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Abstract

The clinical effectiveness and cost-effectiveness of treat-to-target strategies in rheumatoid arthritis: a systematic review and cost-effectiveness analysis

Allan Wailoo,[1]* Emma S Hock,[1] Matt Stevenson,[1] Marrissa Martyn-St James,[1] Andrew Rawdin,[1] Emma Simpson,[1] Ruth Wong,[1] Naila Dracup,[1] David L Scott[2] and Adam Young[3]

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Background: Treat to target (TTT) is a broad concept for treating patients with rheumatoid arthritis (RA). It involves setting a treatment target, usually remission or low disease activity (LDA). This is often combined with frequent patient assessment and intensive and rapidly adjusted drug treatment, sometimes based on a formal protocol.

Objective: To investigate the clinical effectiveness and cost-effectiveness of TTT compared with routine care.

Data sources: Databases including EMBASE and MEDLINE were searched from 2008 to August 2016.

Review methods: A systematic review of clinical effectiveness was conducted. Studies were grouped according to comparisons made: (1) TTT compared with usual care, (2) different targets and (3) different treatment protocols. Trials were subgrouped by early or established disease populations. Study heterogeneity precluded meta-analyses. Narrative synthesis was undertaken for the first two comparisons, but was not feasible for the third. A systematic review of cost-effectiveness was also undertaken. No model was constructed as a result of the heterogeneity among studies identified in the clinical effectiveness review. Instead, conclusions were drawn on the cost-effectiveness of TTT from papers relating to these studies.

Results: Sixteen clinical effectiveness studies were included. They differed in terms of treatment target, treatment protocol (where one existed) and patient visit frequency. For several outcomes, mixed results or evidence of no difference between TTT and conventional care was found. In early disease, two studies found that TTT resulted in favourable remission rates, although the findings of one study were not statistically significant. In established disease, two studies showed that TTT may be beneficial in terms of LDA at 6 months, although, again, in one case the finding was not statistically significant. The TICORA (TIght COntrol for RA) trial found evidence of lower remission rates for TTT in a mixed population. Two studies reported cost-effectiveness: in one, TTT dominated usual care; in the other, step-up combination treatments were shown to be cost-effective. In 5 of the 16 studies included the clinical effectiveness review, no cost-effectiveness conclusion could be reached, and in one study no conclusion could be drawn in the case of patients denoted low risk. In the remaining 10 studies, and among patients denoted high risk in one study, cost-effectiveness was inferred. In most cases TTT is likely to be cost-effective, except where biological treatment in early disease is used initially. No conclusions could be drawn for established disease.

Limitations: TTT refers not to a single concept, but to a range of broad approaches. Evidence reflects this. Studies exhibit substantial heterogeneity, which hinders evidence synthesis. Many included studies are at risk of bias.

Future work: Future studies comparing TTT with usual care must link to existing evidence. A consistent definition of remission in studies is required. There may be value in studies to establish the importance of different elements of TTT (the setting of a target, the intensive use of drug treatments and protocols pertaining to those drugs and the frequent assessment of patients).

Conclusion: In early RA and studies of mixed early and established RA populations, evidence suggests that TTT improves remission rates. In established disease, TTT may lead to improved rates of LDA. It remains unclear which element(s) of TTT (the target, treatment protocols or increased frequency of patient visits) drive these outcomes. Future trials comparing TTT with usual care and/or different TTT targets should use outcomes comparable with existing literature. Remission, defined in a consistent manner, should be the target of choice of future studies.

Study registration: This study is registered as PROSPERO CRD42015017336.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of tables

List of figures

List of abbreviations

ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
bDMARD	biologic disease-modifying antirheumatic drug
BeSt	BehandelStrategieën in Reumatoïde Artritis
BROSG	British Rheumatoid Outcome Study Group
CAMERA	Computer-Assisted Management in Early Rheumatoid Arthritis
CareRA	Care in early Rheumatoid Arthritis
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
COBRA	COmBination theRApy with rheumatoid arthritis
CRP	C-reactive protein
D-HAQ	Dutch version of the Health Assessment Questionnaire
DAS	Disease Activity Score
DAS28	Disease Activity Score, 28 joints
DAS28-CRP	Disease Activity Score, 28 joints with C-reactive protein concentration
DAS28-ESR	Disease Activity Score, 28 joints with erythrocyte sedimentation rate
DAS44	Disease Activity Score, 44 joints
DAS44-CRP	Disease Activity Score, 44 joints with C-reactive protein concentration
DMARD	disease-modifying antirheumatic drug
DREAM	Dutch Rheumatoid Arthritis Monitoring
EQ-5D	EuroQol-5 Dimensions
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FIN-RACo	FINnish Rheumatoid Arthritis Combination therapy
GC	glucocorticoid
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IQR	interquartile range
JSN	joint space narrowing
LDA	low disease activity
LEF	leflunomide
MACTAR	McMaster Toronto Arthritis Patient Preference Disability Questionnaire
mHAQ	modified Health Assessment Questionnaire
MMP-3	matrix metalloproteinase 3
mTSS	modified total Sharp score
MTX	methotrexate
MTX-TSU	methotrexate tight step-up
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PBO	placebo

PDN	prednisone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
SAE	serious adverse event
ScHARR	School of Health and Related Research
SD	standard deviation
SDAI	Simple Disease Activity Index
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
SHS	Sharp/van der Heijde score
SJC	swollen joint count
SSZ	sulfasalazine
STREAM	STRategies in Early Arthritis Management
T-4	TreaTing to Twin Targets
TA	Technology Appraisal
TEAR	Treatment of Early Aggressive Rheumatoid arthritis
TICORA	TIght COntrol for Rheumatoid Arthritis
TJC	tender joint count
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
TOC	tocilizumab
TTT	treat to target
U-Act-Early	early rheumatoid arthritis treated with tocilizumab, methotrexate or their combination
VAS	visual analogue scale

Plain English summary

This report investigates the value of so-called 'treat-to-target' (TTT) strategies in patients with rheumatoid arthritis (RA). Patients with RA, together with the doctors who treat them, can jointly agree targets that they hope to achieve from treatment. TTT involves monitoring the condition of the patient and adjusting treatments in order to attempt to reach the target. TTT can involve a more intensive use of drug treatments and more frequent monitoring and treatment adjustments than normal care. A systematic literature review was conducted to identify relevant existing studies. Sixteen studies were found. Eleven studies were in patients who had RA for < 3 years, three studies were in patients who had RA for > 3 years and two studies mixed both sets of RA patients. The evidence for the benefit of TTT strategies in reducing the severity of RA is mixed and it is difficult to draw strong conclusions. The studies we identified often compared TTT strategies that differed from each other in terms of the drugs and doses that patients received. However, there is some evidence that TTT works better than usual treatment, in terms of the numbers of patients achieving remission, particularly in those who have had RA for < 3 years. In patients with more established disease we found some limited evidence that TTT works better in terms of patients achieving low disease activity.

We also estimated that, in early disease, TTT strategies are likely to offer good value for money.

Scientific summary

Background

Patients with rheumatoid arthritis (RA) have seen dramatic improvements in their care in the last 20 years, particularly through the development of more targeted biologic disease-modifying antirheumatic drugs (bDMARDs) and non-bDMARDs. Treat to target (TTT) in rheumatology is a more recent concept encompassing a range of broad features. The central component of the TTT concept is the setting of a treatment target. Recommendations in RA typically specify low disease activity (LDA) or remission as an appropriate target, but, in addition to the setting of a target, there are a range of different features that lead to a continuum of 'weak' to 'strong' TTT principles. These can include an increased frequency of rheumatology visits for the assessment of the target and any associated changes in the management of the patient. Treatment changes within a TTT strategy may also be protocolised, specifying how treatments are to be altered in response to the target assessment.

Objectives

To identify and evaluate the evidence for the clinical effectiveness and cost-effectiveness of TTT strategies compared with routine care for adult patients with RA.

Methods

Review methods

Scoping searches were carried out to identify the extent of potentially relevant literature. Databases including MEDLINE and EMBASE were searched from 2008 to August 2016. A full systematic review of clinical effectiveness data was then conducted following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched for evidence from studies of adults with clinically diagnosed RA, which included TTT. At a minimum, TTT had to include the setting of an explicit target.

Only randomised controlled trials were included. Data were extracted on measures of treatment goals, including the number/proportion of patients in each arm meeting the target; disease activity; mortality; health-related quality of life; serious adverse events (SAEs); treatments; and dosages given. The methodological quality of each included study was assessed.

Evidence examining the clinical effectiveness of TTT was synthesised according to the TTT comparison, namely (1) TTT compared with usual care; (2) a comparison of different targets against each other; and (3) a comparison of different treatment protocols against each other. Two trials did not fit into this framework and so were examined separately under 'other comparisons'. Trials were further grouped according to whether or not they used early RA populations (disease duration < 3 years) or established RA populations.

A systematic review of cost-effectiveness was undertaken. Titles and abstracts were examined by one reviewer and a random 5% were checked by another reviewer. Study selection based on full texts was decided by two reviewers, with discrepancies resolved by discussion. Data were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer.

Evaluation of cost-effectiveness

As study heterogeneity precluded meta-analysis, it was deemed most informative to analyse each study included in the clinical effectiveness review and to assess the implications of the results for the cost-effectiveness of each strategy. A simplistic approach was taken and costs that were assumed to be similar between arms were ignored.

Results

A total of 16,591 records were identified from electronic databases. Forty-two articles describing 16 trials were included in the review. Eleven trials examined an early RA population. Three trials examined an established RA population. Two trials examined populations that included both patients with early RA and those with established RA. The only trial rated as having a low risk of bias was the TICORA (TIght COntrol for RA) trial, which examined TTT compared with usual care in a mixed population.

