National Institute for Health and Care Excellence

Consultation

Rheumatoid arthritis in adults: diagnosis and management

Evidence review C Treat-to-target

NICE guideline CG79

Evidence review

January 2018

Consultation

This evidence review was developed by the National Guideline Centre

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1 Treat-to-target in rheumatoid arthritis

1.1 Review question: In adults with rheumatoid arthritis (RA), what is the clinical and cost effectiveness of a treat-to-target management strategy, compared with usual care?

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 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[25] 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
Intervention	Treat-to-target management strategy
Comparison	Usual care
Outcomes	CRITICAL • Disease activity score (continuous) at 12 months • Quality of life (continuous) at 12 months • Function (continuous) at 12 months

	IMPORTANT • Remission (dichotomous) at 12 months • Low disease activity (dichotomous) at 12 months • Fatigue at 12 months (continuous) at 12 months • Pain at 12 months (continuous) at 12 months • Radiological progression (continuous) at longest reported time point • Withdrawal/adherence (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.[2] 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 treat-to-target management strategies to usual care in adults with rheumatoid arthritis. Five studies (9 papers) were included in the review;[1, 7, 9, 17, 32, 44, 45, 49, 50] these are summarised in Table 2 below. The studies reported a variety of single or combined targets in their treat-to-target management approaches:

- Two studies calculated the disease activity score (DAS28).
- One three-armed study compared using the DAS28, or a zero swollen joint count (0-SJC) as targets to usual care.
- One four-armed study compared the single targets DAS28, and matrix metalloproteinase (MMP) 3 normalisation, and the combination of both targets to usual care.
- One study used a combination of predefined criteria to calculate response to treatment as target.

The aim of all studies was to assess whether a treat-to-target management approach was more effective than usual care in people with rheumatoid arthritis.

Evidence from these studies 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
CAMERA	Treat-to-target	People with early	• Function (HAQ)	2 year study with 5 year follow-up

Study	Intervention and comparison	Population	Outcomes	Comments
trial Verstappen 2007[50] Jurgens 2014[17] Bakker 2011[1] Verstappen 2010[49]	management strategy (n=151) versus usual care (n=148) Both groups followed the same drug escalation protocol but usual care used no computer decision programme, less frequent visits and differing response criteria.	RA (disease duration <1 year) Age (mean): 54	at 1 year • Remission at 1 year • Pain (VAS) at 1 year • Radiological progression at 1 year • Discontinuation at 2 years	
Fransen 2005[7]	Treat-to-target management strategy (n=205) versus usual care (n=179) DAS group used systematic monitoring at weeks 0, 4, 12, and 24 using DAS28. In usual care, no systematic monitoring was done and no guideline for treatment strategy supplied.	Outpatients ≤18 years of age with RA who had medical need for NSAID treatment Age (mean): 58	• Disease Activity Score (DAS28) at 24 weeks • Low disease activity at 24 weeks • Discontinuation at 24 weeks	24 weeks cluster-randomised trial
TICORA trial Grigor 2004[9]	Treat-to-target (n=55) versus usual care (n=55) Treat-to-target group was seen every month and DAS28 calculated. Usual care group was seen every three months, with no formal composite measure of disease activity used in clinical decision-making.	Patients aged between 18 and 75 years who had had RA <5 years. Age (mean): 53	• Disease Activity Score (DAS28) at18 months • Quality of life (SF12 physical) at 18 months • Quality of life (SF12 mental) at 18 months • Function (HAQ) at 18 months • DAS remission at 18 months • Pain (VAS)at 18 months • Radiological progression at 18 months • Discontinuation at 18 months	18 months trial

Study	Intervention and comparison	Population	Outcomes	Comments
Pope 2013[32]	Treat-to-target/DAS group (n=100) versus treat-to-target/0-SJC group (n=99) versus usual care (n=109) DAS group aimed to achieve DAS28<2.6, 0-SJC group had the target of achieving a swollen joint count of zero. All groups were seen at 0, 6, 12, and 18 months. Target groups were also assessed at 2, 4 and 9 months.	Patients with RA aged ≥18 years who were to initiate treatment with adalimumab independent of study participation. Age (mean): 54	• Function (HAQ) at 12 months • Work limitations questionnaire at 12 months • Low disease activity at 18 months • DAS remission at 18 months • Discontinuation at 18 months	18 months cluster-randomised trial with three study arms
T-4 Study Urata 2014[44] Urata 2012[45]	Treat-to-target/DAS28 (n=60) versus treat-to-target/MMP-3 (n=60) versus twin treat-to-target/DAS28 plus MMP-3 (n=61) versus usual care (n=62) The study used the following visiting times: weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56.	Patients with early RA with a disease duration of <3 years and a DAS28 >3.2, aged >18 years. Age (mean): 60	• Disease Activity Score (DAS28) at 56 weeks • Function (mHAQ) at 56 weeks • DAS remission at 56 weeks • Radiological progression at 56 weeks • Discontinuation at 56 weeks	Four study arms for first 56 weeks of trial; then all patients were switched to treat-to-target treatment. Only results of first 56 weeks are reported.

1 See appendix D for full evidence tables.

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1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Treat-to-target versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Treat-to-target (95% CI)
Disease Activity Score Change in DAS28. Scale from: 0 to 9.4	467 (3 studies) 6-18 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean DAS (change) in the control groups was -1.3	The mean DAS (change) in the intervention groups was 0.78 lower (1.57 lower to 0.01 higher)
Quality of life Change in SF12 - physical. Scale from: 0 to 100.	103 (1 study) 18 months	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, imprecision		The mean QOL - SF12 (change) - physical in the control groups was 4.0	The mean QOL - sf12 (change) - physical in the intervention groups was 5.3 higher (0.86 to 9.74 higher)
Quality of life Change in SF12 - mental Scale from: 0 to 100.	103 (1 study) 18 months	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, imprecision		The mean QOL - SF12 (change) - mental in the control groups was 6.0	The mean QOL - SF12 (change) - mental in the intervention groups was 4.9 higher (1.69 lower to 11.49 higher)
Function Change in HAQ. Scale from: 0 to 3.	932 (4 studies) 12-18 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, inconsistency		The mean HAQ (change) in the control groups was -0.29	The mean HAQ (change) in the intervention groups was 0.03 lower (0.18 lower to 0.12 higher)
Remission Various: DAS < 1.6, DAS28 < 2.6, other Scale from 0 to 10 (DAS) or 0 to 9.4 (DAS28).	854 (4 studies) 12-18 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, inconsistency	RR 1.71 (1.05 to 2.78)	199 per 1000	141 more per 1000 (from 10 more to 354 more)
Low disease activity DAS28 <3.2	344 (2 studies)	⊕⊖⊖⊖ VERY LOW[1,2,3]	RR 1.12	316 per 1000	38 more per 1000 (from 98 fewer to 256 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Treat-to-target (95% CI)
	6-18 months	due to risk of bias, inconsistency, imprecision	(0.69 to 1.81)		
Pain Change in VAS. Scale from: 0 to 100.	402 (2 studies) 12 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean pain VAS (change) in the control groups was -22	The mean pain VAS (change) in the intervention groups was 17.82 lower (30.49 to 5.15 lower)
Radiological progression Change in modified Sharp/van der Heijde score. Scale from: 0 to 448.	421 (2 studies) 12-18 months	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean radiological progression in the control groups was 2.0	The mean radiological progression in the intervention groups was 0.92 lower (1.58 to 0.26 lower)
Radiological progression (median (IQR)) Change in median modified Sharp/van der Heijde score. Scale from: 0 to 448.	103 (1 study) 18 months	⊕⊕⊕⊖ MODERATE[1,4] due to risk of bias		The radiological progression (median (IQR)) in the control groups was 8.5 (2.0-15.5)	The radiological progression (median (IQR)) in the intervention groups was 4.5 (1.0-9.9) (median difference 4.0)
Work limitations questionnaire (target: DAS28) Scale from: 0 to 100.	308 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision		The mean work limitations questionnaire (target: DAS28) in the control groups was -4.2	The mean work limitations questionnaire (target: DAS28) in the intervention groups was 0.5 lower (2.86 lower to 1.86 higher)
Work limitations questionnaire (target: 0-SJC) Scale from: 0 to 100.	308 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision		The mean work limitations questionnaire (target: 0-sjc) in the control groups was -4.2	The mean work limitations questionnaire (target: 0-sjc) in the intervention groups was 0.6 higher (1.63 lower to 2.83 higher)
Study discontinuation	1344 (5 studies) 6-24 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency,	RR 0.72 (0.42 to	217 per 1000	61 fewer per 1000 (from 126 fewer to 48 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Treat-to-target (95% CI)
		imprecision	1.22)		

[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] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Cannot assess imprecision using median (IQR)

1 See appendix F for full GRADE tables.

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1.6 Economic evidence

1.6.1 Included studies

Two health economic studies were identified with the relevant comparison and have been included in this review.[9, 23] These are summarised in the health economic evidence profile below (Table 5) and the health economic evidence tables in appendix H.

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

1.6.2 Excluded studies

None.

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

1.6.4 Summary of studies included in the economic evidence review

Table 5: Health economic evidence profile: treat to target versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Nair 2015[23] (Netherlands)	Partially applicable[(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis (QALYs) • Clinical data from the Dutch CAMERA trial (Verstappen 2007[50]) • Population: adults with early RA. All received methotrexate and ciclosporin as first- and second-line treatment • Two comparators: 1. Usual care (visits every 3 months) 2. Treat to target 'tight control' (monthly visits) • Time horizon: 2 years	£1,530 in favour of the tight control strategy	0.06 QALYs in favour of the tight control strategy	The tight control strategy dominated usual care due to being less costly and more effective	The tight control strategy resulted in less medical consumption and improved quality of life due to better DAS28/HAQ, however drug costs were higher. In the probabilistic analysis, in approximately 80%-90% of the simulations the tight control strategy dominated usual care (under the study base-case societal perspective).
Grigor 2004[9] (UK)	Partially applicable[(c)]	Potentially serious limitations[(d)]	• Within-trial analysis based on UK RCT (TICORA trial, same paper) • Cost–consequences analysis (various health outcomes) • Population: Adults with RA <5 years and	£3,652 in favour of treat to target	From clinical review (2 vs 1) • Disease activity score: MD -1.6 • Quality of life (SF12 physical summary score): MD 5.3	Treat to target dominates usual care due to being less costly and more effective	No detailed analysis of uncertainty conducted. Although the 95% CI indicate there is some uncertainty in the costs and health outcomes.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
			active disease • Two comparators: 1. Usual care (visits every 3 months) 2. Treat to target (monthly visits) • Follow-up: 18 months		• Quality of life (SF12 mental summary score): MD 4.9 • Health assessment questionnaire: -0.5		

Abbreviations: ICER: incremental cost-effectiveness ratio; MD: mean difference; QALY: quality-adjusted life years.

(a) Inadequate details are given about the treatment protocol of the conventional approach (described as usual practice), discounting is not in line with the NICE reference case (3.5%), direct medical costs included some non-NHS incurred costs

(b) 2-year time horizon, it might omit some relevant cost and outcomes, analysis is based on evidence on CAMERA which was 1 of 5 studies identified in the clinical review for treat to target versus usual care and so does not reflect full body of evidence for this comparison, unit costs are representable of the Dutch healthcare system

(c) Resource use and unit costs old (2001-2002) and so may not reflect current NHS context. QALYs were not used as the health outcome measure. No discounting, although follow up is only 18 months and so this may not impact outcome.

(d) Within-trial analysis and so does not reflect full body of evidence for this comparison; Grigor 2004 is 1 of 5 studies included in the clinical review for treat to target versus usual care. No exploration of uncertainty. Short follow-up so may omit some relevant costs and outcomes.

1.7 Resource costs

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

1.8 Evidence statements

1.8.1 Clinical evidence statements

- Treat-to-target versus Usual care

Evidence showed a clinically important benefit of treat-to-target in terms of disease activity (3 studies, very low quality, n=467), quality of life (1 study, low quality, n=103), remission (4 studies, very low quality, n=854), pain (2 studies, very low quality, n=402), radiological progression (3 studies, moderate quality, n=524), and fewer withdrawals from the trial (5 studies, very low quality, n=1344). No clinical difference between the interventions was found in terms of function (4 studies, very low quality n=932), low disease activity (2 studies, very low quality, n=344) or work limitations (1 study, very low quality, n=308).

