

Rheumatoid arthritis in adults: diagnosis and management

Evidence review D Target for monitoring

NICE guideline CG79

Intervention evidence review

January 2018

Consultation

*This evidence review was developed by
the National Guideline Centre*

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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 adaptations depending on the disease activity level and degree of response to treatment.

The 2009 NICE guideline: Rheumatoid arthritis in adults: management⁹ 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 \geq 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: <ul style="list-style-type: none">• Disease activity score 28 (DAS28). DAS28 < 2.6 = remission

	<ul style="list-style-type: none"> • Original disease activity score (DAS). DAS < 1.6 = remission • Simplified disease activity index (SDAI). SDAI ≤ 3.3 = remission <p>The different disease activity measures will be pooled in the analysis.</p>
Comparison(s)	<p>Monitoring a composite measure of disease activity with a target of low disease activity</p> <p>The following composite measures will be considered:</p> <ul style="list-style-type: none"> • 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 <p>The different disease activity measures will be pooled in the analysis.</p>
Outcomes	<p>CRITICAL</p> <ul style="list-style-type: none"> • Disease Activity Score (continuous) at 12 months • Quality of life (continuous) at 12 months • Function (continuous) at 12 months <p>IMPORTANT</p> <ul style="list-style-type: none"> • 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	<p>RCT</p> <p>Systematic review of RCTs</p>

1.4 1 Methods and process

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

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

1.5 6 Clinical evidence

1.5.1 7 Included studies

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

11 No relevant clinical studies were identified.

12 See also the study selection flow chart in appendix C.

1.5.2 3 Excluded studies

14 See the excluded studies list in appendix I.

1.5.3 1 Summary of clinical studies included in the evidence review

2 No relevant clinical studies were identified.

3

1.5.4 1 Quality assessment of clinical studies included in the evidence review

2 No relevant clinical studies were identified.

3

4

5

1.6 1 Economic evidence

1.6.1 2 Included studies

3 No relevant health economic studies were identified.

1.6.2 4 Excluded studies

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

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

1.6.3 8 Unit costs

9 **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 10 Resource costs

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

1.8 13 Evidence statements

1.8.1 14 Clinical evidence statements

15 No relevant clinical studies were identified.

1.8.2 16 Health economic evidence statements

17 • No relevant economic evaluations were identified.

18

1

1.9 2 Recommendations

- 3 D1. Treat active RA in adults with the aim of achieving a target of remission or low disease
4 activity if remission cannot be achieved (treat-to-target).
- 5 D2. Consider making the target remission rather than low disease activity for people with an
6 increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-
7 ray at baseline assessment).
- 8 D3. In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a
9 composite score such as DAS28) monthly until the target of remission or low disease activity
10 is achieved.
- 11 D4. Ensure that all adults with RA have:
- 12 • rapid access to specialist care for worsening disease or flares
 - 13 • information about when and how to access specialist care, and
 - 14 • ongoing drug monitoring.
- 15 D5. Consider a review appointment to take place 6 months after achieving treatment target
16 (remission or low disease activity) to ensure that the target has been maintained.
- 17 D6. Offer all adults with RA, including those who have achieved the treatment target, an
18 annual review to:
- 19 • assess disease activity and damage, and measure functional ability (using, for
20 example, the Health Assessment Questionnaire [HAQ])
 - 21 • check for the development of comorbidities, such as hypertension, ischaemic
22 heart disease, osteoporosis and depression
 - 23 • assess symptoms that suggest complications, such as vasculitis and disease
24 of the cervical spine, lung or eyes
 - 25 • organise appropriate cross referral within the multidisciplinary team
 - 26 • assess the need for referral for surgery (see section 1.6)
 - 27 • assess the effect the disease is having on a person's life.