Study heterogeneity precluded meta-analyses. This heterogeneity was evident in the substantial differences between studies in the targets that were set, the nature of the treatment protocol (where one existed) and the frequency of patient visits.

Overall, the evidence for TTT is mixed. For several outcome measures, studies produced a mixture of results or found no difference between TTT and conventional care. However, there does seem to be some support for the use of TTT in specific patient groups for some outcomes.

Two studies in patients with early disease found that TTT resulted in favourable remission rates, though in one case the findings were not statistically significant: an odds ratio (OR) of 0.52 [95% confidence interval (CI) 0.21 to 1.28] in the STRategies in Early Arthritis Management (aggressive therapy in patients with early arthritis results in similar outcome as conventional care) study at 2 years; an OR of 0.43 (95% CI 0.19 to 0.95) for Disease Activity Score, 28 joints (DAS28)-driven TTT at 1 year in the TreaTing to Twin Targets (T-4) study; and an OR of 0.21 (95% CI 0.10 to 0.47) for DAS28-driven and matrix metalloproteinase 3 (MMP-3)-driven TTT at 1 year in the T-4 study. The T-4 study found usual care to be more effective than the MMP-3 target (21% vs. 13%; OR 1.72, 95% CI 0.66 to 4.52). There were mixed findings for DAS28/ Disease Activity Score, 44 joints (DAS44) and joint erosion, and no difference between targeted arms and usual care on Health Assessment Questionnaire (HAQ) score. There were no differences in the proportions of patients experiencing any adverse event (AE), SAE, death, withdrawals as a result of AEs or specific AEs.

Two studies in patients with established disease found that TTT may be beneficial in terms of LDA at 6 months, although, again, in one case the result was not statistically significant [an OR of 0.42 (95% CI 0.19 to 0.94) in the Fransen *et al.* study at 6 months; an OR of 0.81 (95% CI 0.45 to 1.45) using a DAS28 target in the Optimisation of Adalimumab study; and an OR of 0.91 (95% CI 0.50 to 1.66) in the same study using a swollen joint count (SJC) of 0 targets]. There was no difference between TTT and usual care in terms of DAS28, SJC, tender joint count or HAQ response. The proportion of patients who withdrew as a result of AEs (as reported in the Optimisation of Adalimumab study) and experienced specific AEs (dermatological and gastrointestinal AEs as reported in Fransen *et al.*) was lower in the TTT arms.

Of the trials that included both patients with early disease and those with established disease, only the TICORA trial found evidence favouring TTT in terms of remission at 18 months (65% vs. 16%; $p < 0.0001$). The TICORA trial also reported results in favour of a TTT approach compared with usual care in terms of American College of Rheumatology 20/50/70 response rates. The evidence, however, was equivocal for other outcome measures. A smaller proportion of patients reported any and specific AEs (dermatological, gastrointestinal and infectious AEs, significance not reported) in the TTT arm than the usual-care arm of the TICORA trial.

Support for TTT in early disease is stronger if evidence from the TICORA trial, which had an inclusion criterion of disease duration < 5 years, is considered generalisable to the early RA population.

There was little difference in outcomes where different targets were used as part of TTT strategies across all RA populations.

Two papers on the cost-effectiveness of TTT were identified. One, related to the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry, estimated that TTT would be dominant at 3 years. Savings compared with usual care were estimated at €462 (2011 values). The second, related to the BehandelStrategieën in Reumatoïde Artritis trial, estimated that step-up combination therapy was the most cost-effective strategy, even when compared with a strategy that included combination therapy with a biologic drug, and saved €2743 per patient (2008 values) compared with sequential monotherapy.

Literature relating to 16 studies was found. In five of these studies, and for low-risk patients (criteria not defined) in one study, no clear conclusion regarding cost-effectiveness could be made. In the remaining 10 studies, and for the high-risk patients (criteria not defined) in one study, we were able to estimate whether or not the strategy was likely to be cost-effective. Almost all of the estimates from these studies indicated that TTT would be considered cost-effective other than where the TTT strategy included the use of bDMARDs in early disease. No conclusions could be made in relation to TTT in established disease.

Discussion

Treat to target refers not to a single concept, but to a range of broad approaches to the treatment of patients with RA. The evidence reflects this, with studies exhibiting a great degree of heterogeneity, particularly in relation to the TTT strategies they sought to examine. Studies varied in terms of the treatment target, treatment protocols and frequency of assessments. Targets were often defined in terms of Disease Activity Scores, but different variants of the measure (DAS44, DAS28) and different cut-off points were used. Even in the case of TTT strategies that were broadly similar, the precise therapies used exhibited significant variation. For example, in those studies that used both a steroid step-down and a disease-modifying antirheumatic drug (DMARD) step-up combination treatment protocol, the doses of steroid varied substantially and the specific DMARD and dose also varied. This variation makes it complex to synthesise evidence and draw general conclusions. This applies equally to the assessment of clinical effectiveness and cost-effectiveness. This is further weakened by the risk of bias in many included studies. Despite this, there does seem to be some support for the broad TTT concept in RA, particularly in early RA, or for patients with a disease duration < 5 years if the TICORA trial is considered representative of early RA patients. However, it remains unclear which elements of TTT are important or if all are required. It is not possible to ascertain if it is the setting of a target, the more intensive management of patients or the treatment protocols that drive better outcomes. Furthermore, we cannot identify if any particular treatment target is more appropriate.

Owing to the heterogeneity of the evidence and the potential of changes in usual care across time, no modelling evaluating all strategies within a fully incremental analysis could be performed. For this reason, only those studies that have been trialled in the same study can be compared. In early RA, the components of care that together constitute 'TTT' are likely to form a cost-effective approach. There were insufficient studies in established RA to discern a pattern in cost-effectiveness.

Conclusions

Treat to target is a broad concept and does not refer to a single treatment strategy. In early RA there is some limited evidence to suggest that strategies that have been tested in clinical studies as TTT lead to better outcomes, particularly in terms of the number of patients achieving remission. In established disease

there is evidence that TTT leads to more patients achieving LDA. However, it is unclear which of the various elements of TTT drive these findings.

Intensive drug therapy is frequently included as part of TTT strategies that have been tested in trials. These trials do seem to indicate that intensive conventional disease-modifying antirheumatic drug (cDMARD) treatment is more cost-effective than routine practice, particularly in early RA. However, whether or not these results require the inclusion of a specific target in addition is uncertain. The use of bDMARDs before intensive cDMARDs as part of a TTT strategy is unlikely to be cost-effective.

Future trials comparing TTT with usual care and/or different TTT targets should use outcomes comparable with existing literature. Remission, defined in a consistent manner, should be the target of choice of future studies.

Study registration

This study is registered as PROSPERO CRD42015017336.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of health problem

Rheumatoid arthritis (RA) is a common chronic inflammatory disease that typically affects the joints of the body that are lined with synovium, such as those in the hands and feet. It is characterised by progressive, irreversible joint damage, impaired joint function and pain and tenderness caused by swelling of the synovial lining of joints (synovitis), and manifests as increasing disability and reduced quality of life.[1] As RA is a systemic disease, it affects much more than the joints. The primary symptoms are pain, morning stiffness, swelling, tenderness, loss of movement, fatigue and redness of the peripheral joints.[2,3] Fever, sweats and weight loss may be experienced. More significant inflammatory manifestations may lead to serious pathology.[4] RA has long been reported as being associated with increased mortality,[5,6] particularly as a result of cardiovascular events,[7] which may result from reduced mobility and ongoing inflammation. For example, a 50-year-old woman with RA is expected to die 4 years earlier than a 50-year-old woman without RA.[4]

The costs of RA are substantial. Treatment costs associated with drug acquisition and hospitalisation are major components of this. Reduced work productivity is also a significant cost burden in this patient group.[3] The total costs of RA in the UK, including indirect costs and work-related disability, have been estimated at between £3.8B and £4.75B per year.[8]

Epidemiology

Symmons *et al.*[9] estimated a prevalence of 0.8% in a study of the population in Norfolk. This leads to an estimated 400,000 people in England and Wales with RA,[10] with approximately 10,000 incident cases per year.[11] The disease is about 2–4 times more common in women (1.16%) than in men (0.44%),[11] with the majority of cases being diagnosed when patients are aged between 40 and 80 years,[12] with peak incidence among those in their seventies.[11] Thus, a large proportion of people affected by RA are of working age.

Significance for the NHS

The treatment of RA is costly to the NHS and the wider economy. Many of the treatment options for patients are based on drug therapy, some of which (particularly biologic therapies) are extremely costly. The cost of treating patients whose disease is not well controlled from an early stage is also driven substantially by the need for joint surgery and hospitalisation.

Treat to target (TTT) has the potential to allow more effective treatment strategies to be given to patients. Given in early disease, this may result in better disease control. Remission has been shown to correlate strongly with long-term structural damage identifiable on radiographs and with patient function. Disease control may also allow the tapering of drug doses over time and avoid the need to progress to costlier biologic therapies.

Current service provision

A series of drug-based treatments have contributed to the rapid improvement in the care of patients with RA over the last 20 years. Traditionally, patients have been treated with conventional disease-modifying antirheumatic drugs (cDMARDs), which include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), ciclosporin and gold injections, as well as corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). More recently, a group of drugs has been developed consisting of monoclonal antibodies and soluble receptors that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B lymphocytes).[4] Such drugs have been labelled as biologic disease-modifying antirheumatic drugs (bDMARDs).

Given the number of treatments available, there is a vast number of potential treatment strategies for patients in both early and established disease.

Clinical guidelines

For people with newly diagnosed RA, the National Institute for Health and Care Excellence (NICE) clinical guideline number 79[4] recommends a combination of cDMARDs [including MTX and at least one other disease-modifying antirheumatic drug (DMARD) plus short-term glucocorticoids (GCs)] as a first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate (e.g. where there are comorbidities or pregnancy), DMARD monotherapy is recommended, this was considered a more standard treatment approach prior to the NICE guidelines.

