hospital follow-up for rheumatoid arthritis extended to 4 years. Rheumatology. 2003; 42(3):422-426

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. Paudyal P, Perry M, Child S, Gericke CA. Evaluation of a patient-initiated review system in rheumatoid arthritis: an implementation trial protocol. BMC Musculoskeletal Disorders. 2012; 13:120

12. 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

13. Smolen JS, Aletaha D. Monitoring rheumatoid arthritis. Current Opinion in Rheumatology. 2011; 23(3):252-258

14. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the Rheumatic Diseases. 2010; 69(4):631-637

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. Taneja A, Su'a B, Hill AG. Efficacy of patient-initiated follow-up clinics in secondary care: a systematic review. Internal Medicine Journal. 2014; 44(12a):1156-1160

17. van Riel P, Alten R, Combe B, Abdulganieva D, Bousquet P, Courtenay M et al. Improving inflammatory arthritis management through tighter monitoring of patients and the use of innovative electronic tools. RMD Open. 2016; 2(2):e000302

18. Zatarain E, Strand V. Monitoring disease activity of rheumatoid arthritis in clinical practice: contributions from clinical trials. Nature Clinical Practice Rheumatology. 2006; 2(11):611-618

Appendices

Appendix A: Review protocols

Table 5: Review protocol: Frequency of monitoring

Field	Content
Review questions	In adults with rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)? In adults with poor prognosis rheumatoid arthritis, what is the optimum frequency of disease activity monitoring (outside of the annual review)?
Type of review question	Intervention
Objective of the review	The aim of this review is to identify how often measures of disease activity should be monitored 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. The population will be split into strata: People with active RA– patients who are newly diagnosed and starting their first DMARD, or patients who are changing treatment strategy (new drug/dose/regimen; will include most patients with moderate or active disease activity). People with active RA with poor prognostic factors People with controlled RA – patients whose treatment is not being changed (including patients in remission or low disease activity) People with controlled RA with poor prognostic factors
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Monitoring at any of the below frequencies: monthly 3–4 monthly 6 monthly annually rapid access/review on request Monitoring must include (at a minimum) an examination of the joints (including recognition of whether swollen) and the measurement of inflammatory markers (either ESR or CRP).
Eligibility criteria – comparator(s) / control or reference (gold) standard	All of the above frequencies compared with each other.
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

Field	Content
	IMPORTANT Remission (dichotomous) at 12 months Low disease activity (dichotomous) at 12 months Fatigue (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 due to adverse events (dichotomous) at longest reported time point Withdrawal due to inefficacy (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 RA patients. Studies in patients with RA as well as another rheumatic disease (e.g. lupus) will be excluded. Studies will be excluded if there are differences between the interventions in each group, other than the frequency of monitoring. For example, studies where one arm includes a target or aggressive escalation protocol and the other does not will be excluded from the review.
Proposed sensitivity / subgroup analysis, or meta-regression	In the case of heterogeneity, the following subgroup analyses will be considered: In controlled RA: whether the patients are in remission versus low disease activity disease duration (≤ 5 years versus > 5 years) In active RA: whether or not target was used in monitoring disease duration (≤ 2 years versus > 2 years)
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). 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

Field	Content
	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: management9 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 will be 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 will be 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-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.

Field	Content
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 6: 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 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.

Review question	All questions – health economic evidence
	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 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 06 October 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (Ovid)	1974 – 06 October 2017	Exclusions

Database	Dates searched	Search filter used
		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 Experimentation/
24.	exp Models, Animal/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	((monit* or assess* or reassess* or re-assess* or review* or follow-up or followup) adj5 (month* or bimonth* or quarter* or annual* or frequen* or schedul* or interval* or regular* or intens* or routine* or timing)).ti,ab.
30.	(rapid* adj1 access*).ti,ab.
31.	(review* adj2 request*).ti,ab.
32.	or/29-31

33.	28 and 32
34.	randomized controlled trial.pt.
35.	controlled clinical trial.pt.
36.	randomi#ed.ti,ab.
37.	placebo.ab.
38.	randomly.ti,ab.
39.	Clinical Trials as topic.sh.
40.	trial.ti.
41.	or/34-40
42.	Meta-Analysis/
43.	exp Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(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.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	33 and (41 or 52)