1.10 Rationale and impact

1.10.2 Why the committee made the recommendations

30 Strategy and treatment target

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

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

1 Frequency of monitoring for active disease

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

10 People at risk of poor outcomes

11 There was no evidence that people with a poor prognosis should have different management
12 in terms of the treatment target or the frequency of monitoring. However, in the committee's
13 experience RA often responds less well to standard management in this group. The
14 committee agreed that the recommendations on treat-to-target with monthly monitoring
15 should ensure that people with a poor prognosis receive effective treatment, but they decided
16 to make a research recommendation to inform future guidance for management of RA in this
17 group (see evidence review B: Risk factors).

18 Frequency of monitoring when treatment target has been achieved

19 No evidence was identified on monitoring frequency once the treatment target has been
20 achieved. However, the committee agreed that a recommendation was needed to improve
21 consistency and avoid under- or over-monitoring. The committee used their experience to
22 recommend that providers should consider a review appointment to take place 6 months
23 after achieving the treatment target, to assess whether disease control has been maintained.

24 In people with established RA (RA for at least 2 years), the evidence suggested that patient-
25 initiated rapid access and scheduled medical review every 3 to 6 months were similarly
26 effective. The committee agreed that when the treatment target was sustained at 6-month
27 follow-up, there was no need for appointments other than the annual review. All people with
28 RA should have an annual review, including those with sustained disease levels below the
29 treatment target.

30 The committee agreed that all adults with RA should have rapid access to specialist care for
31 worsening disease or disease flares, and ongoing drug monitoring.

1.1032 Why we need recommendations on this topic

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

39 The 2009 NICE guideline: Rheumatoid arthritis in adults: management⁹ suggested a treat-to-
40 target approach in the recommendations that said to measure inflammatory markers and
41 disease activity monthly "until treatment has controlled the disease to a level previously
42 agreed with the person with RA". However, the committee agreed that the evidence for a
43 treat-to-target strategy should be reviewed, to make this recommendation clearer and more
44 direct if supported by the evidence.

45 The committee also agreed that greater clarity was needed on how frequently people with
46 rheumatoid arthritis should be monitored, as there was currently variation in practice and
47 some uncertainty about how frequent monitoring should be in different groups of people with
48 rheumatoid arthritis with varying degrees of disease activity. However, the frequency of

1 monitoring review excluded an update of the annual review recommended in the previous
2 guideline, as it is an essential and well-established practice and therefore was not included
3 within the scope of this update.

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

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

1.10.3 Impact of the recommendations on practice

10 A treat-to-target strategy is current best practice in most NHS settings. The 2016 National
11 Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis indicated that
12 healthcare professionals set a treatment target for about 90% of their patients. Although the
13 2018 recommendation specifies a target of remission or low disease activity, rather than a
14 disease level previously agreed with the person, the committee agreed that these are the
15 targets commonly used and so this is unlikely to involve a significant change in practice.

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

1.114 The committee's discussion of the evidence

1.1126 Interpreting the evidence

1.11.126 The outcomes that matter most

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

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

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

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

1.11.142 The quality of the evidence

43 Treat-to-target versus usual care

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

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

22 The committee agreed that it was not possible to establish definitively which of these factors
23 (if any) might explain the differences in the magnitude of the effect between the studies.
24 However, the committee noted that while there was some inconsistency in the magnitude of
25 the benefit of treat-to-target in improving disease activity, function and pain, in general the
26 majority of evidence across outcomes favoured treat-to-target over usual care. The few
27 results that did suggest a benefit of usual care were generally from the non- DAS-based
28 target arms of 2 studies (which used targets of zero swollen joint count and matrix
29 metalloproteinase 3 levels). The results of the DAS-based target arms of those studies
30 favoured the intervention arm, consistent with the other study results.

31 **Remission or low disease activity as the target**

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

34 **Frequency of monitoring**

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

45 No studies were found comparing any other frequencies of monitoring.

46 People at risk of poor outcomes

47 People with a poor prognosis were pre-specified as a separate stratum in the protocols for
48 the review of remission versus low disease activity as a target and the review of frequency of
49 monitoring. People with a poor prognosis were considered to be those with one or more of
50 the key prognostic factors identified in a separate review, which were anti-CCP positive

- 1 status and the presence of erosions at baseline. No evidence was found in this subgroup of
- 2 people for either question.