Current National Institute for Health and Care Excellence Technology Appraisal guidance

The NICE guidance [Technology Appraisal (TA) number 375[13]] recommends the use of adalimumab (ADA), etanercept (ETN), infliximab (IFX), certolizumab pegol, golimumab, tocilizumab (TOC) and abatacept, in combination with MTX, in people with RA only if:

- disease is severe, that is, Disease Activity Score, 28 joints (DAS28) is > 5.1
- disease has not responded to intensive therapy with a combination cDMARDs
- the manufacturers provide certolizumab pegol, golimumab, abatacept and TOC as agreed in their patient access schemes.

Adalimumab, ETN, certolizumab pegol or TOC can be used as monotherapy for people who cannot take MTX, because it is contraindicated or because of intolerance, when the above criteria are met.

At least a moderate European League Against Rheumatism (EULAR) response must be achieved at 6 months for treatment to continue.

The NICE has also issued guidance on the treatment of RA after the failure of a tumour necrosis factor inhibitor (TNFi) (TA195,[14] TA225[15] and TA247[16]).

Description of technology under assessment

Dramatic improvements in the treatment of RA have been seen in the last 20 years (see Smolen *et al.*[17]), particularly through the development of more targeted bDMARDs and non-bDMARDs. A more recent development that has consolidated these improvements is the concept of TTT. Rather than referring to a single, precise technology or treatment strategy, TTT in rheumatology can be better described as a treatment 'paradigm'[17] encompassing a range of broad features. The American College of Rheumatology (ACR)/EULAR have issued a series of recommendations on TTT based on analysis of a series of trials that test varying treatment strategies. There is therefore no single set of interventions constituting a TTT treatment approach.

Treat to target has a strong history in the treatment of other chronic diseases, such as diabetes mellitus and hypertension. Long-term outcome data supporting the TTT approach in these conditions have motivated the drive for successful TTT approaches in RA.

The central component of the TTT concept is the setting of a treatment target. Recommendations typically specify low disease activity (LDA) or remission as appropriate targets. This was the case in EULAR's 2010 recommendations (see Smolen *et al.*[18]) and EULAR's 2016 updated recommendations (see Smolen *et al.*[17]), both of which recommended clinical remission as the primary treatment goal. The ACR/EULAR's 2011 definition of remission was originally designed specifically to be a predictor of good patient outcomes in terms of a later lack of radiography-detected joint damage and good, stable function and quality of life for

patients,[19] more so than other disease activity states (including LDA).[17] These goals have become realistic targets with the availability of newer drugs.

The ACR/EULAR definition of remission is:

- Boolean-based definition: at any time point, a patient must satisfy all of the following: a tender joint count (TJC) of ≤ 1, a swollen joint count (SJC) of ≤ 1, a C-reactive protein (CRP) concentration of ≤ 1 mg/dl and a patient global assessment of ≤ 1 (on a scale of 0–10) or
- index-based definition: at any time point, a patient must have Simple Disease Activity Index (SDAI) of ≤ 3.3.

Low disease activity as an acceptable, alternative therapeutic goal, particularly in long-standing disease, is a recommendation intended to imply that there are situations where remission may not be a feasible outcome.

However, TTT, as a concept, is also often described as comprising more than just a treatment goal. Different commentators refer to different elements of the TTT strategy that aim to take action to reach and maintain the treatment goal. Common to most is the concept of regular treatment adaptation in response to the assessment of a patient in comparison to the target. Sometimes treatment adaptation is described in broad terms;[17,18] in other instances reference is made to 'aggressive treatment'.[20] Terminology also varies, with some referring to 'tight control'.[21]

Solomon *et al.*[20] also refers to TTT as a 'proactive' treatment approach. In many studies of TTT this is evident through more frequent assessment of patients than would normally be the case in standard practice. Assessments are often made as frequently as monthly under TTT principles. The ACR/EULAR's recommendations state that assessments should be made 'as frequently as monthly' and drug therapy should be altered at least every 3 months, until the target is reached. Less frequent (6-monthly) monitoring of patients is required once the target is reached.

Treat to target can therefore be composed of a range of different features that leads to a continuum of 'weak' to 'strong' TTT principles. We define the entirety of those features as the 'treatment strategy'. The inclusion of a treatment target is a necessary condition for a strategy to be considered a TTT strategy. Additional components of the strategy include the frequency with which patients are assessed against the target and the provision of a treatment protocol that specifies how treatments are to be changed in response to assessments. Thus, the weakest TTT strategy would be one where a treatment target is specified, but no further instruction is provided on which treatment protocols should be used to reach that goal.

Treat-to-target studies have often focused on the optimal strategy for patients with newly diagnosed RA. This links to the concept of there being a 'window of opportunity' that has emerged in the RA literature, which posits that the earlier DMARD therapy is introduced, the greater the impact on long-term health outcomes.[21]

Additional costs associated with TTT depend on the nature of the overall treatment strategy. Of course, the setting of a target itself incurs no additional resources, but the increased frequency of visits to a rheumatologist and the potential for a more intense use of drug treatments can make TTT a more resource-intensive option for the initial treatment period.

A simplified schematic of operationalising a TTT strategy has been provided in *Figure 1*.

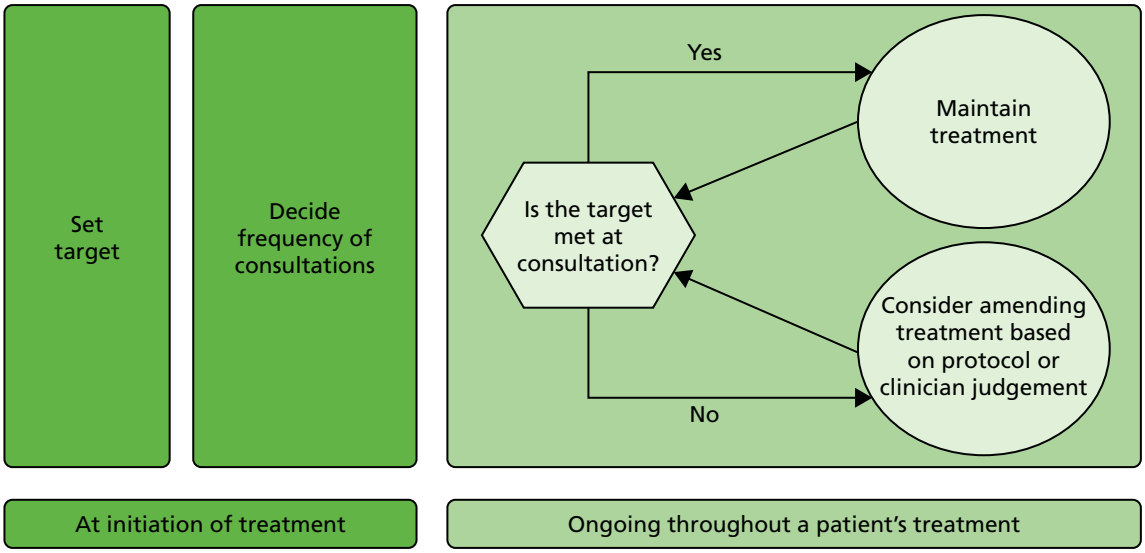

FIGURE 1 A simplified conceptual model of TTT.

Chapter 2 Definition of the decision problem

We aim to systematically review evidence on the use of TTT strategies for the treatment of RA compared with standard care with non-TTT strategies.

Decision problem

Interventions

The intervention of interest is a TTT approach to care. At a minimum, for a treatment strategy to be considered TTT in this review it must contain the explicit setting of a target, assessment of that target and use of that information by the treating clinician. TTT strategies may also include additional elements; for example, in the frequency of assessment or in providing a treatment protocol that provides instruction to the treating clinician on treatment changes in the light of assessments. Our review will seek to distinguish these different types of TTT.

Population including subgroups

Adult patients aged ≥ 18 years with a diagnosis of RA were eligible for the study. We will consider two groups of patients separately: (1) those with early disease (≤ 3 years since diagnosis) and (2) those with established disease (> 3 years since diagnosis). We used definitions of early and established RA as defined in the trials. When no definition was provided, a cut-off point of 3 years was used, which is generally consistent across the literature (e.g. Scott *et al.*[22]), bearing in mind that no fixed consensus exists. Examining definitions and mean disease durations across trials, a 3-year cut-off point seems appropriate.

Relevant comparators

The comparator is treatment of patients without a TTT strategy. This includes sequential non-bDMARD therapy in early disease, clinician preference and any treatment protocol that lacks an explicit treatment target.

Outcomes

A number of outcomes were assessed. Primarily, we examined the proportion of patients achieving target, remission and LDA. We also examined changes in DAS28/ Disease Activity Score, 44 joints (DAS44), SJC, TJC, Health Assessment Questionnaire (HAQ), joint erosion and quality of life, as well as EULAR and ACR response.

Overall aims and objectives of assessment

The aim of this review is to identify and evaluate the evidence for the clinical effectiveness and cost-effectiveness of TTT strategies compared with routine care for adult patients with RA.

Patient and public involvement

Two members of the public who have RA were asked to peer review the following sections of the report: the abstract; plain English summary; scientific summary; discussion; and conclusions. The full report was provided to supply further information and the patient and public involvement representatives could comment on other sections too. The report was then amended based on the comments received to improve the clarity and readability of the text.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

The search for evidence of clinical effectiveness was undertaken systematically following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (URL: www.prisma-statement.org/; accessed 30 October 2017). Search strategies are described in *Appendix 1*.

Identification of studies

There were two search phases conducted for this review.

Phase I scoping searches were carried out to identify the extent of potentially relevant literature, the range and types of TTT strategies that have been subject to clinical study, the types of clinical study and the relevance of these strategies to UK NHS practice.