1.8.2 Health economic evidence statements

- One cost–utility analysis the compared a treat-to-target approach and usual practice in people with rheumatoid arthritis found that:
  - The treat-to-target approach dominated usual care being less costly by £1530 and more effective by 0.06 QALYs

  This analysis was assessed as partially applicable with potentially serious limitations
- One cost–consequences analysis that compared a treat-to-target approach and usual practice in people with rheumatoid arthritis found that:
  - The treat-to-target approach dominated usual care being less costly by £3,652 and more effective (various health outcomes)

  This analysis was assessed as partially applicable with potentially serious limitations

1.9 Recommendations

C1. Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target).

C2. Consider making the target remission rather than low disease activity for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-ray at baselines assessment).

C3. In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly until the target of remission or low disease activity is achieved.

C4. Ensure that all adults with RA have:

- rapid access to specialist care for worsening disease or flares
- information about when and how to access specialist care, and
- ongoing drug monitoring.

C5. Consider a review appointment to take place 6 months after achieving treatment target (remission or low disease activity) to ensure that the target has been maintained.

C6. Offer all adults with RA, including those who have achieved the treatment target, an annual review to:

- assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
- check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression
- assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes
- organise appropriate cross referral within the multidisciplinary team
- assess the need for referral for surgery (see section 1.6)
- assess the effect the disease is having on a person's life.

1.10 Rationale and impact

1.10.1 Why the committee made the recommendations

Strategy and treatment target

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

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

Frequency of monitoring for active disease

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

People at risk of poor outcomes

There was no evidence that people with a poor prognosis should have different management in terms of the treatment target or the frequency of monitoring. However, in the committee's experience RA often responds less well to standard management in this group. 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 (see evidence review B: Risk factors.

Frequency of monitoring when treatment target has been achieved

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

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

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

1.10.2 Why we need recommendations on this topic

Current consensus amongst the rheumatology community is that a treat-to-target strategy should be used when treating people with rheumatoid arthritis 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[25] 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?

1.10.3 Impact of the recommendations on practice

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

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

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The outcomes that matter most

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

Pain, radiographic progression, fatigue and the number of people who withdrew from the trial were agreed to be important outcomes for all three 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.

1.11.1.2 The quality of the evidence

Treat-to-target versus usual care

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

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

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

Remission or low disease activity as the target

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

Frequency of monitoring

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

No studies were found comparing any other frequencies of monitoring.

<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.

1.11.1.3 Benefits and harms

Treat-to-target versus usual care

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

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

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

Remission or low disease activity as the target

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

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

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

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

Frequency of monitoring

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

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

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

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

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

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

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

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

1.11.2 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.

1

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1 Appendices

2 Appendix A: Review protocols

3 **Table 6: Review protocol: Treat-to-target**

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of a treat-to-target management strategy, compared with usual care?
II	Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	The aim of this review is to determine the clinical and cost effectiveness of a treat-to-target management strategy, compared with usual care, in adults with rheumatoid arthritis.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis (RA) according to validated classification criteria. All studies will be pooled in the analysis, regardless of disease duration of the participants
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Treat to target management strategy. Defined as a strategy that defines a treatment target (for example, remission or low disease activity) and applies tight control (for example, monthly visits and action) and respective therapeutic adaptions to reach this target. The treatment strategy often follows a protocol. Treat to target trials will be included regardless of the particular interventions or drugs used to achieve the target, including biologics. Studies of any target (except for targets that are only based on patient reported outcomes) will be included and these will be pooled in the analysis.
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Usual care. Usual care typically consists of less frequent visits, and less clearly defined criteria for what constitutes a good outcome. Typically, it is patient/physician global assessments that drive management choices, and a degree of disease activity is accepted. It is typically a more reactive and less aggressive approach to disease management, and is usually not protocol driven.
VII	Outcomes and prioritisation	CRITICAL • Disease Activity Score (DAS; continuous) at12 months • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument; continuous) at 12 months • Function (for example, Health Assessment Questionnaire, activities of daily living; continuous) at 12 months IMPORTANT • Low disease activity (dichotomous) at 12 months • Remission (dichotomous) at 12 months • Fatigue (for example, fatigue severity scale, FACIT, BRAF; continuous) at 12 months

ID	Field	Content
		• Pain (for example, visual analogue scale) (continuous) at 12 months • Radiological progression (continuous) at 12 months • Withdrawal from trial/adherence to strategy (dichotomous) at longest reported time point Outcomes must be reported at least 6 months from start of trial. If multiple time points, take closest time point to 12 months. For radiological progression, data must be at least 12 months, and the longest time point will be taken.
VIII	Eligibility criteria – study design	RCTs Systematic Reviews of RCTs
IX	Other inclusion exclusion criteria	Studies in mixed populations will be excluded, unless the results are presented separately for RA patients. Studies in patients with RA as well as another rheumatic disease (for example, lupus) will be excluded.
X	Proposed sensitivity / subgroup analysis, or meta-regression	Disease duration will be considered when interpreting the findings. Subgroup analyses if there is heterogeneity: • Nature of the target (composite targets, biomarkers, ultrasound targets, other) – there is not a single measure of disease activity. Some composite targets may be more beneficial, and some may be better for different endpoints for example, CRP for radiological progression • Disease duration (≤2 years versus > 2 years)
XI	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.
XII	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
XIII	Information sources – databases and dates	Clinical search databases: The databases to be searched are Medline, Embase and the Cochrane Library. Date limits for search: None Language: English Health economics search databases: Medline, Embase, NHSEED and HTA Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
XIV	Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[25] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.
XV	Author	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014

ID	Field	Content
	contacts	
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details, please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	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).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) 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 the 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

ID	Field	Content
		manual
XX VII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XX VIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXI X	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XX X	PROSPERO registration number	Not registered

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2 **Table 7: 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).[26] 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

Review question	All questions – health economic evidence
	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. 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.

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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 8: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/

15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	(tight* adj control*).ti,ab.
30.	t2t.ti,ab.
31.	((mission or aiming or aim or aimed or aims or achiev* or sustain* or reach*) adj2 remission).ti,ab.
32.	((treat* or therap*) adj2 (target* or goal*)).ti,ab.
33.	(symptom* adj2 (reduc* or improv* or control*)).ti,ab.
34.	low disease activity.ti,ab.
35.	(abrogat* adj2 inflammat*).ti,ab.
36.	optimi*.ti,ab.
37.	or/29-36
38.	28 and 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ti,ab.
42.	placebo.ab.
43.	drug therapy.fs.
44.	randomly.ti,ab.
45.	trial.ab.
46.	groups.ab.
47.	or/39-46
48.	Clinical Trials as topic.sh.
49.	trial.ti.
50.	or/39-42,44,48-49
51.	Meta-Analysis/
52.	Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.

58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	38 and (50 or 61)

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.21 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 9: 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)

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

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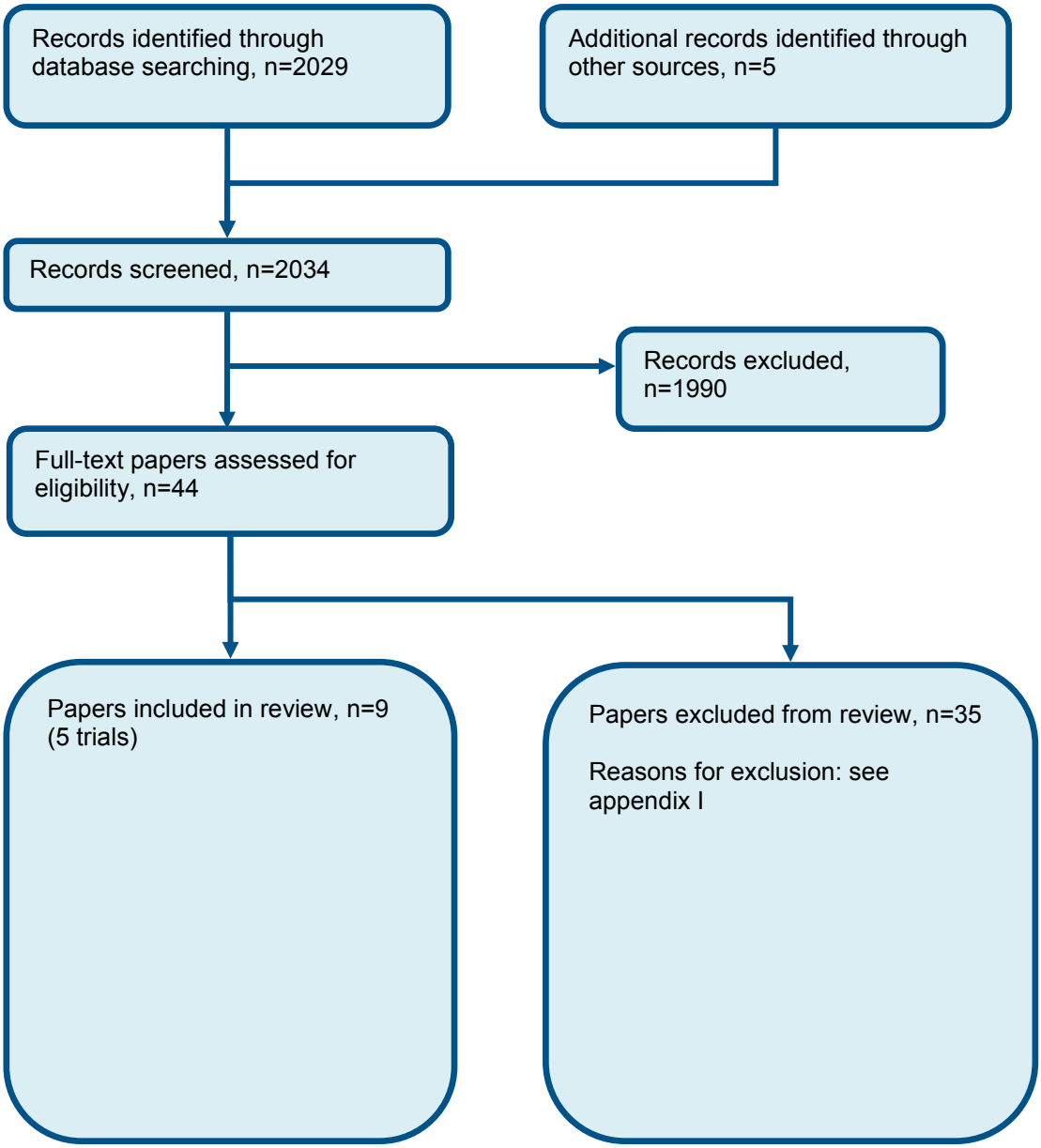
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of treat-to-target



1 Appendix D: Clinical evidence tables

Study (subsidiary papers)	CAMERA trial: Verstappen 2007[50] (Jurgens 2014[17], Bakker 2011[1], Verstappen 2010[49])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=299)
Countries and setting	Conducted in Netherlands; Setting: Six outpatient clinics
Line of therapy	Not applicable
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptoms < 1 year, age > 16 years.
Exclusion criteria	Previous use of glucocorticoids or any DMARD, use of cytotoxic or immunosuppressive drugs within a period of three months before inclusion, alcohol abuse (> 2 units / day) and psychological problems making adherence impossible.
Recruitment/selection of patients	From 1999 - 2003, all eligible patients were asked to participate.
Age, gender and ethnicity	Age - Mean (SD): T2T - 54 (14), UC - 53 (15). Gender (M:F): 98:201. Ethnicity: NR
Further population details	1. Disease duration: < 2 years
Extra comments	All mean (SD): ESR, mm/h: T2T - 36 (27), UC - 39 (25) Morning stiffness, min: T2T - 87 (55), UC - 88 (54) VAS general well-being, mm: T2T - 54 (22), UC - 52 (23) VAS pain, mm: T2T - 51 (26), UC - 47 (25) RF +ve: T2T - 66%, UC - 62% HAQ: T2T - 1.2 (0.7), UC - 1.2 (0.7) Radiographic damage (modified Sharp / van der Heijde) score: T2T - 1.6 (4.2), UC - 2.2 (5.3).
Indirectness of population	No indirectness
Interventions	(n=151) Intervention 1: Treat-to-target management strategy - Treat-to-target. Both groups followed the same drug dose escalation protocol (see below), but the strategy in the intensive treatment group differed in three ways:

	1. The use of a computer decision program. At each visit, data on swollen joint count, tender joint count, erythrocyte sedimentation rate (ESR), and visual analogue scale (VAS) for general well-being were entered by the rheumatologist. The program then calculated whether or not predefined criteria of response to treatment were met. As ESR values were only known the next day, the participating rheumatologists informed their patient the following day by telephone whether a dose change was necessary or not. 2. The response criteria. Response compared to previous visit was measured by > 20 % improvement in number of swollen joints and > 20% improvement in 2 out of 3 criteria: ESR, number of tender joints, and VAS general well-being. Inadequate response was ≤ 50% improvement from baseline for number of swollen joints and ≤ 50% improvement from baseline for 2 out of 3 criteria: ESR, number of tender joints, and VAS general well-being. Sustained response was no swollen joints and 2 out of 3 criteria: number of painful joints ≤ 3, ESR ≤20 mm/h, VAS general wellbeing ≤ 20 mm. Sustained response had be to fulfilled for 12 weeks (4 subsequent visits). 3. The frequency of evaluations leading to therapeutic decisions (every four weeks); fast step-up and step down of MTX dosage (maximum dose of 30 mg/week MTX could be reached after 18 weeks). . Duration 2 years. Concurrent medication/care: Protocol in both groups: The starting dose of oral MTX was 7.5 mg/week. In both groups, the dosage of MTX was not changed if patients had responded compared with the previous visit; otherwise the dosage was increased stepwise by 5 mg/week, to a maximum of 30 mg/ week. If the maximum (tolerable) dose of MTX was reached and patients did not fulfill the criteria for sustained response, MTX was administered subcutaneously (sc). For patients on MTX sc having an inadequate response, ciclosporin was added to the MTX, while the dosage of MTX was reduced to 15 mg/week. The starting dose of ciclosporin was 2.5 mg/kg/day; this was increased stepwise by 0.5 mg/ kg/day to a maximum of 4 mg/kg/day, if no response was reached. If patients fulfilled the criteria for sustained response, MTX was reduced stepwise by 2.5 mg/week as long as patients met these criteria; otherwise the dose of MTX was continued or increased again according to protocol. Folic acid was prescribed to every patient (0.5 mg/day). Use of non-glucocorticoid anti-inflammatory drugs (NSAIDs) was allowed in both strategy groups. Intra-articular injections were avoided in so far as possible because this might lead to bias with respect to treatment effect between the two treatment groups. Oral glucocorticoids were not allowed during the trial unless unavoidable, which then had to be approved by another rheumatologist participating in this study. . Indirectness: No indirectness Further details: 1. Nature of the target: Composite target (Sustained response as described above). (n=148) Intervention 2: Usual care. Both groups followed the same drug dose escalation protocol (see below), but the strategy in the conventional strategy treatment group differed in three ways: 1. No use of a computer decision program. Response criteria assessment based on opinion of individual rheumatologist. 2. The response criteria. Response compared to previous visit: - decrease of number of swollen joints. If number of swollen joints unchanged, decision of response depended on assessors' judgement looking at

	number of tender joints, ESR and VAS general wellbeing. Inadequate response: Number of swollen joints ≥ 6, number of painful joints ≥ 3, ESR ≥28 mm/h, and morning stiffness ≥ 45 min. Sustained response: as for intensive (T2T) group, except that criteria had to be fulfilled for 6 months (three subsequent visits). 3. The frequency of evaluations leading to therapeutic decisions. Patients visited the clinic every three months (minimum time to reach the highest dose of 30mg/week MTX was 52 weeks). This strategy was similar to common practice in the Netherlands in 1998 when this study was designed. . Duration 2 years. Concurrent medication/care: The starting dose of oral MTX was 7.5 mg/week. In both groups, the dosage of MTX was not changed if patients had responded compared with the previous visit; otherwise the dosage was increased stepwise by 5 mg/week, to a maximum of 30 mg/ week. If the maximum (tolerable) dose of MTX was reached and patients did not fulfill the criteria for sustained response (fig 1), MTX was administered subcutaneously (sc). For patients on MTX sc having an inadequate response, ciclosporin was added to the MTX, while the dosage of MTX was reduced to 15 mg/week. The starting dose of ciclosporin was 2.5 mg/kg/day; this was increased stepwise by 0.5 mg/ kg/day to a maximum of 4 mg/kg/day, if no response was reached. If patients fulfilled the criteria for sustained response, MTX was reduced stepwise by 2.5 mg/week as long as patients met these criteria; otherwise the dose of MTX was continued or increased again according to protocol. Folic acid was prescribed to every patient (0.5 mg/day). Use of non-glucocorticoid anti-inflammatory drugs (NSAIDs) was allowed in both strategy groups. Intra-articular injections were avoided in so far as possible because this might lead to bias with respect to treatment effect between the two treatment groups. Oral glucocorticoids were not allowed during the trial unless unavoidable, which then had to be approved by another rheumatologist participating in this study. . Indirectness: No indirectness Further details: 1. Nature of the target: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET versus USUAL CARE

Protocol outcome 1: Function at 12 months
- Actual outcome: Health assessment questionnaire at 1 year; Group 1: mean -0.44 (SD 0.59); n=151, Group 2: mean -0.39 (SD 0.66); n=148; Health assessment questionnaire 0-3 Top=High is poor outcome; Comments: All patients' data as numbers of completers at 1 year not given
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: exact numbers unknown at 1 year; Group 2 Number missing: , Reason: exact numbers unknown at 1 year

Protocol outcome 2: Remission at 12 months
- Actual outcome: Remission for at least 3 months (no swollen joints, and at least 2 out of 3 of the following criteria: number of tender joints ≤3, ESR ≤20 mm/h and VAS general wellbeing ≤20 mm) at 1 year; Group 1: 53/151, Group 2: 21/148; Comments: ITT as unknown how many drop-outs after 1 year
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

	Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Does not use validated measure of disease remission (eg DAS, DAS28 or SDAI); Group 1 Number missing: , Reason: exact numbers unknown at 1 year; Group 2 Number missing: , Reason: exact numbers unknown at 1 year Protocol outcome 3: Pain at 12 months - Actual outcome: Visual analogue scale at 1 year; Group 1: mean -36 (SD 31); n=151, Group 2: mean -24 (SD 30); n=148; Visual analogue scale 0-100 Top=High is poor outcome; Comments: ITT, number of drop-outs at 1 year not provided Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: exact numbers unknown at 1 year; Group 2 Number missing: , Reason: exact numbers unknown at 1 year Protocol outcome 4: Radiological progression at 12 months - Actual outcome: Radiographic progression (modified Sharp/van der Heijde score) at 2 years; Group 1: mean 1.9 (SD 4.0583); n=90, Group 2: mean 2.1 (SD 3.9503); n=109; Sharp score 0-448 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - results at 1 year: ITT analysis (last available data were carried forward) as exact numbers of drop-outs at that time point not given. This was not done for radiographic scores (here completers data only) results at 2 years: completers only (available case analysis). High rate of drop-outs: T2T group: 59 (39.07%), UC group: 35 (23.65%) due to adverse events MTX (T2T 17; UC 10), adverse events ciclosporin (T2T 10; UC 1), lack of efficacy (T2T 13, UC 7), otherwise (T2T 16; UC 13), reason unknown (T2T 3; UC 4); Indirectness of outcome: No indirectness ; Group 1 Number missing: 61; Group 2 Number missing: 39 Protocol outcome 5: Withdrawal from trial / adherence to strategy at Longest reported by study - Actual outcome: Withdrawal from study (adverse events MTX or ciclosporin, lack of efficacy, otherwise, reasons unknown) at 2 years; Group 1: 59/151, Group 2: 35/148 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - results at 1 year: ITT analysis (last available data were carried forward) as exact numbers of drop-outs at that time point not given. This was not done for radiographic scores (here completers data only) results at 2 years: completers only (available case analysis). High rate of drop-outs: T2T group: 59 (39.07%), UC group: 35 (23.65%) due to adverse events MTX (T2T 17; UC 10), adverse events ciclosporin (T2T 10; UC 1), lack of efficacy (T2T 13, UC 7), otherwise (T2T 16; UC 13), reason unknown (T2T 3; UC 4); Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Disease activity score at 12 months; Quality of life at 12 months; Low disease activity at 12 months; Fatigue at 12 months

Study	Cluster randomised trial of systematic monitoring of rheumatoid arthritis disease activity trial: Fransen 2005[7]
Study type	RCT (Site (cluster) randomised; Parallel)
Number of studies (number of participants)	1 (n=384)
Countries and setting	Conducted in Netherlands; Setting: Twenty four rheumatology outpatient centres throughout the Netherlands.
Line of therapy	Not applicable
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients of at least 18 years of age with rheumatoid arthritis according to the ACR criteria; medical need for NSAID treatment; adequate anticonception measures; and provision of informed consent.
Exclusion criteria	History of allergy to NSAIDs; serious bowel, liver, kidney, or heart disease; coagulopathy; (suspicion of) peptic ulcer or gastrointestinal bleeding; malignancy; and substance abuse or mental disorders that would interfere with study participation.
Recruitment/selection of patients	Centres were allocated randomly to DAS (12 centres) or usual care (12 centres. All patients within a centre were treated the same way. Recruitment started in March 2000 and ended in March 2001. Patients with rheumatoid arthritis who were in need of NSAID treatment were asked by their treating rheumatologist to participate. All patients included started treatment with celecoxib 200 mg twice daily (the results of which were reported separately).
Age, gender and ethnicity	Age - Mean (SD): main sample - DAS group: 57.0 (11.0), usual care: 59.0 (13.0); subsample - DAS group: 57.0 (10.0), usual care: 59.0 (12.0). Gender (M:F): 7/25. Ethnicity: NR
Further population details	1. Disease duration: Not stated / Unclear
Extra comments	To determine the proportion of patients with a DAS28 ≤3.2 in this trial, the DAS28 had to be assessed independently. These independent assessments only took place in a subgroup of patients, consisting of all patients from the participating centres in a predetermined geographical region.
Indirectness of population	No indirectness
Interventions	(n=205) Intervention 1: Treat-to-target management strategy - Treat-to-target. DAS group: In the DAS group, systematic monitoring of disease activity was carried out at week 0, 4, 12, and 24 by assessment of the DAS28 by the treating rheumatologist. According to the study guidelines, the aim was to reach a DAS28 ≤3.2 (low disease activity) by changing DMARD treatment if the score was above 3.2. The

	rheumatologist of the DAS group had been instructed in performing the joint counts and in using a special calculator for the DAS28. . Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Nature of the target: Composite target Comments: The authors state that for reasons of efficiency, independent DAS28 assessments only took place in a subgroup of patients, consisting of all patients from the participating centres in a predetermined geographical region. main sample: 205 participants (12 centres) in DAS group; subsample: 61 participants (3 centres) in DAS group (n=179) Intervention 2: Usual care. Usual care: No systematic monitoring of disease activity was done and no guideline to adapt treatment strategy was supplied. Otherwise the study visits were identical in both groups.. Duration 24 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Nature of the target: Not applicable Comments: The authors state that for reasons of efficiency, independent DAS28 assessments only took place in a subgroup of patients, consiting of all patients from the participating centres in a predetermined geographical region. Main sample: 179 participants (12 centres) in usual care group; subsample: 81 participants (4 centres) in usual care group
Funding	Study funded by industry (Pharmaceutical company (Pfizer), manuscript proof-read by Pfizer staff)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET versus USUAL CARE