1.11.1.3 Benefits and harms

4 Treat-to-target versus usual care

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

17 In further support of treat-to-target despite the differences in the included studies, the
18 committee agreed that one included study most closely reflected the treat-to-target and usual
19 care approaches used in clinical practice in England, whereas some of the other included
20 studies used more unusual designs. This study was the only study that utilised more frequent
21 monitoring and a protocol-driven treatment strategy in the intervention group, compared with
22 less frequent visits and treatment at the discretion of treating doctor in the usual care group.
23 The committee noted that this trial found consistent and substantial benefits of treat-to-target
24 approach over usual care, which further reinforced their view that treat-to-target was more
25 effective than usual care. In addition, the committee noted that many of the included studies
26 in the separate evidence review of DMARD treatment, which reported positive outcomes for
27 people with rheumatoid arthritis, were strategy trials that employed a treat-to-target
28 approach. This provided further indirect evidence of the importance of treating-to-target to
29 achieve good outcomes for people with rheumatoid arthritis.

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

43 Remission or low disease activity as the target

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

49 In the absence of available evidence the committee discussed which of the 2 targets was
50 most appropriate based on their experience and expertise. The committee agreed that the

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

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

20 **Frequency of monitoring**

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

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

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

47 The committee discussed whether people with sustained disease levels below the treatment
48 target required regular monitoring between annual reviews in the absence of worsening
49 symptoms or deterioration (annual reviews were not updated in this guideline). The
50 committee considered the study included in the frequency of monitoring review to be
51 somewhat applicable to this situation, as it enrolled participants with long term, established
52 disease. The evidence suggested that patient-initiated rapid access (median 8 reviews over

1 6 years) was no less effective than traditionally scheduled medical review every 3-6 months
2 (median 13 reviews over 6 years) in this group of people with rheumatoid arthritis. The
3 committee acknowledged the limitations of this evidence (discussed above), but agreed it
4 reflected their experience that regular scheduled appointments (over and above an annual
5 review) were not necessary in people with well-controlled disease.

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

14 People at risk of poor outcomes

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

1.1120 **Cost effectiveness and resource use**

21 For the treat-to-target review, 2 economic evaluations were identified, comparing a treat-to-
22 target approach to usual care (Nair 2015, Grigor 2004). Nair 2015 was a cost-utility analysis
23 based on a cohort of people with early RA. This evaluation used clinical effectiveness data
24 from the CAMERA trial, which was also included in the clinical review for treat-to-target.
25 Analysis within this study identified treat-to-target to be cost effective, and in fact cost saving
26 compared to usual practice (being less costly and more effective). The treat-to-target
27 strategy resulted in less medical consumption and improved quality of life due to better
28 DAS28/HAQ; however, drug costs were higher. The committee noted the relatively short time
29 horizon of the study and questioned the ability of the study to capture the long-term cost
30 benefits associated with the treat-to-target approach. The second analysis (Grigor 2004) was
31 a cost-consequences analysis based on the TICORA RCT (same paper) which was also
32 included in the clinical review. This analysis also found that treat-to-target was less costly
33 and more effective than usual care. No analysis of uncertainty was conducted however;
34 confidence intervals indicate that there is some uncertainty in both the costs and outcomes.
35 The committee considered these confidence intervals and concluded that at a minimum
36 treat-to-target was likely to be cost neutral.