Four databases and one clinical trials registry were searched (*Table 1*). Terms for RA (see *Appendix 2*, statements 1 and 2) were combined with TTT terms (see *Appendix 2*, statements 4–18). Terms for TTT were obtained and adapted from the review by Schoels *et al.*[23]

TABLE 1 Sources searched in Phases I and II

Source, date searched from	Phase (date of search)	
	I (May 2015)	II (January 2016 and August 2016)
MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (via Ovid), from 1948	✓	✓
EMBASE (via Ovid), from 1980	✓	✓
CDSR (via Wiley Online Library), from 1996	✓	✗
CENTRAL (via Wiley Online Library), from 1898	✓	✓
NHS EED (via Wiley Online Library), from 1995 to 2015	✓	✓
HTA database (via Wiley Online Library), from 1995	✓	✗
DARE (via Wiley Online Library), from 1995	✓	✗
WoS Citation Index Expanded (Thomson Reuters), from 1900	✓	✓
WoS Citation Index and Conference Proceedings Index (Thomson Reuters), from 1990	✓	✓
BIOSIS Previews (Thomson Reuters), from 1969	✗	✓
CINAHL (via EBSCO*host*), from 1982	✗	✓
EconLit (via Ovid), from 1886	✗	✓
EULAR (via Web of Science, Thomson Reuters)	✓	✗
ACR (via Web of Science, Thomson Reuters))	✓	✗
ClinicalTrials.gov (US National Institutes of Health) (www.clinicaltrials.gov)	✓	✓
ICTRP (www.who.int/ictrp/en/)	✗	✓
NICE Evidence (www.nice.org.uk/)	✗	✓

BIOSIS, Bioscience Information Service; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects; EconLit, American Economic Association's electronic bibliography; HTA, Health Technology Assessment; ICTRP, International Clinical Trials Registry Platform; NHS EED, NHS Economic Evaluation Database; WoS, Web of Science.

The search was combined with specific search filters for randomised controlled trials (RCTs) (see *Appendix 2*, statements 21 and 22), systematic reviews (see *Appendix 2*, statements 26–28) and economic evaluations (see *Appendix 2*, statements 32–34). The RCT and systematic reviews search was limited by date from 2008 until May 2015, whereas for recent cost-effectiveness studies, the last 2 years were searched (2013–15).

The Phase II search was informed by the literature identified from the Phase I searches to refine and carry out a full systematic search of the evidence.

Additional free-text terms for TTT were added to the Phase I search strategies to increase the sensitivity of the search (see *Appendix 2*). Only RCT and economic evaluations were searched by combining the strategies with sensitive search filters. Three further databases, one trials registry and a search engine were searched (see *Table 1*). No date or language limits were applied in the search. Records retrieved from the search were combined and duplicate titles were removed from the Phase I search.

The number of records retrieved from the various sources in Phase I and II searches can be found in *Table 2*.

TABLE 2 Summary of records retrieved in Phase I and II searches

	Phase					
	I			II		
Source	RCTs (specific and 2008–)	SRs (specific and 2008–)	Cost-effectiveness (2013–)	RCTs	RCT update (August 2016)	Cost-effectiveness
MEDLINE	475	168	73	3778	294	417
EMBASE	1315	302	290	7633	423	923
CDSR	–	81	–	–	–	–
DARE	–	79	–	–	–	–
CENTRAL	1588	–	–	2243	45	0
HTA database	–	7	–	–	–	–
NHS EED	–	–	9	0	0	45
WoS Citation Index Expanded and WoS Citation Index and Conference Proceedings Index	2179	641	199	5435	245	444
BIOSIS	–	–	–	1753	32	0
CINAHL	–	–	–	789	66	642
EconLit	–	–	–	0	–	6
EULAR	650	–	–	–	–	–
ACR	792	–	–	–	–	–
ClinicalTrials.gov	122	–	–	26	6	0
ICTRP	–	–	–	0	0	0
NICE Evidence	–	–	–	0	–	2
Total retrieved	7121	1278	571	21,657	1115	2479
Unique	4937	946	436	10,093[a]	635[b]	913[a]

BIOSIS, Bioscience Information Service; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; EconLit, American Economic Association's electronic bibliography; HTA, Health Technology Assessment; ICTRP, International Clinical Trials Registry Platform; NHS EED, NHS Economic Evaluation Database; SR, systematic review; WoS, Web of Science.

a Records retrieved from the Phase II search were combined and the duplicate titles removed from Phase I search.

b Records retrieved from the Phase II update search were combined and the duplicate titles removed from the earlier Phase I and Phase II searches.

Inclusion and exclusion criteria

Population
The population was adults with clinically diagnosed RA, with or without prior cDMARDs or bDMARDs, commencing or currently undergoing treatment anywhere on the RA treatment pathway.

Intervention
The intervention is the use of TTT strategies to guide treatment decisions for individual patients, as defined in *Methods for reviewing clinical effectiveness*. Sufficient description of the intervention needed to be reported for a study to be included in the review.

Comparators
The following comparators were permitted: (1) usual care, in which TTT strategies were not used, (2) a different TTT strategy, in which an alternative target was used and (3) a different TTT strategy, in which an alternative treatment protocol was used.

Outcomes
A number of outcomes were assessed. Primarily, we examined the proportion of patients achieving target, remission and LDA. We also examined score changes in the DAS28/DAS44, SJC, TJC and HAQ, joint erosion and quality of life, as well as EULAR and ACR response. According to the TTT ACR/EULAR international task force, TTT strategies should use composite measures that include joint counts to assess disease activity as related to the target.[17]

Study design
Randomised controlled trials were included. The reference lists of any systematic reviews identified through the searches were checked for potentially relevant trials.

Exclusion criteria

- Animal models.
- Pre-clinical and biological studies.
- Narrative reviews, editorials, opinions.
- Non-English-language papers.
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.
- Trials of personalised medicine.
- Non-randomised clinical trials and other study types, such as cohort studies.
- Trials designed to test an active drug versus placebo (PBO) where both arms pursue the same target and treatment strategy.

Study selection
Titles and abstracts were examined by one reviewer and 5% were checked by another reviewer. Study selection based on full texts was decided by two reviewers, with discrepancies resolved by discussion.

Data extraction strategy
Data relevant to the decision problem were extracted from all studies by one reviewer using a standardised data extraction form. Data on the study characteristics (population, type of comparison, study type, method of RA diagnosis, sample size, treatment arms relevant to the review, duration of RCT phase, duration of follow-up, primary outcome, geographical location and funding source); population characteristics (mean age, number and percentage female, number and percentage rheumatoid factor positive, mean disease duration, mean baseline DAS28, mean baseline SJC, mean baseline TJC, mean baseline pain score, mean baseline HAQ score); TTT characteristics (target, treatment protocol, frequency of assessment); and key outcomes (number and percentage completing randomised phase, reasons for withdrawal, number and

percentage meeting study target, number and percentage attaining LDA, number and percentage attaining remission, treatment adaptations, total dose of each drug given over the trial period, mean DAS28, mean DAS44, mean SJC, mean TJC, EULAR response, ACR 20/50/70 response, mean HAQ, joint erosion, quality of life), including adverse events (AEs) [proportion of patients experiencing any AE, any serious adverse event (SAE), death, withdrawal as a result of an AE, musculoskeletal AEs, endocrine and metabolic AEs, cardiovascular AEs, dermatological AEs, ophthalmological AEs, gastrointestinal AEs, infectious AEs, psychological AEs and other AEs] were extracted.

All data extracted were checked thoroughly by a second reviewer, who checked the first reviewer's extraction against the article(s). Data were extracted without blinding to authors or journal. Discrepancies were discussed and an agreement was reached. We planned that a third reviewer would be consulted when no consensus could be reached; however, this was not necessary in any instance.

Quality assessment strategy

The methodological quality of each included study was assessed by one reviewer, and checked by a second reviewer, who checked the first reviewer's quality assessment against the article(s). Discrepancies were discussed and an agreement was reached. We planned that a third reviewer would be consulted when no consensus could be reached; however, this was not necessary in any instance.

The methodological quality of RCTs, identified from the literature search for inclusion, was assessed using the Cochrane Collaboration risk-of-bias assessment criteria. This tool addresses specific domains, namely sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective outcome reporting.[24] Judgements for domains are made as low, high, or unclear risk of bias. For cluster RCTs we also included three additional domains for recruitment bias (were participants recruited prior to clusters being randomised), risk of baseline differences between clusters and attrition of clusters. We classified RCTs as being at overall 'low risk' of bias if they were rated as 'low' for each of three key domains – allocation concealment, blinding of outcome assessment and completeness of outcome data (> 10% attrition[25]). RCTs judged as being at 'high risk' of bias for any of these domains were judged as overall 'high risk'. RCTs not judged as being at 'high risk' for any of these domains, or 'low risk' for all of these domains, were judged as overall 'unclear risk'.

Methods of analysis/synthesis

Evidence examining the clinical effectiveness of TTT was reported according to the TTT comparison, namely (1) TTT compared with usual care, (2) a comparison of different targets against each other and (3) a comparison of different treatment protocols against each other. Two trials did not fit into this framework and so were examined separately, under 'other comparisons'. Within these comparisons, trials were further grouped according to whether they used early RA populations or established RA populations, as patients with early and established RA may respond to treatment differently.[17,18,22] We used definitions of early and established RA as defined in the trials, and, when no definition was provided, a cut-off point of 3 years was used, which is generally consistent across the literature (e.g. Scott *et al.*[22]), bearing in mind that no fixed consensus exists. Examining definitions and mean disease durations across trials, a 3-year cut-off point seems appropriate. Two trials used populations with both early and established RA patients, so these trials were reported separately from those with early RA and those with established RA populations. Statistical meta-analysis was planned where the evidence allowed. Because of the heterogeneity in treatment protocols, the data from trials in comparison 3 were not narratively combined and examined by outcome, as with the previous two comparisons, and results were reported separately by trial.