Protocol outcome 1: Disease activity score at 12 months
- Actual outcome: Mean changes in DAS28 score (in a subset of the sample) at 24 weeks; Group 1: mean -0.4 (SD 1); n=61, Group 2: mean -0.14 (SD 1.2); n=81; DAS28 0-10; a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The DAS28 was assessed independently in a subgroup of patients at baseline and at 24 weeks; this subgroup consisted of all patients from the participating centres in a predetermined geographical region. Specifically trained nurses carried out these joint counts. The rheumatologists did not have access to the results of these assessments. It is unclear whether the assessors, patients and caregiver were blind to group allocation.
It is unclear whether there was missing data in the subsample, i.e. was it treated as ITT or available case analyis, and if yes, how much data was missing. In the paper it states that 'an intention to treat approach with last observation carried forward was used for the analysis of primary outcomes.' The DAS28 was a primary outcome.; Indirectness of outcome: No indirectness; Baseline details: in both the main and sub-sample the DAS group had a significantly higher rheumatoid factor positivity (p<0.05); Group 1 Number missing: , Reason: unclear if there was missing data in the subsample and, if so, how much;

	Group 2 Number missing: , Reason: unclear if there was missing data in the subsample and, if so, how much Protocol outcome 2: Low disease activity at 12 months - Actual outcome: DAS28 ≤3.2 (in a subset of the sample) at 24 weeks; Group 1: 19/61, Group 2: 13/81 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The DAS28 was assessed independently in a subgroup of patients at baseline and at 24 weeks; this subgroup consisted of all patients from the participating centres in a predetermined geographical region. Specifically trained nurses carried out these joint counts. The rheumatologists did not have access to the results of these assessments. It is unclear whether the assessors, patients and caregiver were blind to group allocation. It is unclear whether there was missing data in the subsample, i.e. was it treated as ITT or available case analyis, and if yes, how much data was missing. In the paper it states that 'an intention to treat approach with last observation carried forward was used for the analysis of primary outcomes.' The DAS28 was a primary outcome.; Indirectness of outcome: No indirectness; Baseline details: in both the main and sub-sample the DAS group had a significantly higher rheumatoid factor positivity (p<0.05); Group 1 Number missing: , Reason: unclear if there was missing data in the subsample and, if so, how much; Group 2 Number missing: , Reason: unclear if there was missing data in the subsample and, if so, how much Protocol outcome 3: Withdrawal from trial / adherence to strategy at Longest reported by study - Actual outcome: Dropouts (adverse events, patients wish, other reason) at 24 weeks; Group 1: 16/205, Group 2: 20/179; Comments: DAS group: adverse events (n=3), patient wish (n=5), other reason (n=8) usual care group: adverse events (n=9), patient wish (n=7), other reason (n=4) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The DAS28 was assessed independently in a subgroup of patients at baseline and at 24 weeks; this subgroup consisted of all patients from the participating centres in a predetermined geographical region. Specifically trained nurses carried out these joint counts. The rheumatologists did not have access to the results of these assessments. It is unclear whether the assessors, patients and caregiver were blind to group allocation. It is unclear whether there was missing data in the subsample, i.e. was it treated as ITT or available case analyis, and if yes, how much data was missing. In the paper it states that 'an intention to treat approach with last observation carried forward was used for the analysis of primary outcomes.' The DAS28 was a primary outcome. Dropouts were reported for the entire dataset.; Indirectness of outcome: No indirectness; Baseline details: in both the main and sub-sample the DAS group had a significantly higher rheumatoid factor positivity (p<0.05); Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life at 12 months; Function at 12 months; Remission at 12 months; Pain at 12 months; Fatigue at 12 months; Radiological progression at 12 months

Study	Cluster-randomised adalimumab trial with 3 study arms trial: Pope 2013[32]
Study type	RCT (Site (cluster) randomised; Parallel)
Number of studies (number of participants)	1 (n=308)
Countries and setting	Conducted in Canada; Setting: 18 month, real-life, multicenter, parallel group, single (patient)-blind, cluster-randomised trial in patients with established active rheumatoid arthritis who were initiating adalimumab as part of their usual care, in Canada.
Line of therapy	Not applicable
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: 'All patients had established active rheumatoid arthritis.' No more details.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with rheumatoid arthritis for whom a decision to initiate treatment with adalimumab was reached prior to and independently of the current study were considered for enrollment. Additional inclusion criteria were: diagnosis of RA, age ≥18 years, no previous treatment with adalimumab, access to reimbursable standard of care for adalimumab as per the respective province of residence, and provision of informed consent.
Exclusion criteria	A history of cancer within the past 5 years (other than successfully treated basal cell carcinoma and/or localised carcinoma in situ of the cervix); history of lymphoma or leukemia; history of untreated active tuberculosis, listeriosis, or other currently active infections (suggestive of significant or profound immuno-suppression); known positive hepatitis B surface antigen test result; severe infection requiring hospitalisation or treatment with intravenous antibiotics (within 30 days) or oral antibiotics (within 14 days); breastfeeding (for female patients); and a clinically significant concurrent illness that, according to the investigator's judgment, might have influenced the study outcomes. The protocol allowed 20% of patients to be previously TNF inhibitor exposed with the exception of previous adalimumab.
Recruitment/selection of patients	Patients were recruited from the practices of 31 Canadian rheumatologists. Patients had established, active rheumatoid arthritis and were initiating adalimumab as part of their usual care.
Age, gender and ethnicity	Age - Mean (SD): routine care: 56.0 (12.9), DAS group: 55.3 (13.7), 0-SJC group: 51.5 (13.2) . Gender (M:F): 1/5. Ethnicity: NR
Further population details	1. Disease duration: Not applicable
Extra comments	Participating physicians were randomised to 1 of the following 3 groups: routine care (RC), achieving a DAS28<2.6 (DAS group), or achieving a swollen joint count (SJC) of zero (0-SJC group). Physician randomisation took place prior to initiation of enrollment using a computer-generated, site-stratified blocked schedule that assigned physicians from the same geographic region to 1 of 3 groups at a 1:1:1 ratio.

Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Treat-to-target management strategy - Treat-to-target. DAS group: target of achieving a DAS28<2.6 Patients were seen by the same physician throughout the trial period. All patients could be seen at any time as per the judgment of the treating physician but for the study, recommended visits were at 0, 6, 12, and 18 months. For the targeted groups, assessments at 2, 4, and 9 months were also recommended. There was no specific drug algorithm for any physician, as many patients had tried 2 or more DMARDs before receiving adalimumab in routine care. Thus, the targeted physicians were encouraged to make treatment changes in patients when the target was not achieved. The dose of adalimumab was not increased beyond 40 mg subcutaneously every 2 weeks, as that is the approved dose in Canada. Therefore, much of the targeted treatment was expected to be intensification of background therapies.. Duration 18 months. Concurrent medication/care: Patients were treated with DMARDs, non-glucocorticoidl anti-inflammatory drugs, and injectable, oral or intraarticular glucocorticoids as required per the clinical judgment of the treating physicians.. Indirectness: No indirectness Further details: 1. Nature of the target: Composite target (DAS28 compared to usual care). (n=99) Intervention 2: Treat-to-target management strategy - Treat-to-target. 0-SJC group: target of achieving a swollen joint count of zero. Patients were seen by the same physician throughout the trial period. All patients could be seen at any time as per the judgment of the treating physician but for the study, recommended visits were at 0, 6, 12, and 18 months. For the targeted groups, assessments at 2, 4, and 9 months were also recommended. There was no specific drug algorithm for any physician, as many patients had tried 2 or more DMARDs before receiving adalimumab in routine care. Thus the targeted physicians were encouraged to make treatment changes in patients when the target was not achieved. The dose of adalimumab was not increased beyond 40 mg subcutaneously every 2 weeks, as that is the approved dose in Canada. Therefore, much of the targeted treatment was expected to be intensification of background therapies.. Duration 18 months. Concurrent medication/care: Patients were treated with DMARDs, non-glucocorticoid anti-inflammatory drugs, and injectable, oral or intraarticular glucocorticoids as required per the clinical judgment of the treating physicians. . Indirectness: No indirectness Further details: 1. Nature of the target: Other (define) (Zero swollen joint count compared to usual care). (n=109) Intervention 3: Usual care. Routine care. Patients were seen by the same physician throughout the trial period. All patients could be seen at any time as per the judgment of the treating physician but for the study, recommended visits were at 0, 6, 12, and 18 months. The dose of adalimumab was not increased beyond 40 mg subcutaneously every 2 weeks, as that is the approved dose in Canada. . Duration 18 months. Concurrent medication/care: Patients were treated with DMARDs, non-glucocorticoid anti-inflammatory drugs, and injectable, oral or intraarticular glucocorticoids as required per the clinical

	judgment of the treating physicians.. Indirectness: No indirectness Further details: 1. Nature of the target: Not applicable
Funding	Study funded by industry (Abbott Canada, Pharmaceutical company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET (DAS GROUP) versus USUAL CARE

Protocol outcome 1: Function at 12 months
- Actual outcome: Health assessment questionnaire at 12 months; Group 1: mean -0.47 (SD 0.6); n=100, Group 2: mean -0.57 (SD 0.62); n=109; 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 - High, Measurement - Low, Crossover - Low, Comments - 12 month data was extracted and ITT analysis assumed; lack of information in the paper.; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used n the DAS group.; Group 1 Number missing: 27, Reason: Loss to follow-up (n=3), lack of response (n=4), withdrawal of consent (n=5), adverse events (n=12), protocol violation (n=0), other reason (n=3).
; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).
- Actual outcome: Work limitations questionnaire at 12 months; Group 1: mean -4.7 (SD 8); n=100, Group 2: mean -4.2 (SD 9.4); n=109; Work limitations questionnaire 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - 12 month data was extracted and ITT analysis assumed; lack of information in the paper.; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used by patients in the DAS group.; Group 1 Number missing: 27, Reason: Loss to follow-up (n=3), lack of response (n=4), withdrawal of consent (n=5), adverse events (n=12), protocol violation (n=0), other reason (n=3).
; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 2: Remission at 12 months
- Actual outcome: DAS28<2.6 at 18 months; Group 1: 38/73, Group 2: 20/52
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Analysed at 18 months rather than 12, unclear what time point people dropped out of trial.; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group; Group 1 Number missing: 27, Reason: Loss to follow-up (n=3), lack of response (n=4), withdrawal of consent (n=5), adverse events (n=12), protocol violation (n=0), other reason (n=3).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 3: Low disease activity at 12 months
- Actual outcome: DAS28<3.2 at 18 months; Group 1: 46/73, Group 2: 29/52

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Primary outcome measure was change in DAS score but authors report no SDs, just means and then dichotomous outcomes of patients scoring below a certain DAS score.; Indirectness of outcome: Serious indirectness, Comments: Analysed at 18 months rather than 12, unclear what time point people dropped out of trial.; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group; Group 1 Number missing: 27, Reason: Loss to follow-up (n=3), lack of response (n=4), withdrawal of consent (n=5), adverse events (n=12), protocol violation (n=0), other reason (n=3).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 4: Withdrawal from trial / adherence to strategy at Longest reported by study
- Actual outcome: Withdrawal of consent, loss to follow-up, lack/loss of response, adverse events, protocol violation, other. at 18 months; Group 1: 27/100, Group 2: 57/109; Comments: DAS group:
loss to follow-up (n=3), Lack/loss of response (n=4), withdrawal of consent (n=5), adverse event (n=12), protocol violation (n=0), other (n=3)
routine care group:
loss to follow-up (n=20), Lack/loss of response (n=17), withdrawal of consent (n=6), adverse event (n=10), protocol violation (n=1), other (n=3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Unclear at what point the patients dropped out.; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used by the DAS group; Group 1 Number missing: , Reason: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET (0-SJC GROUP) versus USUAL CARE