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.	((monit* or assess* or reassess* or re-assess* or review* or follow-up or followup) adj5 (month* or bimonth* or quarter* or annual* or frequen* or schedul* or interval* or regular* or intens* or routine* or timing)).ti,ab.
28.	(rapid* adj1 access*).ti,ab.
29.	(review* adj2 request*).ti,ab.
30.	or/27-29
31.	26 and 30
32.	random*.ti,ab.
33.	factorial*.ti,ab.
34.	(crossover* or cross over*).ti,ab.
35.	((doubl* or singl*) adj blind*).ti,ab.
36.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
37.	crossover procedure/
38.	single blind procedure/
39.	randomized controlled trial/
40.	double blind procedure/
41.	or/32-40
42.	systematic review/
43.	meta-analysis/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(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.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	31 and (41 or 52)

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.	((monit* or assess* or reassess* or re-assess* or review* or follow-up or followup) near/5 (month* or bimonth* or quarter* or annual* or frequen* or schedul* or interval* or regular* or intens* or routine* or timing)):ti,ab
#10.	(rapid* near/1 access*):ti,ab
#11.	(review* near/2 request*):ti,ab
#12.	#9 or #10 or #11
#13.	#9 and #12

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 8: 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/

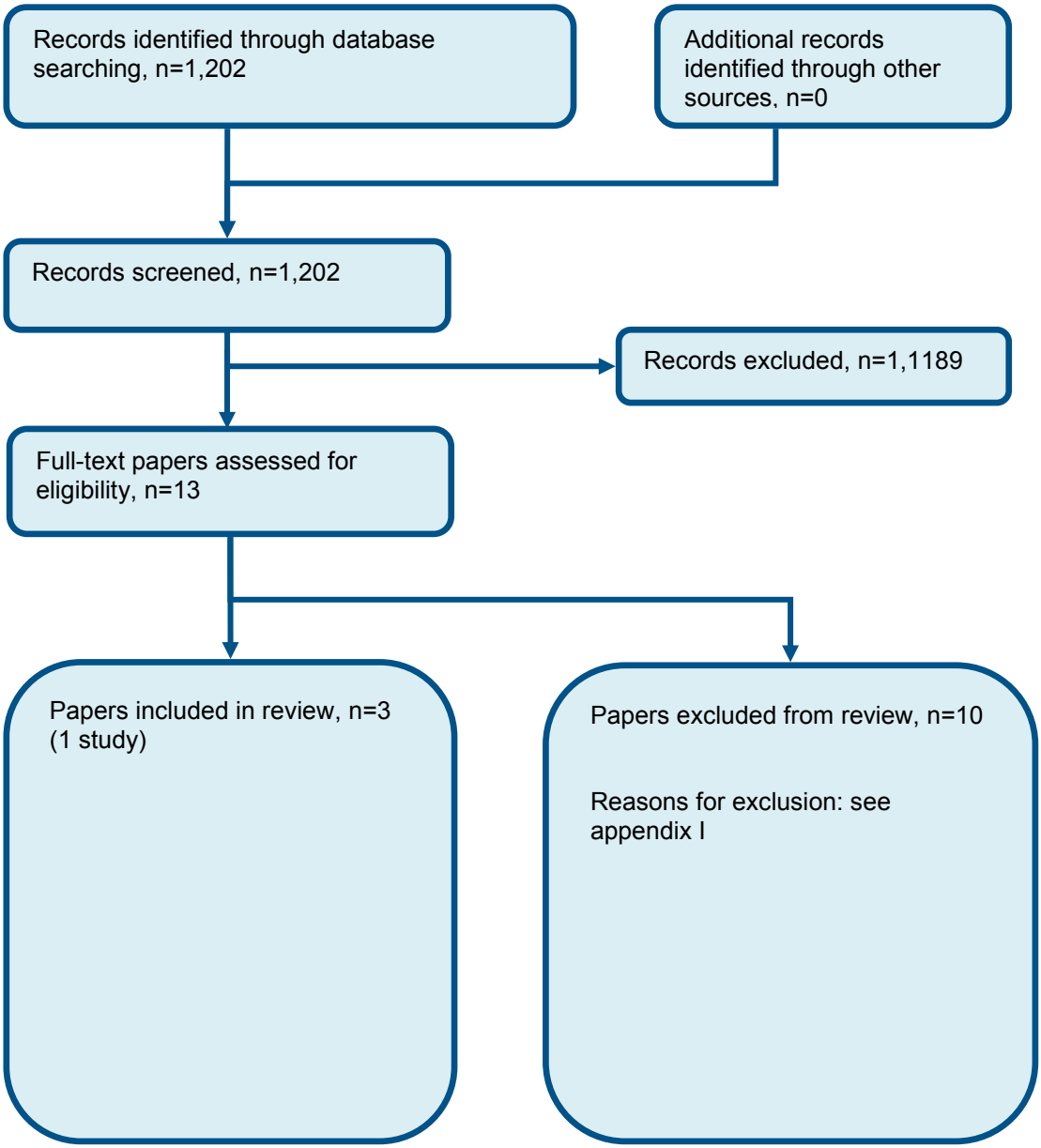
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
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 Frequency of monitoring