Results

Quantity and quality of research available

A total of 16,591 records were identified from electronic databases for the clinical effectiveness systematic review, following deletion of duplicates. The study selection process is represented as a PRISMA flow

diagram (*Figure 2*). A total of 16,412 records were excluded at title and abstract level and 137 articles (reporting 53 separate studies) were excluded in the full-paper sift (see *Appendix 3* for a comprehensive list with rationale for exclusion). A total of 42 articles describing 16 trials were included in the review (*Table 3*).

Table 3 displays the characteristics of the studies included in this review. Eleven trials[26–36,38–49,51,54–60,62,64–67] examined an early RA population (defined as disease duration of < 3 years; see *Chapter 4*, *Inclusion and exclusion criteria*) [i.e. BehandelStrategieën in Reumatoïde Artritis (BeSt),[26–34,64–66] the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) studies,[35,36,67] Care in early Rheumatoid Arthritis (CareRA) trial,[38–43] the COmBination theRApy with rheumatoid arthritis (COBRA)-light trial,[44,45] FINnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial,[46–49] Hodkinson *et al.*,[51] Saunders *et al.*,[54] the STRategies in Early Arthritis Management (STREAM) trial,[55] the TreaTing to Twin Targets (T-4) study,[56,57] the Treatment of Early Aggressive Rheumatoid arthritis (TEAR) trial[58–60] and the early rheumatoid arthritis treated with tocilizumab, methotrexate or their combination (U-Act-Early) trial[62]], three trials[9,50,52,53] examined an established RA population [i.e. British Rheumatoid Outcome Study Group (BROSG) trial,[9] Fransen *et al.*[50] and the Optimisation of Adalimumab study[52,53]] and two trials[61,63] examined populations that include both patients with early RA and those with established RA [i.e. the TIght COntrol for RA (TICORA) trial[61] examined patients with a disease duration of < 5 years and van Hulst *et al.*[63] reported including both newly diagnosed patients and those with established disease (and did not report on the findings for these patients separately at all)]. Six studies[50,52,53,55–57,61,63] compared one or more TTT approaches with usual care (i.e. Fransen *et al.*,[50] the Optimisation of Adalimumab study,[52,53] the STREAM trial,[55] the T-4 study,[56,57] the TICORA trial[61] and van Hulst *et al.*[63]), four studies[51–53,56–60] compared different targets against each other (Hodkinson *et al.*,[51] the Optimisation of Adalimumab study,[52,53] the T-4 study[56,57] and the TEAR trial[58–60]) and six studies[26–34,38–42,44–49,54,58–60] compared different treatment protocols against each other (BeSt,[26–34] the CareRA trial,[38–42] the COBRA-light trial,[44,45] the FIN-RACo trial,[46–49] Saunders *et al.*[54] and the TEAR trial[58–60]). Two studies[9,35,36,67] made other comparisons which did not seem to fit with any of the above comparisons (i.e. the BROSG trial[9] and the

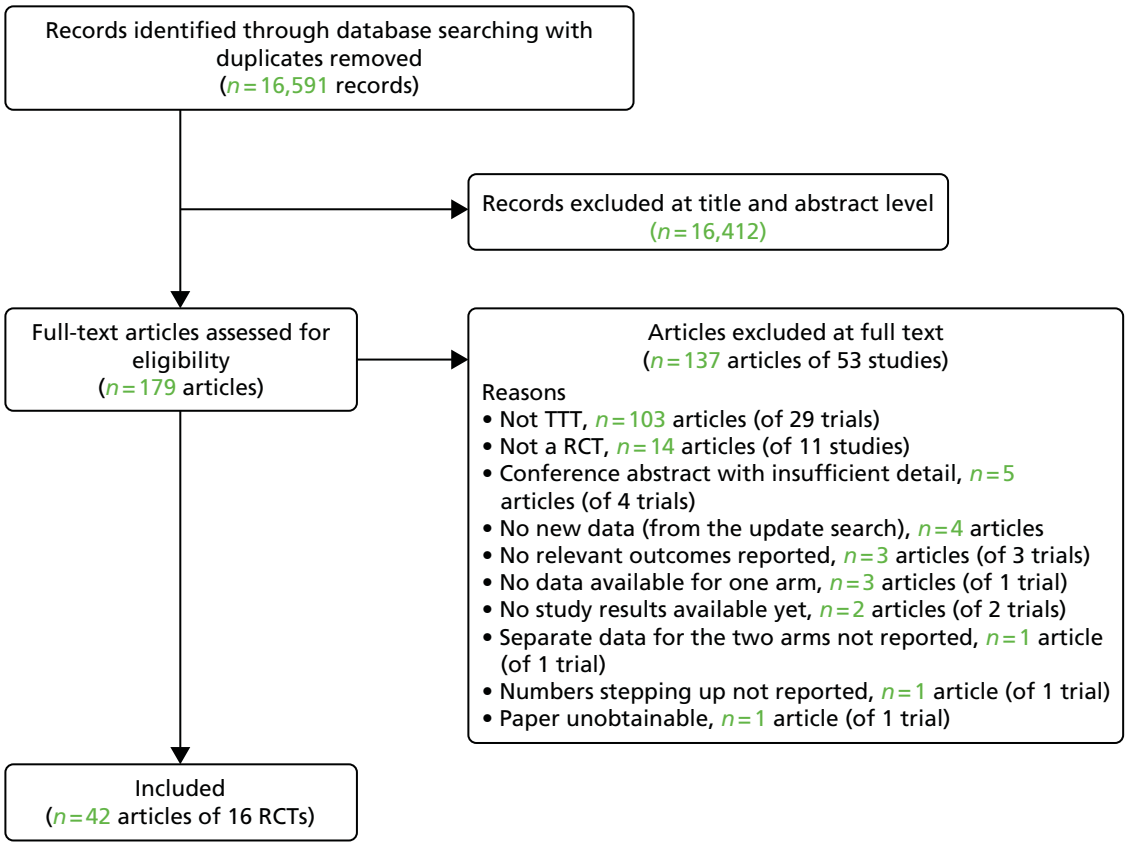

FIGURE 2 Flow diagram of study inclusion.

TABLE 3 Characteristics of included studies

Trial acronym or first author and year of publication	RA population	Type of comparison	Study type	Trial start date	RA diagnosis	Sample size (randomised)	Treatment arms for which data extraction performed	Duration of RCT phase	Duration of follow-up	Primary outcome	Geographical location	Funding source
BeSt[26–34]	Early RA	Comparison of different treatment protocols	RCT	April 2000	ACR 1987	508	1. Sequential monotherapy 2. Step-up combination therapy 3. Initial combination therapy with PDN 4. Initial combination therapy with IFX	12 months	10 years	Functional ability (D-HAQ), and radiographic joint damage (modified SHS)	The Netherlands	Dutch College of Health Insurances, Schering-Plough B.V. (Houten, the Netherlands) and Centocor Inc. (Horsham, PA, USA)
BROSG trial[9]	Established RA	Other comparisons	RCT	1997	ACR 1987	466	1. Symptomatic treatment (shared care) 2. Aggressive therapy (hospital)	3 years	3 years	HAQ score	UK	HTA
CAMERA[35–37]	Early RA	Other comparisons	RCT	1999	ACR 1987	299	1. Conventional strategy group 2. Intensive strategy group	2 years	2 years	Sustained remission (no swollen joints and any two of number of painful joints ≤ 3, ESR of ≤ 20 mm/hour, VAS general well-being ≤ 20 mm for ≥ 3 months)	The Netherlands	NR
CareRA trial[38–43]	Early RA	Comparison of different treatment protocols	RCT	January 2009	ACR 1987	289 high-risk patients; 90 low-risk patients	High-risk patients: 1. COBRA Classic 2. COBRA Slim 3. COBRA Avant-Garde Low-risk patients: 1. MTX-TSU 2. COBRA Slim	16 weeks	16 week	Proportion of patients in remission (DAS28-CRP of < 2.6) at week 16	Flemish countries	Flemish governmental grant
COBRA-light[44,45]	Early RA	Comparison of different treatment protocols	RCT	March 2008	ACR 1987	164	1. COBRA; COBRA-light	12 months	24 months	Change in DAS44 after 26 weeks of treatment compared with baseline (ΔDAS44)	The Netherlands	The Dutch Top Institute Pharma (TIPharma, Leiden, the Netherlands) and Pfizer (New York City, NY, USA)