Protocol outcome 1: Function at 12 months
- Actual outcome: Health assessment questionnaire at 12 months; Group 1: mean -0.39 (SD 0.6); n=99, Group 2: mean -0.57 (SD 0.62); n=109; 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 - High, Measurement - Low, Crossover - Low, Comments - 12 month data was extracted and ITT analysis assumed; lack of information in the paper.; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group.; Group 1 Number missing: 22, Reason: Loss to follow-up (n=5), lack of response (n=4), withdrawal of consent (n=6), adverse events (n=4), protocol violation (n=2), other reason (n=1).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).
- Actual outcome: Work limitations questionnaire at 12 months; Group 1: mean -3.6 (SD 6.96); n=99, Group 2: mean -4.2 (SD 9.4); n=109; Work limitations questionnaire 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - 12 month data was extracted and ITT analysis assumed; lack of information in the paper.; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group.; Group 1 Number missing: 22, Reason: Loss to follow-up (n=5), lack of response (n=4), withdrawal of consent (n=6), adverse events (n=4), protocol violation (n=2), other reason (n=1).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 2: Remission at 12 months
- Actual outcome: DAS28<2.6 at 18 months; Group 1: 25/77, Group 2: 20/52
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Primary outcome measure was change in DAS score but authors report no SDs, just means and then dichotomous outcomes of patients scoring below a certain DAS score.; Indirectness of outcome: Serious indirectness, Comments: Analysed at 18 months rather than 12, unclear what time point people dropped out of trial.; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group; Group 1 Number missing: 22, Reason: Loss to follow-up (n=5), lack of response (n=4), withdrawal of consent (n=6), adverse events (n=4), protocol violation (n=2), other reason (n=1).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 3: Low disease activity at 12 months
- Actual outcome: DAS28<3.2 at 18 months; Group 1: 31/77, Group 2: 29/52
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Primary outcome measure was change in DAS score but authors report no SDs, just means and then dichotomous outcomes of patients scoring below a certain DAS score.; Indirectness of outcome: Serious indirectness, Comments: Analysed at 18 months rather than 12, unclear what time point people dropped out of trial.; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group.; Group 1 Number missing: 22, Reason: Loss to follow-up (n=5), lack of response (n=4), withdrawal of consent (n=6), adverse events (n=4), protocol violation (n=2), other reason (n=1).; Group 2 Number missing: 57, Reason: Loss to follow-up (n=20), lack of response (n=17), withdrawal of consent (n=6), adverse events (n=10), protocol violation (n=1), other reason (n=3).

Protocol outcome 4: Withdrawal from trial / adherence to strategy at Longest reported by study
- Actual outcome: Withdrawal of consent, loss to follow-up, lack/loss of response, adverse events, protocol violation, other. at 18 months; Group 1: 22/99, Group 2: 57/109; Comments: 0-SJC group:
loss to follow-up (n=5), lack/loss of response (n=4), withdrawal of consent (n=6), adverse event (n=4), protocol violation (n=2), other (n=1)
routine care group:
loss to follow-up (n=20), Lack/loss of response (n=17), withdrawal of consent (n=6), adverse event (n=10), protocol violation (n=1), other (n=3)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Unclear at what point the patients dropped out. ; Indirectness of outcome: No indirectness ; Baseline details: People in 0-SJC group were significantly younger; and a significantly higher number of DMARDs were used in the DAS group; Group 1 Number missing: , Reason: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Disease activity score at 12 months; Quality of life at 12 months; Pain at 12 months; Fatigue at 12 months; Radiological progression at 12 months

Study (subsidiary papers)	T4 study trial: Urata 2014[44] (Urata 2012[45])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=243)
Countries and setting	Conducted in Japan; Setting: Two teaching hospitals in Aomori, Japan, between August 2008 and April 2010.
Line of therapy	Not applicable
Duration of study	Intervention time: first 56 weeks in 4 different treatment arms; then all subjects were allocated to the treat-to-target group. 3 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American College of Rheumatology 1987 criteria for rheumatoid arthritis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with early rheumatoid arthritis and a disease duration of <3 years and a DAS28 >3.2, aged >18 years.
Exclusion criteria	Previous use of glucocorticoids or any disease-modifying antirheumatic drugs (DMARD) or any biological agents; relevant concurrent liver (aspartate aminotransferase >100 IU/l or alkaline phosphatase >100 IU/l), renal (serum creatinine >1.5 mg/dl), haematological (total white blood cell count <4000/ml, platelet count <150000/ml), or severe respiratory disease; pregnancy, plans to become pregnant, or unwillingness to use effective contraception; presence of hepatitis B, hepatitis C, or HIV; and psychological problems that would make adherence to the study protocol impossible.
Recruitment/selection of patients	People were randomly allocated to 1 of 4 strategy groups to receive: routine care (R group); DAS28-driven therapy (D group); MMP-3-driven therapy (M group); or both DAS28 and MMP-3-driven therapy (twin, T group).
Age, gender and ethnicity	Age - Mean (SD): Routine care group: 62.0 (11.0); treatment group: 57.0 (13.0). Gender (M:F): 1/5. Ethnicity:
Further population details	1. Disease duration: Not applicable
Extra comments	Please note: after 56 weeks all patients received treat-to-target care, only the information, outcomes, and results of the first 56 weeks have been extracted from these papers.
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: Treat-to-target management strategy - Treat-to-target. Twin treatment group (T group): DAS28 plus matrix metalloproteinase (MMP)-3-driven therapy The study used the following visiting times: weeks 0, 2, 4,6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. At baseline and at predefined assessment points (weeks 0, 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56),clinical

	variables were assessed. In the D and T groups, each physician calculated the DAS28 score of their patient on the same day as clinical variables were assessed. Medication was started with a dose of 1g/day of sulfasalazine in all intervention groups. Target values were both DAS28 less than 2.6 and MMP-3 less than 121 ng/ml (men) or less than 59.7 ng/ml (women) for the T group. If the value in question did not fall below the previously measured level, methotrexate was added. The starting dose of oral methotrexate was 4 mg/week. Folic acid was administered to every patient (5 mg/week) 36 hours after methotrexate dosing. In intensive strategy groups, the dosage of methotrexate was not changed if the patient had responded compared with the previous visit; otherwise the dosage was increased in a step-wise manner to a maximum of 8 mg/week if the patient had not responded. If the maximum tolerable dose that introduced a dose-dependent side-effect was reached and the patient still did not fulfill the criteria for sustained response, tumour necrosis factor (TNF) blockers were allowed. If patients with the administration of TNF blockers did not show improvement compared with the previous measurement, TNF blockers were changed to another biological agent, or the dose of the TNF blocker was increased, or the interval for TNF administration was shortened.. Duration 56 weeks. Concurrent medication/care: DMARD were given as allowed by the rheumatologists at all times. Combination therapy with DMARD other than methotrexate was allowed for two kinds of agents. Intra-articular glucocorticoid (to a maximum of 10 mg triamicinolone acetonide on a single visit) was permitted for persistently swollen and tender joints. Participants were given physiotherapy and/or occupational therapy when needed.. Indirectness: No indirectness Further details: 1. Nature of the target: Other (define) (DAS28 and matrix metalloproteinase (MMP) 3 normalisation combined compared to usual care). (n=62) Intervention 2: Usual care. Routine care (R group): The study used the following visiting times: weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. At baseline and at predefined assessment points (weeks 0, 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56), clinical variables were assessed. Medication was started with a dose of 1g/day ofsulfasalazine in all intervention groups. In the R group, change of therapy was based on the treating physician's clinical judgment according to the improvement in the number of tender joints (0-28), swollen joints (0-26), and value of serum C-reactive protein (CRP) from preassessment values, without access to current DAS28 and MMP-3 values. Mean target values for each physician were the number of tender joints (0-28) two or less, swollen joints (0-26) two or less and serum CRP 0.7 mg/dl or less. . Duration 56 weeks. Concurrent medication/care: DMARD were given as allowed by the rheumatologists at all times. Combination therapy with DMARD other than methotrexate was allowed for two kinds of agents. Intra-articular glucocorticoid (to a maximum of 10 mgtriamicinolone acetonide on a single visit) was permitted for persistently swollen and tender joints. Participants were given physiotherapy and/or occupational therapy when needed.. Indirectness: No indirectness Further details: 1. Nature of the target: Not applicable

	(n=60) Intervention 3: Treat-to-target management strategy - Treat-to-target. DAS28-driven therapy group (D group): The study used the following visiting times: weeks 0, 2, 4,6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. At baseline and at predefined assessment points (weeks 0, 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56), clinical variables were assessed. In the D and T groups, each physician calculated the DAS28 score of their patient on the same day as clinical variables were assessed. Medication was started with a dose of 1g/day of sulfasalazine in all intervention groups. Target values were DAS28 less than 2.6 for the D group. If the value did not fall below the previously measured level, methotrexate was added. The starting dose of oral methotrexate was 4 mg/week. Folic acid was administered to every patient (5 mg/week) 36 hours after methotrexate dosing. In intensive strategy groups, the dosage of methotrexate was not changed if the patient had responded compared with the previous visit; otherwise the dosage was increased in a step-wise manner to a maximum of 8 mg/week if the patient had not responded. If the maximum tolerable dose that introduced a dose-dependent side-effect was reached and the patient still did not fulfill the criteria for sustained response, tumour necrosis factor (TNF) blockers were allowed. If patients with the administration of TNF blockers did not show improvement compared with the previous measurement, TNF blockers were changed to another biological agent, or the dose of the TNF blocker was increased, or the interval for TNF administration was shortened.. Duration 56 weeks. Concurrent medication/care: DMARD were given as allowed by the rheumatologists at all times. Combination therapy with DMARD other than methotrexate was allowed for two kinds of agents. Intra-articular glucocorticoid (to a maximum of 10 mg triamicinolone acetonide on a single visit) was permitted for persistently swollen and tender joints. Participants were given physiotherapy and/or occupational therapy when needed.. Indirectness: No indirectness Further details: 1. Nature of the target: Composite target (DAS28 compared to usual care). (n=60) Intervention 4: Treat-to-target management strategy - Treat-to-target. MMP-3-driven therapy group (M group): The study used the following visiting times: weeks 0, 2, 4,6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. At baseline and at predefined assessment points (weeks 0, 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56), clinical variables were assessed. Medication was started with a dose of 1g/day of sulfasalazine in all intervention groups. Target values were MMP-3 less than 121 ng/ml (men) or less than 59.7 ng/ml (women) for the M group. If the value in question did not fall below the previously measured level, methotrexate was added. The starting dose of oral methotrexate was 4 mg/week. Folic acid was administered to every patient (5 mg/week) 36 hours after methotrexate dosing. In intensive strategy groups, the dosage of methotrexate was not changed if the patient had responded compared with the previous visit; otherwise the dosage was increased in a step-wise manner to a maximum of 8 mg/week if the patient had not responded. If the maximum tolerable dose that introduced a dose-dependent side-effect was reached and the patient still did not fulfill the criteria for

	sustained response, tumour necrosis factor (TNF) blockers were allowed. If patients with the administration of TNF blockers did not show improvement compared with the previous measurement, TNF blockers were changed to another biological agent, or the dose of the TNF blocker was increased, or the interval for TNF administration was shortened.. Duration 56 weeks. Concurrent medication/care: DMARD were given as allowed by the rheumatologists at all times. Combination therapy with DMARD other than methotrexate was allowed for two kinds of agents. Intra-articular glucocorticoid (to a maximum of 10 mg triamicinolone acetonide on a single visit) was permitted for persistently swollen and tender joints. Participants were given physiotherapy and/or occupational therapy when needed.. Indirectness: No indirectness Further details: 1. Nature of the target: Other (define) (Matrix metalloproteinase (MMP) 3 normalisation compared to usual care).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET (TWIN TREATMENT GROUP) versus USUAL CARE

Protocol outcome 1: Disease activity score at 12 months
- Actual outcome: Change in DAS28 score (compared to baseline) at 56 weeks; Group 1: mean -2 (SD 2.2); n=58, Group 2: mean -1.3 (SD 2.7); n=55; DAS28 0-10; a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 7

Protocol outcome 2: Function at 12 months
- Actual outcome: Change in modified health assessment questionnaire (mHAQ) from baseline at 56 weeks; Group 1: mean 0 (SD 0.6); n=58, Group 2: mean 0 (SD 0.7); n=55; Modified health assessment questionnaire (mHAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 7

Protocol outcome 3: Remission at 12 months
- Actual outcome: Disease activity score 28 <2.6 at 56 weeks; Group 1: 34/61, Group 2: 13/62
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2