Appendix D: Clinical evidence tables

Study (subsidiary papers)	Patient-initiated follow-up trial: Hewlett 2000[7] (Hewlett 2005[6], Kirwan 2003[8])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=209)
Countries and setting	Conducted in United Kingdom; Setting: Rheumatology out-patients department of the Bristol Royal Infirmary, UK
Line of therapy	Part of comparison
Duration of study	Intervention time: 6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All consecutive patients attending the rheumatology out-patients department of the Bristol Royal Infirmary, UK, with established rheumatoid arthritis (more than 2 years) according to international criteria (ARA 1987) were invited to take part.
Exclusion criteria	None
Recruitment/selection of patients	Consecutive patients attending the rheumatology out-patients department who had established rheumatoid arthritis. Patients were invited to take part for 2 year study initially but were afterwards invited to continue the study for a further 4 years.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 57 (13); Control: 59 (13). Gender (M:F): 1/2. Ethnicity: na
Further population details	1. Stable RA: disease activity: Not applicable 2. Stable RA: disease duration: Not applicable 3. Unstable RA: disease duration: Not applicable
Extra comments	Of the 302 subjects invited to participate, 209 (69.2%) agreed. Patients who declined were older, had a higher mean articular index and were more disabled. No patient declined to take part after randomisation. Baseline demographics of randomised patients: disease duration in years, mean (SD): intervention group 11 (9), control group 12 (8) HAQ, mean (SD): intervention group 1.4 (0.8), control group 1.4 (0.8) articular index, mean (SD): intervention group 97 (93), control group 110 (112).
Indirectness of population	Serious indirectness: Population indirect as it is mixed: stable and unstable RA.
Interventions	(n=105) Intervention 1: Monitoring - Rapid access/review on request. Shared care group: shared care with

	the GP (no routine hospital review was offered but rapid access on request) Shared care group patients or GPs requested review with a rheumatologist, physiotherapist, or occupational therapist through a nurse-led telephone helpline, whereby general advice or assistance was also given immediately. Fortnightly ring-fenced rheumatology clinics gave a maximum wait of 10 working days for review. . Duration 6 years . Concurrent medication/care: All patients were managed according to clinical need and further follow-up was given as clinically indicated, shared care group patients eventually returning to patient-initiated review and controls to routine review. Postal assessments (3 monthly in the first 2 years and annual thereafter) of pain, patient's opinion of disease activity, early morning stiffness, HAQ, anxiety and depression, helplessness, self efficacy and satisfaction. At 4, 5 and 6 years SF-36 was added. Every two years (baseline, 2, 4 and 6 years) plasma viscosity, C reactive protein, haemoglobin concentration, grip strength, range of movement, and hand x-rays were assessed. A safety net, using the 3-monthly questionnaires was set up to monitor all patients' clinical status as half were no longer receiving reviews. An increase of 20 percent or more in pain, disease activity or disability was deemed a safety net failure and patients were contacted and encouraged to be reviewed.. Indirectness: No indirectness Further details: 1. Unstable RA: target utilised: Not applicable (n=104) Intervention 2: Monitoring - 3-4 monthly . Control group patients had a traditional medical review ordered routinely every 3-4 months or according to standard practice (up to 6 months). Requests for medical review ahead of schedule were dealt with according to normal practice, GP requests being assessed by a rheumatologist who decided on the timing of the review. Patients had access to the occupational therapist (OT) and physiotherapist (PT) via the traditional route of GP request, rheumatologist appointment and referral to OT or PT waiting lists.. Duration 6 years . Concurrent medication/care: All patients were managed according to clinical need and further follow-up was given as clinically indicated, shared care group patients eventually returning to patient-initiated review and controls to routine review. Postal assessments (3 monthly in the first 2 years and annual thereafter) of pain, patient's opinion of disease activity, early morning stiffness, HAQ, anxiety and depression, helplessness, self efficacy and satisfaction. At 4, 5 and 6 years SF-36 was added. Every two years (baseline, 2, 4 and 6 years) plasma viscosity, C reactive protein, haemoglobin concentration, grip strength, range of movement, and hand x-rays were assessed. A safety net, using the 3-monthly questionnaires was set up to monitor all patients' clinical status as half were no longer receiving reviews. Based on clinical experience, an increase of 20 percent or more in pain, disease activity or disability was deemed a safety net failure and patients were contacted and encouraged to be reviewed. . Indirectness: Serious indirectness; Indirectness comment: Reviews at 3-4 months (Hewlett 2000) but can be as much as 6 months (Hewlett 2005) Further details: 1. Unstable RA: target utilised: Not applicable
Funding	Academic or government funding (NHS Research and Development National Programme Grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAPID ACCESS/REVIEW ON REQUEST versus 3-4 MONTHLY