Trial acronym or first author and year of publication	RA population	Type of comparison	Study type	Trial start date	RA diagnosis	Sample size (randomised)	Treatment arms for which data extraction performed	Duration of RCT phase	Duration of follow-up	Primary outcome	Geographical location	Funding source
FIN-RACo[46–49]	Early RA	Comparison of different treatment protocols	RCT	April 1993	ACR 1987	199	1. Combination treatment 2. Single-drug treatment	2 years	11 years	Remission – modified version of ACR 1981 definition (no swollen or tender joints)	Finland	Finnish Society for Rheumatology, Rheumatism Research Foundation in Finland, Medical Research Foundation of Turku University Central Hospital and the Finnish Office for Health Care Technology Assessment, Finland
Fransen *et al.*, 2005[50]	Established RA	TTT vs. usual care	Cluster RCT	March 2000	ACR (date NR)	384 (142 in subsample reporting DAS) (24 clusters)	1. DAS28 2. Usual care	24 weeks	24 weeks	Proportion reaching LDA (DAS28 of ≤ 3.2) at week 24 in a subgroup of patients; DMARD treatment changes during 24 weeks, in all patients	The Netherlands	Pfizer
Hodkinson *et al.*, 2015[51]	Early RA	Comparison of different targets	RCT	April 2011	ACR 2010	102	1. SDAI arm; CDAI arm	12 months	12 months	Proportion of patients achieving at least LDA by DAS28 at 12 months	South Africa	Carnegie Corporation (New York, NY, USA) and the Connective Tissue Fund of the University of Witwatersrand, Johannesburg, South Africa
Optimisation of Adalimumab study[52,53]	Established RA	TTT vs. usual care; comparison of different targets	Cluster RCT	August 2006	NR	308 (31 clusters)	1. Routine care 2. DAS28 target 3. SJC target	18 months	18 months	Change in DAS28 between baseline and 12 months of treatment	Canada	Abbott Canada (Abbott Laboratories, Québec, QC, Canada)
Saunders *et al.*, 2008[54]	Early RA	Comparison of different treatment protocols	RCT	February 2003	NR	96	1. Parallel triple therapy 2. Step-up therapy	12 months	12 months	Mean decrease in the DAS28 at 12 months	UK	Chief Scientist Office of the Scottish Executive (Edinburgh, UK)
STREAM[55]	Early RA	TTT vs. usual care	RCT	July 2004	2–5 swollen joints and SHS of < 5	82	1. Aggressive group 2. Conventional care	2 years	2 years	Progression of radiographic joint damage at 2 years	The Netherlands	Abbott (Hoofddorp, the Netherlands)

continued

TABLE 3 Characteristics of included studies (*continued*)

Trial acronym or first author and year of publication	RA population	Type of comparison	Study type	Trial start date	RA diagnosis	Sample size (randomised)	Treatment arms for which data extraction performed	Duration of RCT phase	Duration of follow-up	Primary outcome	Geographical location	Funding source
T-4 study[56,57]	Early RA	TTT vs. usual care; comparison of different targets	RCT	August 2008	ACR 1987	243	1. Routine care 2. DAS28-driven therapy 3. MMP-3-driven therapy 4. DAS28 and MMP-3-driven therapy	56 weeks	56 weeks	Proportion of patients in clinical remission (DAS28 of < 2.6)	Japan	NR
TEAR[58–60]	Early RA	Comparison of different targets; comparison of different treatment protocols	RCT	May 2004	ACR 1987	755	1. Immediate ETN 2. Immediate triple therapy 3. Step-up ETN 4. Step-up triple therapy	102 weeks	102 weeks	Change in DAS28-ESR between week 48 and week 102	USA	Amgen, NIH [study drugs provided by Amgen (Thousand Oaks, CA, USA), Barr Pharmaceuticals (Montvale, NJ, USA) and Pharmacia (Kalamazoo, MIUSA)]
TICORA[61]	Both	TTT vs. usual care	RCT	August 1999	Criteria NR (all patients had a DAS44 of > 2.4)	111	1. Intensive management 2. Routine management	18 months	18 months	Mean fall in DAS, and the proportion of patients with a EULAR good response	UK	Chief Scientist's Office, Scottish Executive (Edinburgh, UK)
U-Act-Early[62]	Early RA	Comparison of different treatment protocols	RCT	January 2010	ACR 1987/2010 or EULAR	317	1. TOC + MTX 2. TOC + PBO–MTX 3. MTX + PBO–TOC	2 years	2 years	Number of patients achieving sustained remission	The Netherlands	Hoffmann-La Roche/ Roche Nederland BV
van Hulst *et al.*, 2010[63]	Both	TTT vs. usual care	Cluster RCT	June 2001	NR	248 (7 clusters)	1. Intervention group 2. Usual-care group	18 months	18 months	Change in DAS28 and the number of medication changes over 18 months	The Netherlands	CVZ/VAZ doelmatigheidsprojecten 'Doelmatigheid Academische Ziekenhuizen' (efficiency projects in academic hospitals)

CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; DAS28-CRP, Disease Activity Score, 28 joints with C-reactive protein concentration; DAS28-ESR, Disease Activity Score, 28 joints with erythrocyte sedimentation rate; D-HAQ, Dutch version of the Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; HTA, Health Technology Assessment; MMP-3, matrix metalloproteinase-; MTX-TSU, methotrexate tight step-up; NIH, National Institutes for Health; NR, not reported; PDN, prednisone; SHS, Sharp/van der Heijde score; VAS, visual analogue scale.

CAMERA trial[35,36,67]). The BROSG trial[9] had two arms: intensive management, which used a DAS44 of ≤ 2.4 target and employed a seven-step treatment protocol based on the target, where patients were seen in a hospital setting; and a routine management arm, which had no target and patients were seen in the community as well as in the clinic, with treatment escalation based on clinical opinion. The CAMERA[35,36,67] trials employed a conventional strategy group and an intensive strategy group, which used (different) compound improvement-based targets, different frequencies of assessment and the same treatment protocol.

Most studies specified a RA diagnosis based on ACR 1987 or 2010 criteria; however, the STREAM trial[55] required patients to have 2–5 swollen joints (and did not require an ACR diagnosis), the TICORA trial[61] required a DAS44 of > 2.4 and RA diagnosis was not reported in the Optimisation of Adalimumab study,[52,53] Saunders *et al.*[54] or van Hulst *et al.*[63] Sample sizes ranged from 82 to 755 participants and study durations (randomised phase) ranged from 24 weeks to 3 years. Six trials took place in the Netherlands,[26–37,44,45,50,55,62,63] three in the UK,[9,54,61] one in Flemish countries (actual countries were not stated),[38–43] one in Finland,[46–49] one in South Africa,[51] one in Canada,[52,53] one in Japan[56,57] and one in the USA.[58–60]

Risk-of-bias assessment

Risk-of-bias judgements for included non-cluster randomised controlled trials

A summary of the risk-of-bias judgements for the included non-cluster RCTs is presented in *Figure 3*, with details presented in *Table 4*.

None of the included non-cluster RCTs was rated as being at high risk of bias for random sequence generation. Only one RCT was rated as being at low risk of bias for allocation concealment.[58] The remaining RCTs were rated as having an unclear risk for this domain.[9,30,36,41,44,46,51,54,55,57,61] Nine RCTs were rated as having a high risk of bias for blinding of participants and personnel,[9,36,41,44,46,54,55,57,61] and one RCT was rated as having an unclear risk for this domain.[30] Only one RCT was rated as having a low risk for this domain.[58] It should, however, be borne in mind that in most cases it would be difficult for patients to be blinded, given the differences in treatment approach between trial arms in most trials. Seven RCTs were rated as having a low risk of bias for blinded outcome assessment,[9,30,44,54,55,58,61] four RCTs were rated as having a high risk of bias[41,46,51,57] and one RCT[36] was rated as having an unclear risk for this domain. Four RCTs reported withdrawals of > 10% and were rated as having a high risk of attrition bias.[9,36,57,58] The remaining RCTs were rated as having a low risk of bias for this domain.[9,36,57,58] Trial protocols were unavailable for six RCTs that were rated as having an unclear risk of selective reporting.[9,36,46,51,57,61] Three RCTs were rated as having a low risk of bias for this domain[30,41,54] and three were rated as having a high risk of bias, as some outcomes were not reported in either the protocol[44,55] or the methods section of the trial report[58]. Based on the judgements for allocation concealment, blinded outcome assessment and attrition domains (see *Quality assessment strategy*), six RCTs were rated as having an overall high risk of bias[36,41,46,51,57,58] and five RCTs were rated as having an overall unclear risk of bias.[9,30,44,54,55] Only one RCT was rated as having an overall low risk of bias.[61]

Risk-of-bias judgements for included cluster randomised controlled trials

A summary of the risk-of-bias judgements for the included cluster RCTs is presented in *Figure 4*, with the details presented in *Table 5*.

Two of the included cluster RCTs were rated as being at low risk of bias for random sequence generation[50,52] and one[63] was rated as being at unclear risk for this domain. All three cluster RCTs were rated as being at unclear risk of bias for allocation concealment.[50,52,63] All three cluster RCTs were rated as being at high risk of bias for blinding of participants and personnel.[50,52,63] One cluster RCT was rated as being at high risk of bias for blinded outcome assessment,[63] whereas the other two cluster RCTs were rated as being at unclear risk for this domain.[50,52] All three cluster RCTs were rated as being at high risk of attrition bias (> 10% participants withdrawing).[50,52,63] A trial protocol was not available for two cluster RCTs that were rated as being at unclear risk of bias for selective reporting.[50,63] One cluster RCT was rated as being at high risk of bias for this domain, as AEs that were reported as an outcome in the trial protocol