Number missing: 7

Protocol outcome 4: Radiological progression at 12 months
- Actual outcome: Change in radiographic score (modified Sharp score) from baseline at 56 weeks; Group 1: mean -0.6 (SD 5.9); n=58, Group 2: mean 2 (SD 2.1); n=55; van der Heijde modification of the Sharp scoring system 0-448 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 7

Protocol outcome 5: Withdrawal from trial / adherence to strategy at Longest reported by study
- Actual outcome: Discontinuation of treatment due to adverse events, lost to follow-up or other at 56 weeks; Group 1: 3/61, Group 2: 7/62
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 7

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET (DAS28 GROUP) versus USUAL CARE

Protocol outcome 1: Disease activity score at 12 months
- Actual outcome: Change in DAS28 score (compared to baseline) at 56 weeks; Group 1: mean -2.5 (SD 3.1); n=56, Group 2: mean -1.3 (SD 2.7); n=55; DAS28 0-10; a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7

Protocol outcome 2: Function at 12 months
- Actual outcome: Change in modified health assessment questionnaire (mHAQ) from baseline at 56 weeks; Group 1: mean 0 (SD 1); n=56, Group 2: mean 0 (SD 0.7); n=55; Modified health assessment questionnaire (mHAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7

Protocol outcome 3: Remission at 12 months
- Actual outcome: Disease activity score 28 <2.6 at 56 weeks; Group 1: 23/60, Group 2: 31/62

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7

Protocol outcome 4: Radiological progression at 12 months
- Actual outcome: Change in radiographic score (modified Sharp score) from baseline at 56 weeks; Group 1: mean 1.6 (SD 4.3); n=56, Group 2: mean 2 (SD 2.1); n=55; van der Heijde modification of the Sharp scoring system 0-448 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded. Only radiologists are clearly said to have been blinded to the interventions.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7

Protocol outcome 5: Withdrawal from trial / adherence to strategy at Longest reported by study
- Actual outcome: Discontinuation of treatment due to adverse events, lost to follow-up or other at 56 weeks; Group 1: 4/60, Group 2: 7/62
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded. Only radiologists are clearly said to have been blinded to the interventions.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET (MMP-3 GROUP) versus USUAL CARE

Protocol outcome 1: Disease activity score at 12 months
- Actual outcome: Change in DAS28 score (compared to baseline) at 56 weeks; Group 1: mean -1.3 (SD 2.4); n=53, Group 2: mean -1.3 (SD 2.7); n=55; DAS28 0-10; a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 2: Function at 12 months
- Actual outcome: Change in modified health assessment questionnaire (mHAQ) from baseline at 56 weeks; Group 1: mean -0.1 (SD 0.8); n=53, Group 2: mean 0 (SD 0.7); n=55; Modified health assessment questionnaire (mHAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 3: Remission at 12 months - Actual outcome: Disease activity score 28 <2.6 at 56 weeks; Group 1: 8/60, Group 2: 13/62 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 4: Radiological progression at 12 months - Actual outcome: Change in radiographic score (modified Sharp score) from baseline at 56 weeks; Group 1: mean 0.7 (SD 2.4); n=53, Group 2: mean 2 (SD 2.1); n=55; van der Heijde modification of the Sharp scoring system 0-448 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 5: Withdrawal from trial / adherence to strategy at Longest reported by study - Actual outcome: Discontinuation of treatment due to adverse events, lost to follow-up or other at 56 weeks; Group 1: 7/60, Group 2: 7/62 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - It is not stated who performed the clinical assessment and if the assessor was blinded to the interventions. Likewise it is not stated whether patients and those doing the analysis were blinded. Only the radiologists are said to be blinded.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7	
Protocol outcomes not reported by the study	Quality of life at 12 months; Pain at 12 months; Low disease activity at 12 months; Fatigue at 12 months

Study	TICORA study trial: Grigor 2004[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=111)
Countries and setting	Conducted in United Kingdom; Setting: Two NHS teaching hospitals in Glasgow.
Line of therapy	Not applicable
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged between 18 and 75 years who had rheumatoid arthritis for fewer than 5 years were recruited.
Exclusion criteria	People were excluded if they had previously received combination disease-modifying anti-rheumatic drug treatment, or had relevant concurrent liver (aspartate aminotransferase >80 IU/L, alkaline phosphatase >70L), renal (creatinine >0.2 mmol/L), or haematological disease (white-cell count <4.0x109/L, platelet count <150x109/L).
Recruitment/selection of patients	Patients aged between 18 and 75 years who had rheumatoid arthritis for fewer than 5 years were recruited. All patients had active disease defined by a disease activity score of more than 2.4, between August 1999, and April 2001.
Age, gender and ethnicity	Age - Mean (SD): Intensive group: 51(15) years; routine group: 54(11) years. Gender (M:F): 1/3. Ethnicity: na
Further population details	1. Disease duration: Not applicable
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Treat-to-target management strategy - Treat-to-target. Patients were seen every month by the same rheumatologist and their disease activity score (DAS) was calculated. This score is a validated composite of erythrocyte sedimentation rate, Ritchie articular index, joint swelling count, and patients' global assessment of disease activity. DAS of 3.6, 2.4 and 1.6 represented high, moderate, and low disease activity respectively. At every monthly assessment, they injected any swollen joint amenable to intra-articular glucocorticoid, unless the joint had been injected within the previous 3 months or the patient declined. A maximum of 3 joints were injected per assessment, up to a total dose of 120mg triamcinolone acetonide per visit. Within the first 3 months of starting a new disease-modifying anti-rheumatic drug, if 120 mg of triamcinolone acetonide was not injected intra-articularly, they gave the balance by intramuscular injection if the DAS remained more than 2.4. at every assessment after month 3, patients with a score of

	more than 2.4 received an escalation of their oral treatment according to a protocol, unless they declined or toxic effects precluded this approach. Adverse events, and drug-related toxic effects were managed empirically by the rheumatologist.. Duration 18 months. Concurrent medication/care: Patients in both groups were assessed by a metrologist every 3 months. He was unaware of the group assignment and did not take part in intensive treatment or other outpatient clinics. No intra-articular injections were allowed in the month preceding the assessments. Patients in both groups were assessed by a metrologist every 3 months. He was unaware of the group assignment and did not take part in intensive treatment or other outpatient clinics. No intra-articular injections were allowed in the month preceding the assessments. . Indirectness: No indirectness Further details: 1. Nature of the target: Other (define) (fall in disease activity score, good response, remission). (n=55) Intervention 2: Usual care. Treatment was supervised in the usual rheumatology follow-up clinics, which were led by two consultant rheumatologists and included trainee rheumatologists working under supervision. Patients were reviewed every three months, with no formal composite measure of disease activity used in clinical decision making. Disease-modifying antirheumatic drug monotherapy was given in patients with active synovitis, and failure of treatment (because of toxic effects or lack of effect) resulted in a change to alternative monotherapy, or addition of a second or third drug at the discretion of the attending rheumatologist. Intra-articular injections of glucocorticoid were given to patients assigned to routine care with the same restrictions as those in the intensive group. . Duration 18 months. Concurrent medication/care: Patients in both groups were assessed by a metrologist every 3 months. He was unaware of the group assignment and did not take part in intensive treatment or other outpatient clinics. No intra-articular injections were allowed in the month preceding the assessments. . Indirectness: No indirectness Further details: 1. Nature of the target: Not applicable
Funding	Academic or government funding (Chief Scientists' Office, Scottish Executive)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET versus USUAL CARE

Protocol outcome 1: Disease activity score at 12 months
- Actual outcome: Change in disease activity score from baseline at 18 months; Group 1: mean -3.5 (SD 1.1); n=53, Group 2: mean -1.9 (SD 1.4); n=50; Disease activity score (DAS) 0-10; a DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used.
; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3

patients died, 1 lost to follow-up, 1 withdrew consent

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Change in quality of life (short form-12 physical) at 18 months; Group 1: mean 9.3 (SD 12); n=53, Group 2: mean 4 (SD 11); n=50; Short form 12 physical component 0 to 100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used.
; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent
- Actual outcome: Change in SF12 - mental sub-scale at 18 months; Group 1: mean 10.9 (SD 16); n=53, Group 2: mean 6 (SD 18); n=50; SF12 - mental component 0 to 100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used.
; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent

Protocol outcome 3: Function at 12 months
- Actual outcome: Change in health assessment questionnaire at 18 months; Group 1: mean -0.97 (SD 0.8); n=53, Group 2: mean -0.47 (SD 0.9); n=50; Health assessment questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used.
; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent

Protocol outcome 4: Remission at 12 months
- Actual outcome: Disease activity score < 1.6 at 18 months; Group 1: 36/55, Group 2: 9/55
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used.
; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent

Protocol outcome 5: Pain at 12 months
- Actual outcome: Change in pain (visual analogue scale) at 18 months; Group 1: mean -45 (SD 24); n=53, Group 2: mean -20 (SD 31); n=50; Visual analogue scale 1 to 100 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent Protocol outcome 6: Radiological progression at 12 months - Actual outcome: Change in van der Heijde modification of the Sharp score at 18 months; van der Heijde modification of the Sharp score 0-448. Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent Protocol outcome 7: Withdrawal from trial / adherence to strategy at Longest reported by study - Actual outcome: Withdrawal from trial or lost to follow-up at 18 months; Group 1: 1/55, Group 2: 2/55 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors state that ITT analysis was performed and that patients who died, were lost to follow-up or withdrew consent were regarded as 'non-responders'. It is unclear what computation method was used. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient died, 1 lost to follow-up; Group 2 Number missing: 5, Reason: 3 patients died, 1 lost to follow-up, 1 withdrew consent	
Protocol outcomes not reported by the study	Low disease activity at 12 months; Fatigue at 12 months

1

2

1 Appendix E: Forest plots

E.1 2 Treat-to-target versus usual care

Figure 2: Change in Disease Activity Score (DAS28)

Study or Subgroup	treat-to-target Mean	SD	Total	usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fransen 2005	-0.4	1	61	-0.14	1.2	81	27.8%	-0.26 [-0.62, 0.10]
Grigor 2004	-3.5	1.1	53	-1.9	1.4	50	26.5%	-1.60 [-2.09, -1.11]
Urata (DAS28 plus MMP3) 2014	-2	2.2	58	-1.3	2.7	18	15.7%	-0.70 [-2.07, 0.67]
Urata (DAS28) 2014	-2.5	3.1	56	-1.3	2.7	18	14.4%	-1.20 [-2.69, 0.29]
Urata (MMP3) 2014	-1.3	2.4	53	-1.3	2.7	19	15.6%	0.00 [-1.38, 1.38]
Total (95% CI)			**281**			**186**	**100.0%**	**-0.78 [-1.57, 0.01]**

Heterogeneity: Tau² = 0.55; Chi² = 20.13, df = 4 (P = 0.0005); I² = 80%
Test for overall effect: Z = 1.93 (P = 0.05)

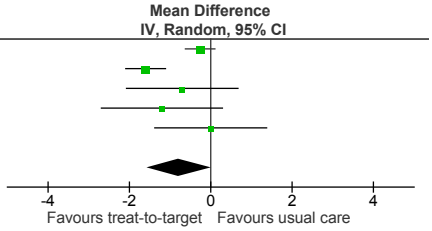


Figure 3: Change in Quality of life (SF12 physical and mental components)

Study or Subgroup	treat-to-target Mean	SD	Total	usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.8.1 Physical							
Grigor 2004	9.3	12	53	4	11	50	5.30 [0.86, 9.74]
1.8.2 Mental							
Grigor 2004	10.9	16	53	6	18	50	4.90 [-1.69, 11.49]

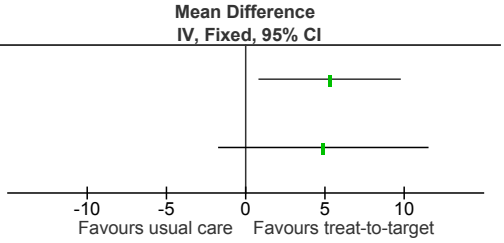


Figure 4: Change in function (HAQ)