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

41 No health economic studies were identified regarding the frequency of monitoring or the
42 target for monitoring. Unit costs were provided for rheumatologist consultations to aid the
43 consideration of cost effectiveness. The committee considered the potential economic impact
44 of increasing frequency of monitoring from monthly to fortnightly and agreed that this would
45 have a substantial impact on NHS resources and that there was no clinical evidence to
46 support it. The committee agreed to keep the previous recommendation of monthly
47 monitoring based on the clinical evidence reviewed. The committee noted that monthly visits
48 may not have been implemented nationwide and this is reflected in a survey of the 2009
49 guideline implementation in the Midlands (25–62% receiving monthly monitoring). If this is
50 reflective of practice across the country, this recommendation will likely involve a change in

1 practice in many clinics around the country and may have a resource impact. Although there
2 was no direct health economic evidence for the frequency of monitoring, the Grigor 2004 and
3 Nair 2015 treat-to-target economic analyses suggested that even with more frequent visits
4 (monthly versus every 3 months), a treat-to-target approach was cost saving. Finally, the
5 committee noted that these monthly visits are often conducted by a nurse specialist rather
6 than a consultant. The unit costs of different healthcare professionals were presented to the
7 committee and it was noted that the cost of a nurse consultation would be less expensive
8 than that of a consultant.

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

13 The committee made a recommendation to consider a review appointment within 6 months
14 of stabilising. This recommendation was made based on expert opinion and consensus. The
15 committee considered that this recommendation might reduce unwarranted variation in
16 follow-up across the country as the prior recommendation may have led to unnecessary
17 consultations for some or others receiving no follow-up.
18

1

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1 Appendices

2 Appendix A: Review protocols

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

Field	Content
Review questions	<p>In adults with rheumatoid arthritis, what is the best target to use when monitoring disease activity (remission or low disease activity)?</p> <p>In adults with poor prognosis rheumatoid arthritis, what is the best target to use when monitoring disease activity (remission or low disease activity)?</p>
Type of review question	Intervention
Objective of the review	<p>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.</p> <p>The aim of this review is to identify whether low disease activity or remission is a better target for monitoring disease activity.</p> <p>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.</p>
Eligibility criteria – population / disease / condition / issue / domain	<p>Adults with rheumatoid arthritis according to validated classification criteria, with at least moderate disease activity (equivalent to DAS28 \geq 3.2). This might also be described as active disease, persistent disease or refractory disease.</p> <p>Studies in adults with poor prognostic factors will be analysed and reported separately.</p>
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	<p>Monitoring a composite measure of disease activity with a target of disease remission</p> <p>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 \leq 3.3 = remission</p> <p>The different disease activity measures will be pooled in the analysis.</p>
Eligibility criteria – comparator(s) / control or reference (gold) standard	<p>Monitoring a composite measure of disease activity with a target of low disease activity</p> <p>The following composite measures will be considered: Disease activity score (DAS28; all versions). DAS28 < 3.2 = low disease activity</p>

Field	Content
	<p>Original disease activity score (DAS; all versions). DAS < 2.4 = low disease activity</p> <p>Simplified disease activity index (SDAI). SDAI ≤ 11.0 = low disease activity</p> <p>The different disease activity measures will be pooled in the analysis.</p>
Outcomes and prioritisation	<p>CRITICAL</p> <p>Disease Activity Score (continuous) at 12 months</p> <p>Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument; continuous) at 12 months</p> <p>Function (for example, Health Assessment Questionnaire, activities of daily living; continuous) at 12 months</p> <p>IMPORTANT</p> <p>Fatigue (for example, fatigue severity scale, FACIT, BRAF; continuous) at 12 months</p> <p>Pain (for example, visual analogue scale; continuous) at 12 months</p> <p>Radiological progression (continuous) at 12 months</p> <p>Withdrawal/adherence (dichotomous) at longest reported time point</p> <p>For outcomes other than those below, data must be least 6 months. If multiple time points, take closest time point to 12 months.</p> <p>For radiological progression, data must be at least 12 months. If multiple time points, take the longest time point.</p> <p>For withdrawal and adherence, take the longest reported time point.</p>
Eligibility criteria – study design	<p>RCTs</p> <p>Systematic review of RCTs</p>
Other inclusion / exclusion criteria	<p>Studies in mixed inflammatory arthritis populations will be excluded, unless the results are presented separately for people with RA.</p> <p>Studies in people with RA as well as another rheumatic disease (e.g. lupus) will be excluded.</p>
Proposed sensitivity / subgroup analysis, or meta-regression	<p>In the case of heterogeneity, the following subgroup analyses will be considered:</p> <p>Disease activity of patients enrolled in trial (active versus moderate versus mixed)</p> <p>Disease duration (≤ 2 years versus > 2 years)</p> <p>Frequency of monitoring (monthly versus less than monthly)</p>
Selection process – duplicate screening / selection / analysis	<p>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.</p>
Data management (software)	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p>