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: Disease activity (Median change from baseline) at 6 years; Median change (IQR): Intervention: 0.25 (-1.35-2.80) Control: 0.25 (-0.88-2.80) DAS 0-10 Top=High is poor outcome;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - States ITT analysis but authors do not state how they dealt with missing data.; Indirectness of outcome: No indirectness ; Baseline details: Comparable at baseline apart from grip strength: stronger in people in the intervention group.; Group 1 Number missing: 37, Reason: Files lost (n=3), GP declined (n=1), died (n=12), ill (n=4), moved (n=1), discharged (n=1), re-diagnosed (n=1), declined to complete the trial (n=14).; Group 2 Number missing: 52, Reason: Died (n=18), ill (n=3), moved (n=5), declined to complete the trial (n=26).

Protocol outcome 2: Function at 12 months
- Actual outcome: Health assessment Questionnaire (Median change from baseline, IQR) at 6 years; Median (IQR): Intervention: 0.19 (-0.125-0.75) Control: 0.25 (0-0.75) Health Assessment Questionnaire 0-3 Top=High is poor outcome;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - States ITT analysis but authors do not state how they dealt with missing data.; Indirectness of outcome: No indirectness ; Baseline details: Comparable at baseline apart from grip strength: stronger in people in the intervention group. ; Group 1 Number missing: 37, Reason: Files lost (n=3), GP declined (n=1), died (n=12), ill (n=4), moved (n=1), discharged (n=1), re-diagnosed (n=1), declined to complete the trial (n=14).
; Group 2 Number missing: 52, Reason: Died (n=18), ill (n=3), moved (n=5), declined to complete the trial (n=26).

Protocol outcome 3: Pain at 12 months
- Actual outcome: Pain (Median change from baseline) at 6 years; Median change (IQR): Intervention: 1.25 (-0.40-3.25) Control: 1.1 (-1.00-3.60) Pain VAS 0-10 Top=High is poor outcome;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - States ITT analysis but authors do not state how they dealt with missing data.; Indirectness of outcome: No indirectness ; Baseline details: Comparable at baseline apart from grip strength: stronger in people in the intervention group.; Group 1 Number missing: 37, Reason: Files lost (n=3), GP declined (n=1), died (n=12), ill (n=4), moved (n=1), discharged (n=1), re-diagnosed (n=1), declined to complete the trial (n=14).
; Group 2 Number missing: 52, Reason: Died (n=18), ill (n=3), moved (n=5), declined to complete the trial (n=26).