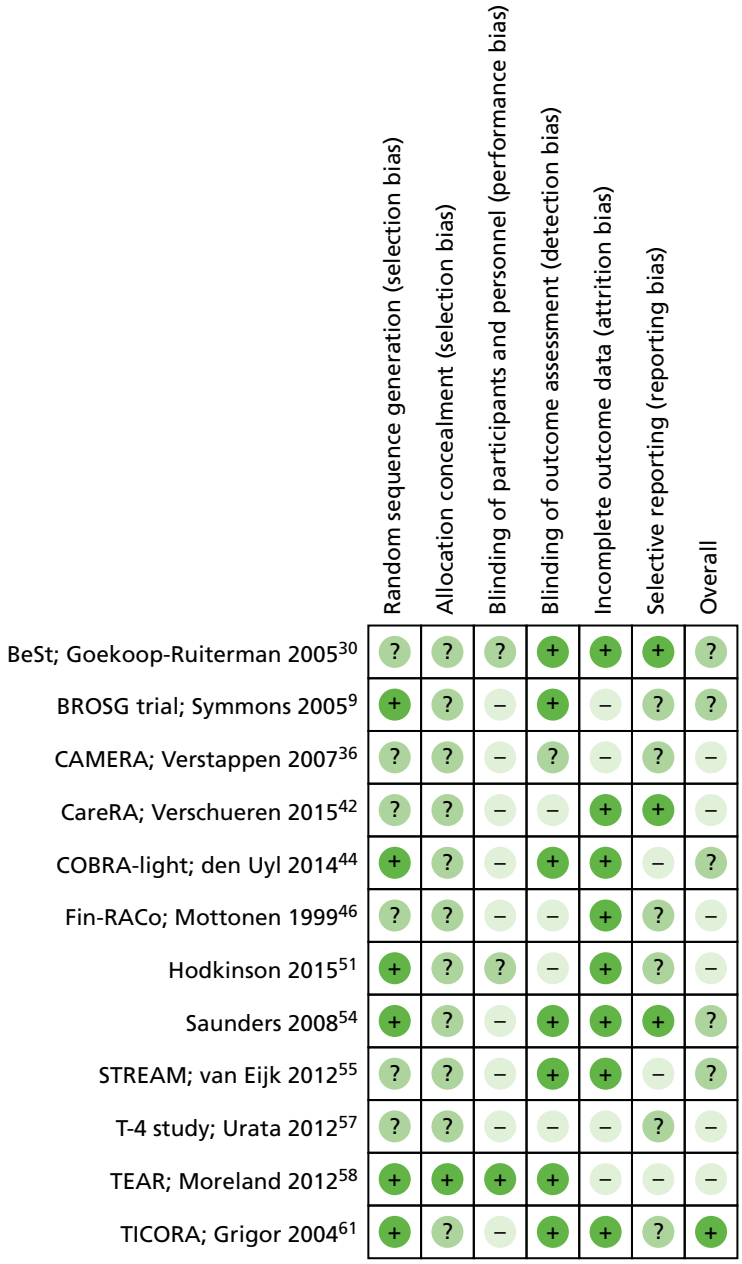

FIGURE 3 Risk-of-bias judgements for included non-cluster RCTs. +, low risk of bias; –, high risk of bias; ?, unclear risk of bias.

were not included in the trial report.[52] Two RCTs reported that participant recruitment occurred after clusters were randomised to treatment allocation, thus these trials were rated as being at high risk of bias for cluster recruitment bias.[50,52] The remaining cluster RCT was rated as being at unclear risk of bias for this domain.[63] Two cluster RCTs reported statistical methods to accommodate for baseline differences across clusters and rated as being at low risk of bias for cluster baseline differences.[50,52] The remaining cluster RCT was rated as being at unclear risk for this domain.[63] One cluster RCT reported that DAS28 outcomes were available for only a subset of the original clusters that were randomised. This RCT was rated as being at high risk of bias for cluster attrition.[50] The other two cluster RCTs were rated as being at unclear risk for this domain.[52,63] All three included cluster RCTs rated as being at an overall high risk of bias.[50,52,63]

TABLE 4 Risk-of-bias judgements for included non-cluster RCTs

Trial acronym; first author and year of publication	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall rating and reason
BeSt; Goekoop-Ruiterman *et al.*, 2005[30]	Unclear: method of random sequence generation not reported	Unclear risk: closed envelopes used but not reported if opaque and sequentially numbered	Unclear risk: blinding of participants and personnel not reported	Low risk: assessors were blinded	Low risk: < 10% withdrew from each group	Low risk: all outcomes in online protocol (reported in van der Kooij 2009[68]) reported	Unclear: allocation method not reported
BROSG trial; Symmons *et al.*, 2005[9]	Low risk: using a minimisation computer program	Unclear: concealment of allocation not reported	High risk: not blinded	Low risk: reported as observer blinded	High risk: > 10% withdrew from both arms	Unclear risk: protocol details 'Not provided at time of registration' from the ISRCTN	Unclear: allocation method not reported
CAMERA; Verstappen *et al.*, 2007[36]	Unclear: method of random sequence allocation not reported	Unclear: reports allocation performed by an independent person, but method not reported	High: patients and clinicians not blinded (not possible, two different monitoring/ treatment strategies)	Unclear: radiographs scored independently by blinded assessors, unclear on other outcomes	High: 31% withdrew	Unclear: no protocol available	High risk: attrition bias
CareRA; Verschueren *et al.*, 2015[42]	Unclear: method of random sequence generation not reported	Unclear: concealment of allocation not reported	High risk: reports that no blinding was implemented	High risk: reports that no blinding was implemented	Low risk: < 10% withdrew from each group	Low risk: all outcomes in online protocol reported	High risk: outcome assessment not blinded
COBRA-light; den Uyl *et al.*, 2014[44]	Low risk: online randomisation software was used	Unclear risk: sequentially numbered envelopes were used, but not reported if sealed and opaque	High risk: reported as open label	Low risk: reports that to minimise influence performed by trained research nurses uninvolved in the routine care	Low risk: < 10% withdrew from each group	High risk: radiological progression reported as an outcome in the protocol, but not reported in publication. Publication states that this outcome will only be reported at 12 months	Unclear: allocation method not reported
Fin-RACo; Mottonen *et al.*, 1999[46]	Unclear: method of sequence generation not reported	Unclear risk: centrally organised, numbered envelopes, but not reported if sequentially numbered and opaque	High risk: open label	High risk: clinical measures not blinded	Low risk: < 10% lost from each group	Unclear: no protocol available	High risk: outcome assessment not blinded

continued

TABLE 4 Risk-of-bias judgements for included non-cluster RCTs (*continued*)

Trial acronym; first author and year of publication	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall rating and reason
Hodkinson *et al.*, 2015[51]	Low: computer-generated sequence	Unclear: concealment of allocation not reported	Unclear: blinding of patients and personnel not reported	High: outcome assessment not blinded	Low risk: < 10% lost from each group	Unclear: no protocol available	High risk: outcome assessment not blinded
Saunders *et al.*, 2008[54]	Low risk: randomisation software used	Unclear: concealment of allocation not reported	High risk: single-blind study (only outcome assessment blind)	Low risk: metrologist was blinded to treatment allocation; also radiologists assessing Sharp score were blinded	Low risk: < 10% attrition both groups	Low risk: outcomes in online protocol reported	Unclear: allocation method not reported
STREAM; van Eijk *et al.*, 2012[55]	Unclear: method of random sequence allocation not reported	Unclear: concealment of allocation not reported	High risk: described as single blind	Low: DAS and radiographs assessed by blinded assessors	Low risk: < 10% lost from each group	High risk: QoL in protocol but not in paper; everything else as per protocol	Unclear: allocation method not reported
T-4 study; Urata *et al.*, 2012[57]	Unclear risk: sequence generation not reported	Unclear: concealment of allocation not reported	High risk: reported limitation that study was 'open'	High risk: primary outcome DAS assessed by physicians not radiologists	High risk: > 10% withdrew from groups 2 and 4; reasons not stated	Unclear risk: trial registration not reported, unable to locate protocol	High risk: attrition bias
TEAR; Moreland *et al.*, 2012[58]	Low risk: treatment was allocated via a computerised data entry system	Low risk: treatment was allocated via a computerised data entry system	Low risk: all subjects and site personnel (including the treating rheumatologists) were blinded (for the duration of the trial) to treatment assignment and change to active medication at the step-up period	Low risk: all subjects and site personnel (including the treating rheumatologists) were blinded (for the duration of the trial) to treatment assignment and change to active medication at the step-up period	High risk: > 10% withdrew from all groups	High risk: methods state SF-12 used to assess HRQoL, but no results presented	High risk: attrition bias
TICORA; Grigor *et al.*, 2004[61]	Low risk: randomisation software used	Unclear risk: treating doctor telephoned an administrative co-ordinator, but not reported if the allocation was concealed	High risk: only the assessors were blind 'single blind'	Low risk: a metrologist assessed patients from both groups, unaware of participants' assigned treatment groups	Low risk: < 10% lost from each group	Unclear: no protocol available	Low risk: allocation, assessor blinding and attrition all low risk

DAS, Disease Activity Score; HRQoL, health-related quality of life; ISRCTN, International Standard Randomised Controlled Trial Number; QoL, quality of life; SF-12, Short Form questionnaire-12 items.

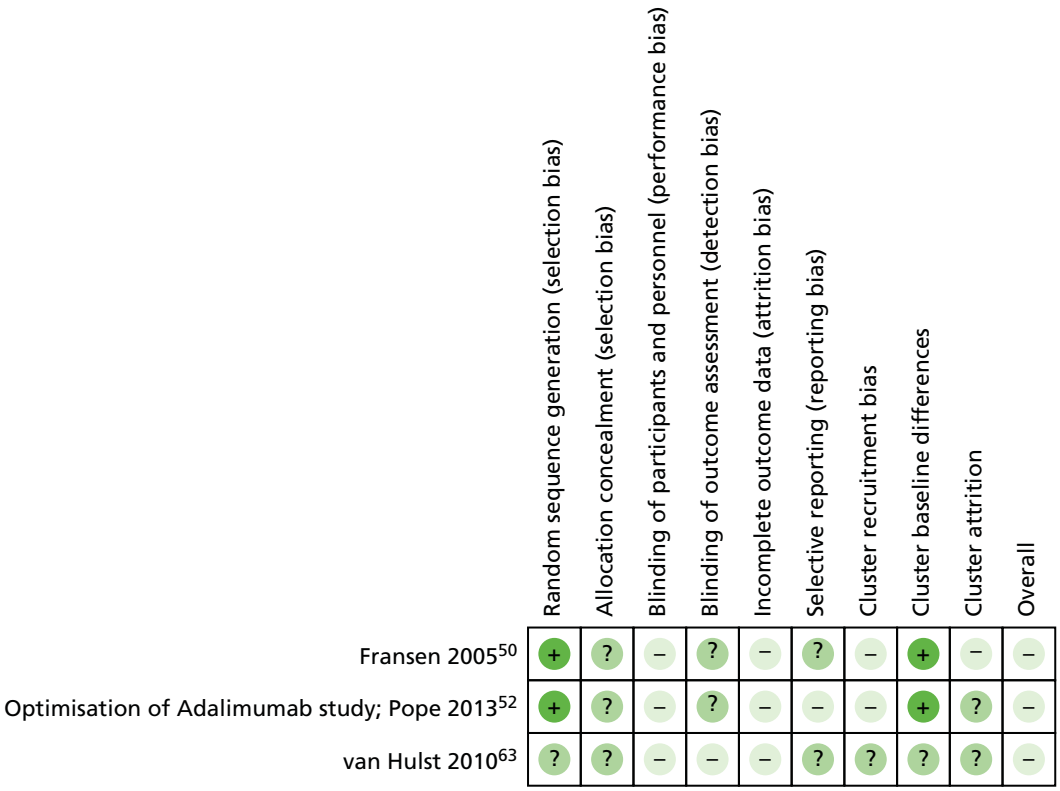

FIGURE 4 Risk-of-bias judgements for included cluster RCTs. +, low risk of bias; –, high risk of bias; ?, unclear risk of bias.