Field	Content
	<p>GRADEpro will be used to assess the quality of evidence for each outcome.</p> <p>Endnote will be used for bibliography, citations, sifting and reference management</p>
Information sources – databases and dates	<p>Clinical search databases: The databases to be searched are Medline, Embase and the Cochrane Library. Date limits for search: None Language: English</p> <p>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</p>
Identify if an update	<p>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.</p>
Author contacts	<p>https://www.nice.org.uk/guidance/indevelopment/gid-ng10014</p>
Highlight if amendment to previous protocol	<p>For details, please see section 4.5 of Developing NICE guidelines: the manual.</p>
Search strategy – for one database	<p>For details, please see appendix B</p>
Data collection process – forms / duplicate	<p>A standardised evidence table format will be used, and published as appendix D of the evidence report.</p>
Data items – define all variables to be collected	<p>For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).</p>
Methods for assessing bias at outcome / study level	<p>Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>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/</p>
Criteria for quantitative synthesis	<p>For details, please see section 6.4 of Developing NICE guidelines: the manual.</p>
Methods for quantitative analysis – combining studies and exploring (in)consistency	<p>For details, please see the separate Methods report for this guideline.</p>
Meta-bias assessment – publication bias, selective reporting bias	<p>For details, please see section 6.2 of Developing NICE guidelines: the manual.</p>
Confidence in cumulative evidence	<p>For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.</p>
Rationale / context – what is known	<p>For details, please see the introduction to the evidence review.</p>
Describe contributions of authors and guarantor	<p>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-</p>

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

1 **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	<p>Populations, interventions and comparators must be as specified in the clinical review protocol above.</p> <p>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).</p> <p>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.)</p> <p>Unpublished reports will not be considered unless submitted as part of a call for evidence.</p> <p>Studies must be in English.</p>
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	<p>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.</p> <p>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</p> <p>Inclusion and exclusion criteria</p> <p>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.</p> <p>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.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</p> <p>Where there is discretion</p> <p>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</p>

Review question	All questions – health economic evidence
	<p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <p>UK NHS (most applicable).</p> <p>OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</p> <p>OECD countries with predominantly private health insurance systems (for example, Switzerland).</p> <p>Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.</p> <p>Health economic study type:</p> <p>Cost–utility analysis (most applicable).</p> <p>Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).</p> <p>Comparative cost analysis.</p> <p>Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.</p> <p>Year of analysis:</p> <p>The more recent the study, the more applicable it will be.</p> <p>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’.</p> <p>Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations.</p> <p>Quality and relevance of effectiveness data used in the health economic analysis:</p> <p>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.</p>

1

2 Appendix B: Literature search strategies

3 The literature searches for this review are detailed below and complied with the methodology
4 outlined in Developing NICE guidelines: the manual 2014, updated 2017.