Study or Subgroup	treat-to-target Mean	SD	Total	usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CAMERA - Verstappen 2007	-0.44	0.59	151	-0.39	0.66	148	22.4%	-0.05 [-0.19, 0.09]
Grigor 2004	-0.97	0.8	53	-0.47	0.9	50	11.7%	-0.50 [-0.83, -0.17]
Pope (0-SJC) 2013	-0.39	0.6	99	-0.57	0.62	54	18.4%	0.18 [-0.02, 0.38]
Pope (DAS28) 2013	-0.47	0.6	100	-0.57	0.62	55	18.5%	0.10 [-0.10, 0.30]
Urata (DAS28 plus MMP3) 2014	0	0.6	58	0	0.7	18	10.6%	0.00 [-0.36, 0.36]
Urata (DAS28) 2014	0	1	56	0	0.7	18	8.7%	0.00 [-0.42, 0.42]
Urata (MMP3) 2014	-0.1	0.8	53	0	0.7	19	9.8%	-0.10 [-0.48, 0.28]
Total (95% CI)			**570**			**362**	**100.0%**	**-0.03 [-0.18, 0.12]**

Heterogeneity: Tau² = 0.02; Chi² = 13.51, df = 6 (P = 0.04); I² = 56%
Test for overall effect: Z = 0.37 (P = 0.71)

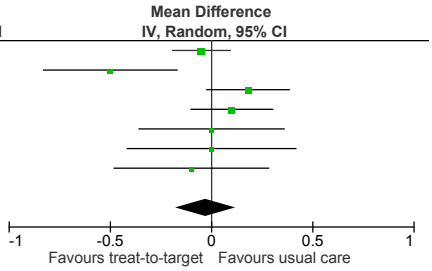


Figure 5: Low disease activity (DAS28 <3.2)

Study or Subgroup	treat-to-target Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fransen 2005	19	61	13	81	27.1%	1.94 [1.04, 3.62]
Pope (0-SJC) 2013	31	77	14	26	34.7%	0.75 [0.48, 1.17]
Pope (DAS28) 2013	46	73	15	26	38.2%	1.09 [0.75, 1.59]
Total (95% CI)		**211**		**133**	**100.0%**	**1.12 [0.69, 1.81]**
Total events	96		42			

Heterogeneity: Tau² = 0.12; Chi² = 6.22, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 0.46 (P = 0.65)

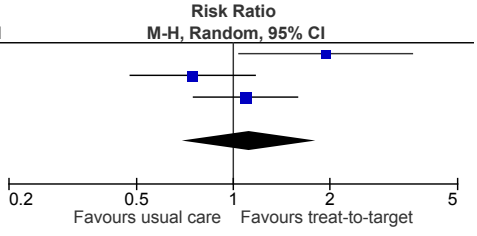


Figure 6: Remission (various measures: DAS < 1.6, DAS28 < 2.6, other)

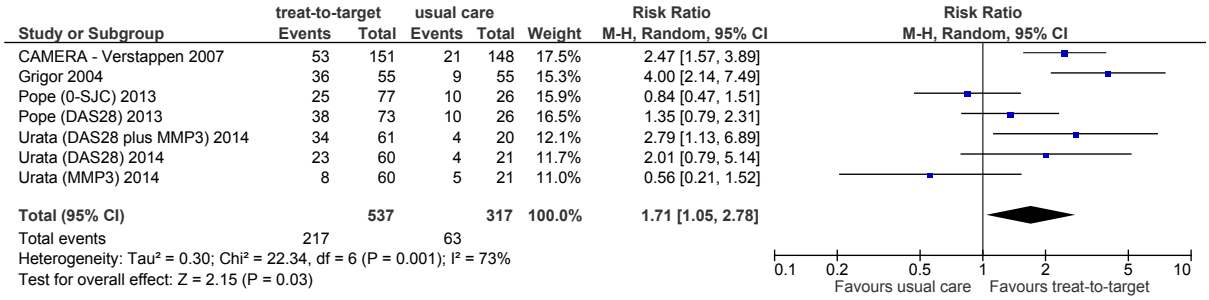


Figure 7: Change in pain (VAS)

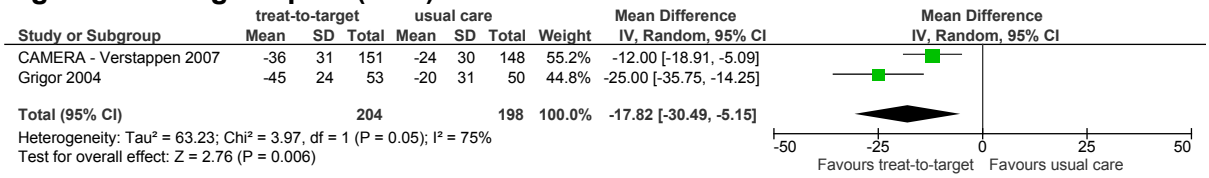


Figure 8: Radiological progression

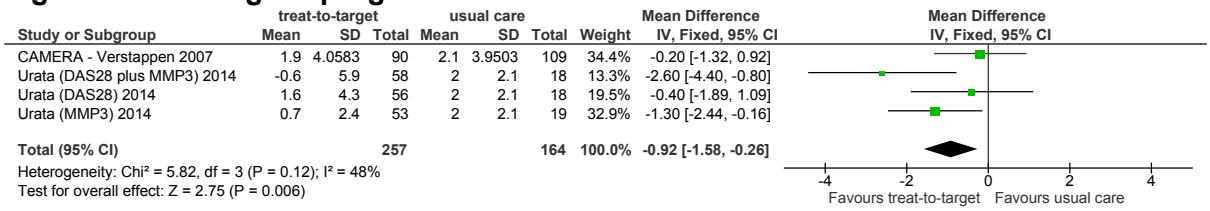


Figure 9: Change in work limitations questionnaire

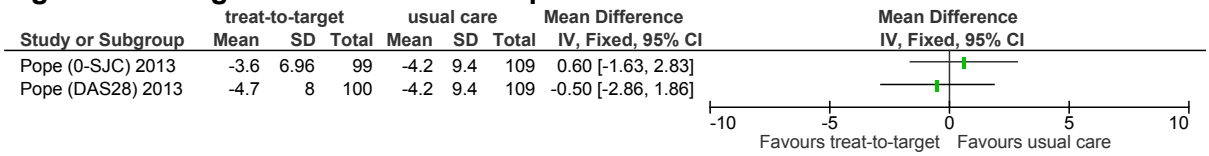
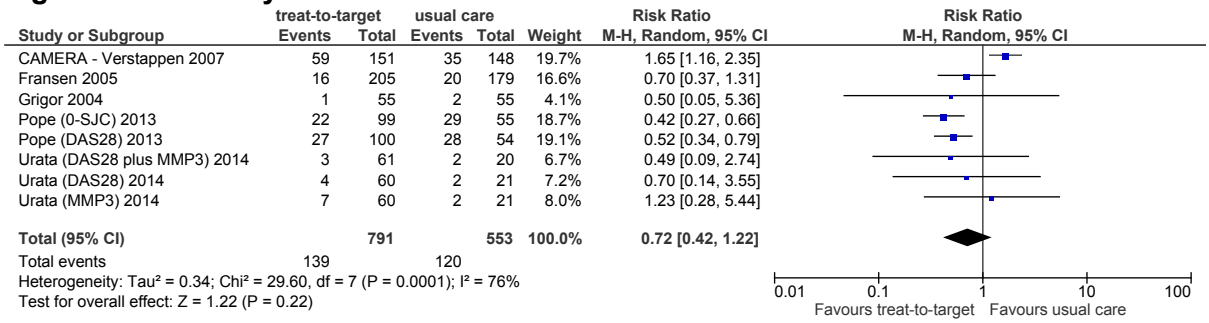


Figure 10: Study discontinuation



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Appendix F:GRADE tables

Table 10: Clinical evidence profile: treat-to-target versus usual care

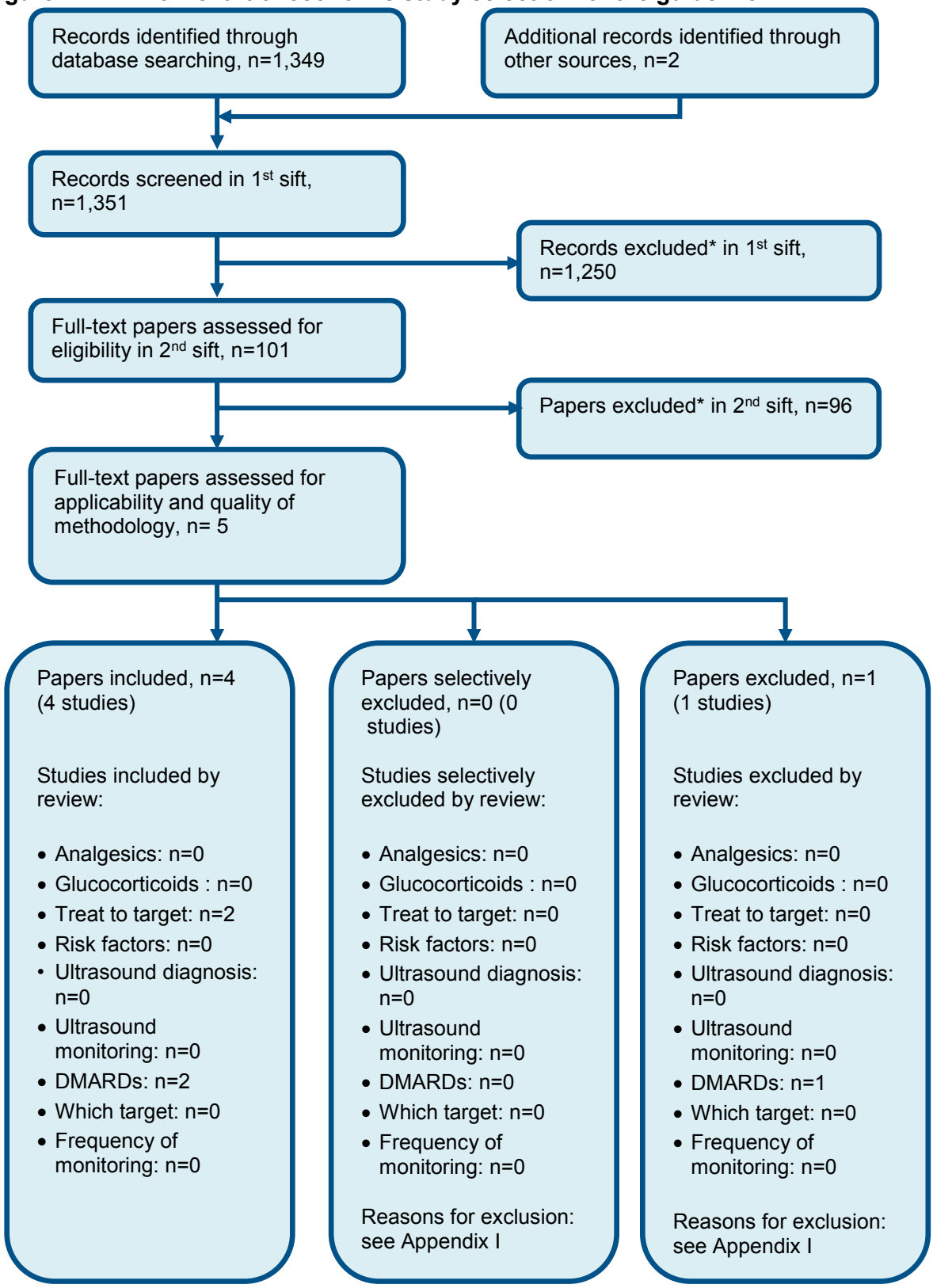
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat-to-target	Usual care	Relative (95% CI)	Absolute		
DAS (change) (follow-up 6-18 months; Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	281	186	-	MD 0.78 lower (1.57 lower to 0.01 higher)	⊕OOO VERY LOW	CRITICAL
QoL - SF12 (change) - Physical (follow-up 18 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	53	50	-	MD 5.3 higher (0.86 to 9.74 higher)	⊕⊕OO LOW	CRITICAL
QoL - SF12 (change) - Mental (follow-up 18 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	53	50	-	MD 4.9 higher (1.69 lower to 11.49 higher)	⊕⊕OO LOW	CRITICAL
HAQ (change) (follow-up 12-18 months; range of scores: 0-3; Better indicated by lower values)												
4	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	570	362	-	MD 0.03 lower (0.18 lower to 0.12 higher)	⊕OOO VERY LOW	CRITICAL
Remission (follow-up 12-18 months; assessed with: (various: DAS < 1.6 / DAS28 <2.6 / other))												
4	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	217/537 (40.4%)	63/317 (19.9%)	RR 1.71 (1.05 to 2.78)	141 more per 1000 (from 10 more to 354 more)	⊕OOO VERY LOW	IMPORTANT
Low disease activity (follow-up 6-18 months; assessed with: DAS28 < 3.2)												
2	randomised trials	very serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	96/211 (45.5%)	53.9%	RR 1.12 (0.69 to 1.81)	65 more per 1000 (from 167 fewer to 437 more)	⊕OOO VERY LOW	IMPORTANT
Pain VAS (change) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	204	198	-	MD 17.82 lower (30.49 to 5.15 lower)	⊕OOO VERY LOW	IMPORTANT
Radiological progression (follow-up 12-18 months; range of scores: 0-448; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	257	164	-	MD 0.92 lower (1.58 to 0.26 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Radiological progression (median (IQR)) (follow-up 18 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	53	50	-	MD 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Work limitations questionnaire (target: DAS28) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	199	109	-	MD 0.5 lower (2.86 lower to 1.86 higher)	⊕OOO VERY LOW	IMPORTANT