Protocol outcome 4: Radiological progression at 12 months
- Actual outcome: Larsen index in both hands at 2 years; Group 1: mean 48.4 (SD 20.4); n=93, Group 2: mean 50.1 (SD 27.3); n=89; Larsen Index 0-190 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - States ITT analysis but authors do not state how they dealt with missing data.; Indirectness of outcome: No indirectness ; Baseline details: 43.7 for intervention group and 48.1 for control group; Group 1 Number missing: 12; Group 2 Number missing: 15, Reason:

Protocol outcome 5: Withdrawal due to not adhering to strategy at longest timepoint reported - Actual outcome: Withdrawal from trial (declined to complete) at 6 years; Group 1: 14/105, Group 2: 26/104 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - States ITT analysis but authors do not state how they dealt with missing data.; Indirectness of outcome: No indirectness ; Baseline details: Comparable at baseline apart from grip strength: stronger in people in the intervention group.; Group 1 Number missing: 23, Reason: Files lost (n=3), GP declined (n=1), died (n=12), ill (n=4), moved (n=1), discharged (n=1), rediagnosed (n=1).; Group 2 Number missing: 26, Reason: Died (n=18), ill (n=3), moved (n=5).	
Protocol outcomes not reported by the study	Quality of life at 12 months; Remission at 12 months; Low disease activity at 12 months; Fatigue at 12 months; Withdrawal due to adverse events at longest timepoint reported

Appendix E: Forest plots

E.1 Patient-initiated rapid access versus 3-6 monthly routinely scheduled reviews

Figure 2: Radiological progression at 12 months

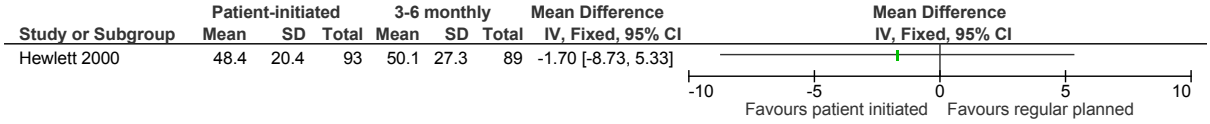
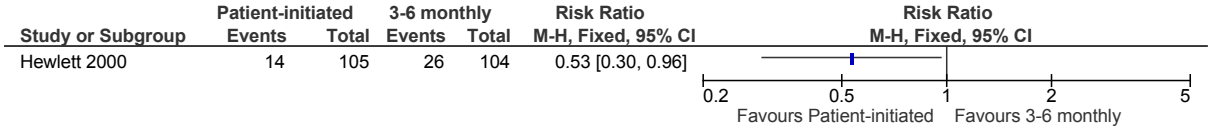


Figure 3: Withdrawal from trial (declined to complete)



No forest plots provided for other outcomes as they were reported as medians with interquartile ranges.