5 [https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-](https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869)
6 [pdf-72286708700869](https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869)

7 *For more detailed information, please see the Methodology Review.*

B.1.8 Clinical search literature search strategy

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

14 **Table 5: Database date parameters and filters used**

Database	Dates searched	Search filter used
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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

1 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)

1 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)

1 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.2.2 Health Economics literature search strategy

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

9 **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

10 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)

1 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)

1 NHS EED and HTA (CRD) search terms

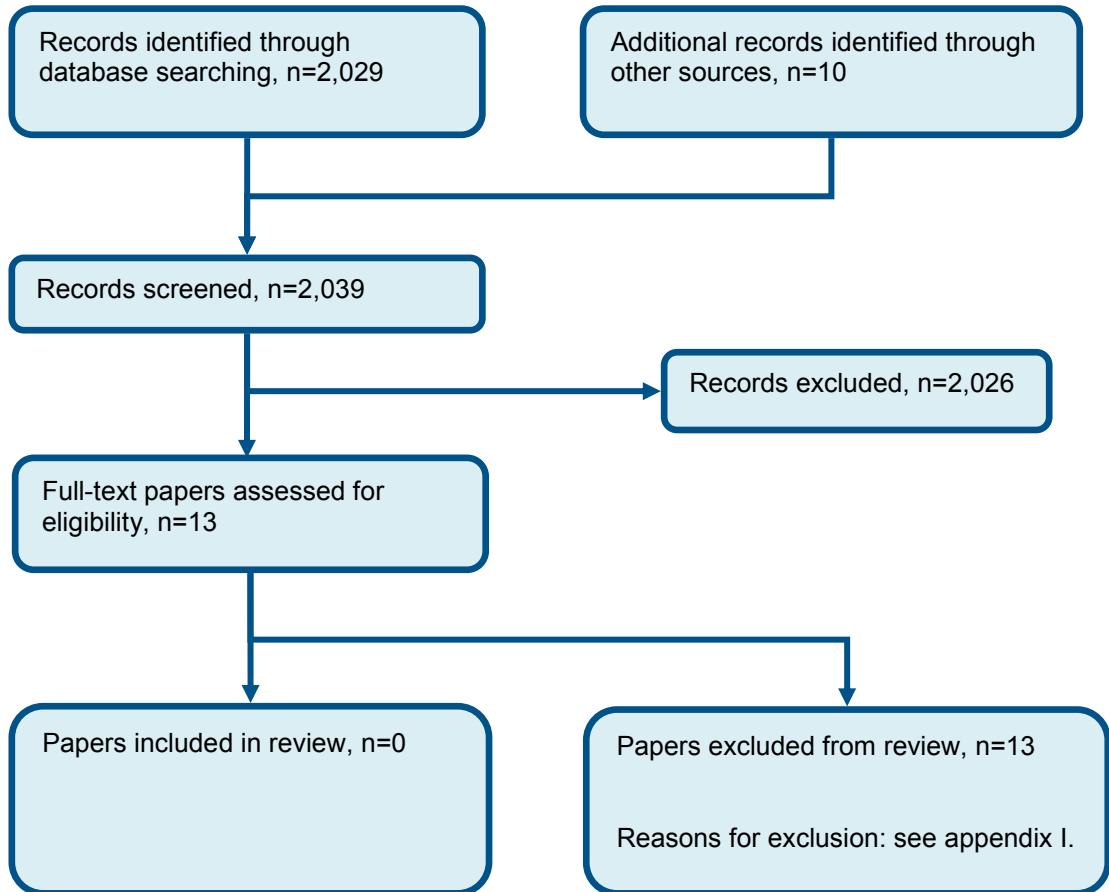
#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))
#5.	((rheumatoid adj2 factor))
#6.	((inflammatory or idiopathic) adj2 arthritis))
#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR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

2

3

1 Appendix C: Clinical evidence selection

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



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1 **Appendix D: Clinical evidence tables**

2 No relevant clinical studies were identified.

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1 **Appendix E: Forest plots**

2 No relevant clinical studies were identified.

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1 **Appendix F: GRADE tables**