Work limitations questionnaire (target: 0-SJC) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	199	109	-	MD 0.6 higher (1.63 lower to 2.83 higher)	⊕OOO VERY LOW	IMPORTANT
Study discontinuation (follow-up 6-24 months)											
5	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	139/791 (17.6%)	10.6%	RR 0.72 (0.42 to 1.22)	30 fewer per 1000 (from 61 fewer to 23 more)	⊕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] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Cannot assess imprecision using median (IQR)

Appendix G: Health economic evidence selection

Figure 11: Flow chart of economic study selection for the guideline



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

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Appendix H: Health economic evidence tables

Study	Nair 2015 [23]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov decision model **Approach to analysis:** Health states were based on disease activity (DAS28) **Perspective:** Dutch public healthcare system **Time horizon**: 2 years **Treatment effect duration:**[(a)] NA **Discounting:** Costs: 4%; Outcomes: 1.5%	**Population:** 299 early RA patients from the Dutch CAMERA trial(Verstappen 2007[50]); both arms received methotrexate and ciclosporin as first and second line treatment **Cohort settings:** Start age:53.5 Male: 32% **Intervention 1:** Usual care; 1 outpatient visit every 3 months, dose adjustments based on opinion of the individual rheumatologist **Intervention 2:** Treat to target (tight control strategy); monthly outpatient visits, management was based on patient response to predefined criteria (swollen/tender joint count, ESR, VAS), overall more frequent, duration), using a computerised	**Total costs (mean per patient)[(e)]:** Intervention 1: £20,529 (95%CI £16,530 – £25,237) Intervention 2: £18,999 (95%CI £15,581 – £23,088) Incremental (2−1): £1,530 in favour of the tight control strategy (p=NA) **Currency & cost year:** 2015 Euros (presented here as 20015 UK pounds[(b)]) **Cost components incorporated:** hospitalisations, rehabilitation, nursing home admittance, home assistive devices, consultations with healthcare workers, alternative therapies, drug costs	**QALYs (mean per patient):** Intervention 1: 1.31 Intervention 2: 1.37 Incremental (2−1): 0.06 in favour of the tight control strategy (95% CI: 0.01 – 0.11; p=NR)	Intervention 2 (tight control) dominates Intervention 1 (usual practice) due to being less costly and more effective **Analysis of uncertainty:** The tight control strategy resulted in less medical consumption and improved quality of life due to better DAS28/HAQ; however, drug costs were higher. In the probabilistic analysis, in approximately 80%-90% of the simulations the tight control strategy dominated usual care (under the study base-case societal perspective). In the scenario where ciclosporin was replaced by adalimumab, the study authors reported higher drug costs for the tight control strategy but no additional QALY incremental gain.

	decision programme.			
Data sources				
Health outcomes: Utility was determined by the EuroQol-5D questionnaire. Half the patients received the postal questionnaire in October 1999 and the other half in April 2000, in order to correct for possible seasonal influences **Quality-of-life weights:** EQ-5D Dutch tariff. **Cost sources:** recorded via questionnaires administered to the Utrecht Rheumatoid Arthritis Cohort, unit costs were relevant to the Dutch healthcare system				
Comments				
Source of funding: Dutch centre for translational molecular medicine and the Dutch arthritis association **Limitations:** Inadequate details are given about the treatment protocol of the conventional approach (described as usual practice), discounting is not in line with the NICE reference case (3.5%), direct medical costs included some non-NHS incurred costs. Two-year time horizon, it might omit some relevant cost and outcomes. Analysis is based on evidence on CAMERA which was 1 of 5 studies identified in the clinical review for treat to target versus usual care and so does not reflect full body of evidence for this comparison. Unit costs are representable of the Dutch healthcare system.				
Overall applicability:[c] partially applicable **Overall quality:**[d] potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2015 purchasing power parities [29]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

(e) Study costs included productivity loss costs, here removed in order to isolate the relevant NHS and PSS perspective

Study	**Grigor 2004[9]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (various health outcomes) **Study design:** Within trial analysis (RCT – same paper, TICORA trial) **Approach to analysis:** Analysis of individual level data for resource use. Unit costs applied.	**Population:** TICORA trial; people 18-75 who had RA for less than 5 years and active disease (disease activity score [DAS] more than 2.4). Those who have had combination DMARDs were excluded. **Cohort settings:** N:111	**Total costs (mean per patient):** Intervention 1: £4,127 Intervention 2: £3,475 Incremental (2−1): saves £652 (95% CI: NR) **Cost breakdown:** **Total hospital costs:** Intervention 1: £2,464	**From clinical review (2 vs 1) Grigor 2004[9]** Disease activity score: MD -1.6 (95% CI: -2.09 to -1.11) • Quality of life (SF12 physical summary score): MD 5.3 (95% CI: 0.86 to 9.74) • Quality of life (SF12 mental summary	**ICER (Intervention 2 versus Intervention 1):** n/a Intervention 2 (treat to target) dominates Intervention 1 (usual practice) due to being less costly and more effective **Analysis of uncertainty:** No detailed analysis of uncertainty conducted. Although the 95% CI indicate there is

Perspective: UK NHS **Follow-up**: 18 months **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: NR; Outcomes: NR	Mean age: Intervention 1: 54 (SD: 11) Intervention 2: 51 (SD: 15) Male: Intervention 1: 31% Intervention 2: 29% **Intervention 1:** Usual care; 3 monthly visit with no formal composite measure of disease activity used in clinical decision making, monotherapy for those with active synovitis, changed or added to if not effective or due to side effects (at discretion of physician) **Intervention 2:** Treat to target (intensive strategy); monthly visit where DAS was measured and glucocorticoid injections in swollen joints (where amenable and not injected in previous 3 months), protocol for increasing DMARDs (number of drugs and dose) used based on DAS >2.4	Intervention 2: £1,919 Incremental (2−1): saves £544 (95% CI: saves £2,737 to £784 more) **Patient travel costs:** Intervention 1: £73 Intervention 2: £129 Incremental (2−1): £56 (95% CI: £12 to £99) **Community costs:** Intervention 1: £1,590 Intervention 2: £1,427 Incremental (2−1): saves £162 (95% CI: saves £602 to £274 more) **Currency & cost year:** 2001/2002 UK pounds **Cost components incorporated:** Hospital costs (outpatient, inpatient, prescribing), patient travel costs, community costs (health professional visits, diagnostic tests)	score): MD 4.9 (95% CI: -1.69 to 11.49) • Health assessment questionnaire: MD -0.5 (95% CI: -0.83 to -0.17) All mean per patient. Other health outcomes reported, see clinical evidence table.	some uncertainty in the costs and health outcomes.
Data sources				

Health outcomes: Within RCT analysis. **Quality-of-life weights:** n/a. **Cost sources:** Costs were calculated using patient level resource use data collected from patient notes review and patient diaries (0, 6 and 12 months). Unit costs were based on UK NHS published unit costs (Scottish health service costs, BNF, PSSRU unit costs and national reference costs).	
Comments	
Source of funding: Chief Scientists' Office, Scottish Executive **Limitations:** Resource use and unit costs old (2001-2002) and so may not reflect current NHS context. QALYs were not used as the health outcome measure. No discounting, although follow up is only 18 months and so this may not impact outcome. Within-trial analysis and so does not reflect full body of evidence for this comparison; Grigor 2004 is 1 of 5 studies included in the clinical review for treat to target versus usual care. No exploration of uncertainty. Short follow-up so may omit some relevant costs and outcomes.	
Overall applicability:[(b)] partially applicable	**Overall quality:**[(c)] potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CCA: cost–consequences analysis; ICER: incremental cost-effectiveness ratio; MD: mean difference; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years, SF-12: short-form 12, 0-100

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 11: Studies excluded from the clinical review**

Study	Exclusion reason
Anon 2015[38]	Unobtainable
Bijlsma 2015[3]	Inappropriate comparison. Systematic review: methods are not adequate/unclear. Incorrect interventions. review on glucocorticoid effectiveness based on CAMERA trial data
Dale 2016[5]	Not review population
Goekoop-ruiterman 2010[8]	Incorrect study design
Gullick 2012[10]	Incorrect study design
Harrold 2014[11]	protocol only, data expected in 2018
Harrold 2017[12]	Incorrect study design
Hetland 2006[14]	Inappropriate comparison. Incorrect interventions
Hetland 2008[15]	Inappropriate comparison. Incorrect interventions. Less than minimum duration
Hetland 2009[13]	Inappropriate comparison. Incorrect interventions
Hodkinson 2015[16]	Incorrect study design
Jurgens 2012[18]	Systematic review: methods are not adequate/unclear
Kievit 2016[19]	No outcomes of interest
Kuusalo 2015[20]	Incorrect study design
Markusse 2016[21]	Inappropriate comparison. Incorrect interventions. not relevant: study looks at adherence to a treat-to-target programme and reasons for compliance. paper not available
Moller-bisgaard 2016[22]	Inappropriate comparison. Incorrect interventions
Nam 2014[24]	Incorrect interventions. Inappropriate comparison
Norton 2014[27]	Incorrect study design. not RCT; prognostic study
Ohrndorf 2016[28]	Not guideline condition
Pincus 2013[30]	Systematic review: methods are not adequate/unclear
Pincus 2015[31]	Systematic review: methods are not adequate/unclear. Inappropriate comparison. Incorrect interventions. review on glucocorticoid use in rheumatoid arthritis
Rantalaiho 2014[33]	Inappropriate comparison. Incorrect interventions. both treatment arms are receiving treat-to-target, only the drugs are different
Salaffi 2016[34]	Incorrect interventions
Schipper 2010[35]	Systematic review: methods are not adequate/unclear
Schoels 2010[36]	Systematic review: methods are not adequate/unclear
Smolen 2016[37]	Systematic review: methods are not adequate/unclear
Stoffer 2016[39]	Systematic review: methods are not adequate/unclear
Symmons 2005[40]	difference in drug availability between groups: intensive group had access to more drugs
Symmons 2006[41]	difference in drug availability between groups: intensive group had access to more drugs
Thurah 2017[42]	Incorrect interventions
Todoerti 2010[43]	Inappropriate comparison. Incorrect interventions. treatment

Study	Exclusion reason
	differed only in their use of glucocorticoids
Van eijk 2012[46]	Not review population. cannot be certain that patients had rheumatoid arthritis
Van hulst 2010[47]	incorrect study and no protocolised treatment strategy in the treat to target group
Verschueren 2016[48]	Inappropriate comparison
Yamanaka 2000[51]	Not relevant to review; thought it was linked to another paper by Urata but it is not . Incorrect interventions. Inappropriate comparison

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I.2 2 Excluded health economic studies

3 None.