Appendix F: GRADE tables

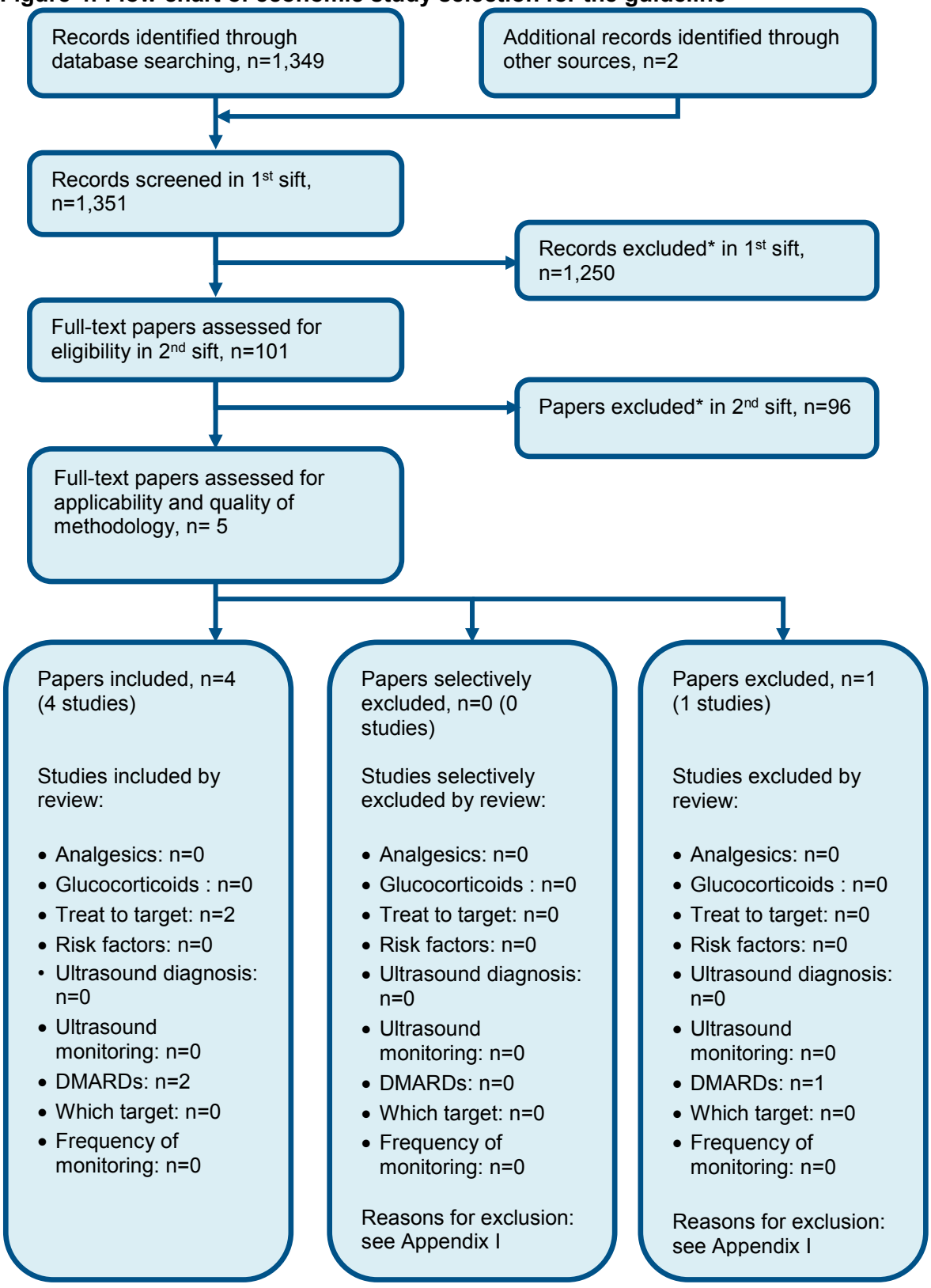
Table 9: Clinical evidence profile: Patient-initiated versus regular planned (3-6 monthly) review

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient-initiated review	Regular planned review	Relative (95% CI)	Absolute		
Health Assessment Questionnaire (change from baseline in HAQ; range of scores: 0-3; Better indicated by lower values; 6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	-[3]	none	68	51	Median difference 0.06 between intervention and comparison groups)	The HAQ change from baseline (median (IQR)) in the intervention group was 0.19 (-0.125 to 0.75)	⊕OOO VERY LOW	IMPORTANT
Pain VAS (change from baseline; range of scores: 0-10; Better indicated by lower values; 6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	-[3]	none	68	52	Median difference 0.15 between intervention and comparison groups)	The Pain VAS change from baseline (median (IQR)) in the intervention group was 1.25 (-0.40 to 3.25)	⊕OOO VERY LOW	IMPORTANT
Radiological progression (Larsen index; range of scores: 0-190; Better indicated by lower values; 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	93	89	-	MD 1.7 lower (8.73 lower to 5.33 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal from trial (declined to complete; 6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	14/105 (13.3%)	26/104 (25%)	RR 0.53 (0.3 to 0.96)	118 fewer per 1,000 (from 10 fewer to 175 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence was based on indirect comparisons and indirect population.
[3] Cannot assess imprecision using median (IQR).
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 4: 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

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Barrett 2001[2]	Incorrect study design
Goodwin 2016[5]	No outcomes of interest reported. Monitoring did not include (at a minimum) an examination of the joints (including recognition of whether swollen) and the measurement of inflammatory markers (either ESR or CRP).
Paudyal 2012[11]	No outcomes of interest reported. Monitoring did not include (at a minimum) an examination of the joints (including recognition of whether swollen) and the measurement of inflammatory markers (either ESR or CRP).
Pincus 2013[12]	Systematic review: methods are not adequate
Smolen 2010[14]	Systematic review: methods are not adequate
Smolen 2011[13]	Systematic review: methods are not adequate
Smolen 2016[15]	Systematic review: methods are not adequate
Taneja 2014[16]	Systematic review: methods are not adequate
van Riel 2016[17]	Systematic review: methods are not adequate
Zatarain 2006[18]	Systematic review: methods are not adequate

I.2 Excluded health economic studies

Table 11: Studies excluded from the health economic review

Reference	Reason for exclusion
None	