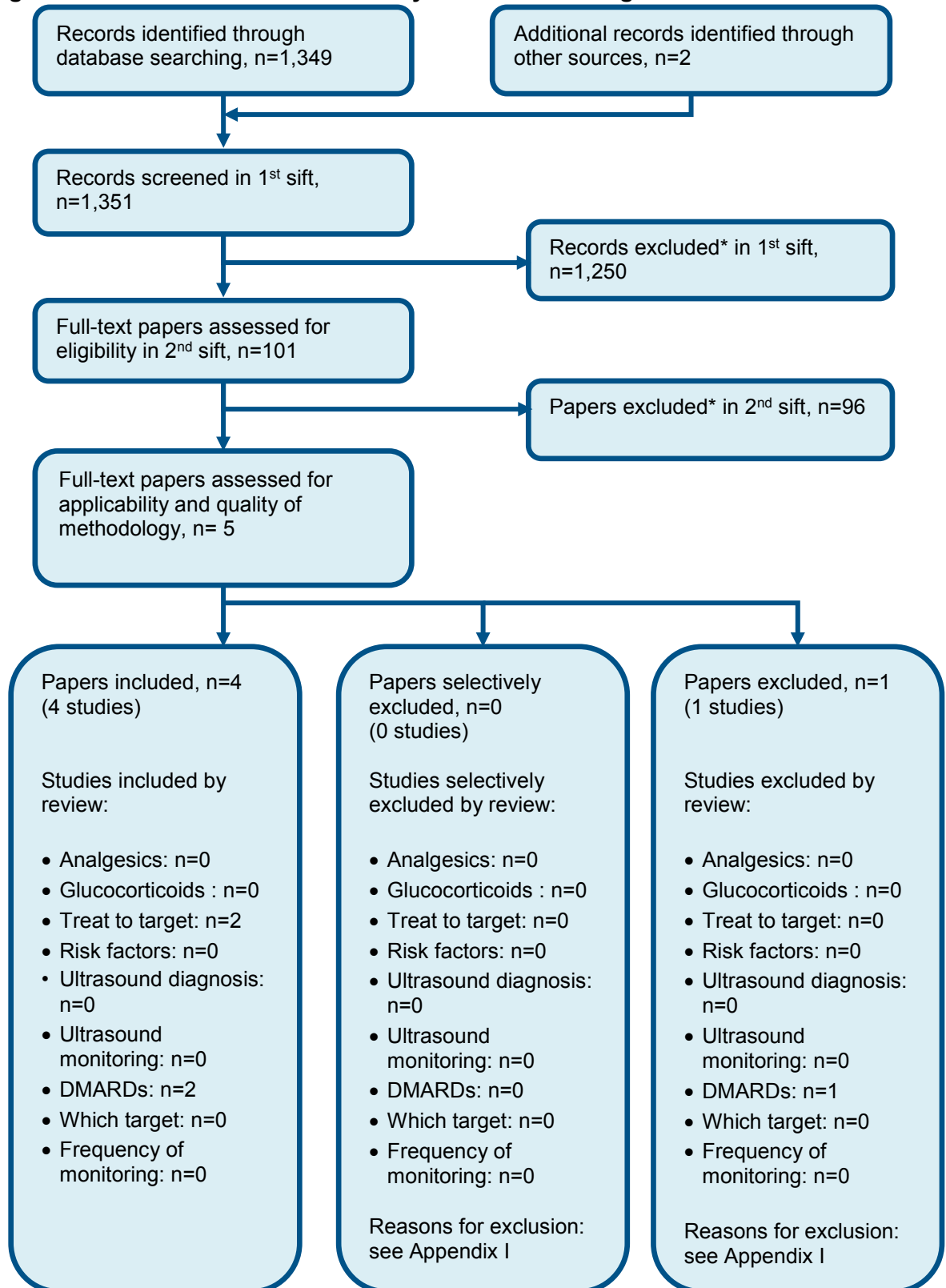
2 No relevant clinical studies were identified.

3

4

1 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*

1

1 **Appendix H: Health economic evidence tables**

2

3 No relevant economic studies were identified.

4

5

1 Appendix I: Excluded studies

I.1.2 Excluded clinical studies

3 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

4

I.2.5 Excluded health economic studies

6 Table 8: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None

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