Assessment of characteristics of individual study arms

We considered the features of each arm of the included studies, with a view to drawing out common features across them. If strategies in different study arms are considered sufficiently similar, that would allow a grouping of TTT 'types' and subsequent analysis at this group level, drawing on evidence from more than one study.

Tables 6–13 display information about each of the study types. We report information on (1) the treatment target, (2) the treatment protocol and (3) the frequency of clinician contacts with the patient. For point 3, the focus is on the frequency of visits during the period while the patient has not achieved the target, as less frequent assessment is often required once target is achieved. These are considered to be the key distinguishing features of 'TTT' strategies as a whole.

In addition, study arms were grouped together using a broad categorisation of the treatment protocol. This approach was taken by the NICE clinical guideline for RA,[4] where the focus was purely on treatment protocols using conventional DMARDs in early disease. We used the following eight classification categories.

Sequential monotherapy without a treatment target

Study arms in this classification would typically be control arms in studies compared with other TTT strategies. The arms identified within this classification category are included in *Table 6*.

Sequential disease-modifying antirheumatic drug monotherapy, or no treatment protocol, with a treatment target

This refers to study arms that could be seen as comprising only a limited component of 'TTT', the weakest form of TTT strategy feasible under our definition of TTT. The arms identified within this classification category are included in *Table 7*.

TABLE 5 Risk-of-bias judgements for included cluster RCTs

Trial acronym; first author and year of publication	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Cluster recruitment bias	Cluster risk of baseline differences	Cluster attrition	Overall rating and reason
Fransen *et al.*, 2005[50]	Low risk: random number generator used to allocate the centres randomly to DAS (12 centres) or UC (12 centres)	Unclear risk: not reported if clusters were randomised at the same time	High risk: single blind	Unclear risk: reports as the participating physicians could not be blinded, it was necessary to measure the DAS28 independently. However, unclear if the independent assessors were blind to treatment allocation	High risk: > 10% withdrew from both groups	Unclear risk: study protocol not available (Dr Jaap Fransen, Radboud University Medical Center, 2016, personal communication)	High risk: centre allocation remained concealed until the start of patient recruitment	Low risk: randomisation took place in two strata: one stratum comprised the participating centres in the predetermined region; the other of all other participating centres. The data were analysed using linear regression with random coefficients (mixed models), correcting for clustering of the data in centres	High risk: only three DAS and four UC centres provided DAS assessments	High risk of recruitment bias, performance bias and participant attrition bias
Optimisation of Adalimumab study; Pope *et al.*, 2013[52]	Low risk: using a computer-generated, site-stratified blocked schedule that assigned physicians from the same geographic region to one of the three groups	Unclear risk: not reported if clusters were randomised at the same time	High risk: only patients blinded	Unclear: not reported	High risk: > 10% withdrew from all groups	High risk: AEs classified according to MedDRA as in the NCT protocol not reported	High risk: physician randomisation took place prior to initiation of enrolment	Low risk: reports clusters were randomised using a site-stratified blocked schedule and models were used with shared frailty to account for the clustered design considering baseline covariates	Unclear risk: loss of clusters not reported	High risk of recruitment bias, performance bias, participant attrition bias and selective reporting
van Hulst *et al.*, 2010[63]	Unclear: method of random sequence allocation not reported	Unclear risk: not reported if clusters were randomised at the same time	High risk: clinicians not blinded	High risk: DAS28 assessment not blinded, HAQ blinding unclear, medication changes blinded	High: attrition was 4% in intervention group, but 12% in usual-care group	Unclear: no protocol available	Unclear risk: not reported if rheumatologists recruited patients before or after randomisation	Unclear: baseline comparability of clusters not reported	Unclear risk: loss of clusters not reported	High as a result of selection bias, differential attrition, unclear blinding and unclear randomisation

DAS, Disease Activity Score; MedDRA, Medical Dictionary for Regulatory Activities; UC, usual care.

TABLE 6 Categorisation of included study arms: sequential monotherapy (or no protocol provided) with a target

Trial acronym or first author and year of publication	Description of target	Protocol	Frequency of assessments
BeSt[26–34]	Treatment adjustments were made every 3 months in an effort to obtain a DAS44 of ≤ 2.4. Remission was defined as a DAS44 of < 1.6	1. 15 mg/week of MTX, increased to 25–30 mg/week if the DAS44 was > 2.4. Subsequent steps for patients with an insufficient response were: 2. 2000–3000 mg/day of SSZ monotherapy 3. 20 mg/day of LEF monotherapy 4. 3–10 mg/kg of MTX with IFX every 8 weeks intravenously (IFX) 5. 50 mg/week intramuscular gold with 120 mg of intramuscular methylprednisolone 6. 2.5 mg/kg/day of MTX with ciclosporin A and 7.5 mg/day of PDN	3 months
Optimisation of Adalimumab study[52,53]	A DAS28 of < 2.6 in the DAS-targeted arm and a SJC of 0 in the SJC-targeted arm	1. There was no specified drug algorithm for any physician, as many patients had tried two or more DMARDs before receiving ADA in routine care 2. Physicians were encouraged to make treatment changes in patients when the target was not achieved 3. The dose of ADA 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 DMARDs, intra-articular steroid injections and oral or intramuscular steroids	0, 6, 12 and 18 months. Assessments at 2, 4 and 9 months were also recommended
Symmons *et al.*, 2005[9]	To control joint pain, stiffness and related symptoms	NSAIDs, intra-articular steroid injections (up to a maximum of one per month), DMARDs (antimalarials, SSZ, intramuscular gold, penicillamine, azathioprine, MTX, LEF) and low-dose steroids (≤ 7.5 mg daily). Non-drug modalities, such as physiotherapy referral, were also used as the GP felt appropriate. DMARD therapy was monitored using the standard guidelines in current use in the five centres	Every 4 months
Fransen *et al.*, 2005[50]	A DAS28 of ≤ 3.2	Systematic monitoring of disease activity by assessment of the DAS28 by the treating rheumatologist. According to the study guidelines the aim was to reach a DAS28 of ≤ 3.2 (LDA) by changing DMARD treatment if the score was > 3.2	Systematic monitoring of disease activity was carried out at weeks 0, 4, 12 and 24
van Hulst *et al.*, 2010[63]	A DAS28 of ≤ 3.2	None	3 months

DAS, Disease Activity Score; GP, general practitioner; PDN, prednisone.

Steroid step-down, disease-modifying antirheumatic drug step-up combination

Study arms classified in this group involved initial combination therapy with steroids and non-bDMARDs (either alone or in combination), with the option of increasing the dose or adding in DMARDs. The steroid dose is tapered downwards over time. The arms identified within this classification category are included in *Table 8*.

TABLE 7 Categorisation of included study arms: sequential monotherapy without a target

Trial acronym or first author and year of publication	Target	Protocol	Frequency of assessments
TICORA[61]	A DAS44 of ≤ 2.4	DMARD monotherapy was given in patients with active synovitis. 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 corticosteroid were given to patients assigned routine care with the same restrictions as those in the intensive group	3 months
T-4 study[56,57]	A DAS28 of < 2.6 (DAS-targeted arm);a MMP-3 concentration of < 121 ng/ml (men)/ < 59.7 ng/ml (women) (MMP-3-targeted arm); and a DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml (men)/ < 59.7 ng/ml (women) (combined DAS- and MMP-3-targeted arm)	1. 1 g/day SSZ plus 4 mg/week of MTX (the dosage of was not changed if the patient had responded compared with the previous visit) otherwise 2. The dosage was increased in a stepwise manner to a maximum of 8 mg/week if patient had not responded. Change of therapy based on improvement in the number of tender joints (0–28), swollen joints (0–26) and concentration of CRP from pre-assessment values, without access to current DAS28 and MMP-3 values 3. If the maximum tolerable dose of MTX that introduced a dose-dependent side effect was reached and the patient still did not fulfil sustained response, 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 TNF blocker dose increased, or the interval for TNF administration was shortened DMARDs (including bucillamine,[a] intramuscular gold, sodium thiomalate, tacrolimus and LEF) were given as allowed by the rheumatologist at all times. Combination therapy with DMARDs other than MTX was allowed for two kinds of agents. Intra-articular GC (to a maximum of 10 mg of triamcinolone acetonide on a single visit) was permitted for persistently swollen and tender joints	20, 24, 28, 32, 36, 40, 44, 48, 52 and 56 weeks
CAMERA[35,36,67]		1. 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 2. The dosage was increased stepwise by 5 mg/week, to a maximum of 30 mg/week 3. If the maximum (tolerable) dose of MTX was reached and patients did not fulfil the criteria for sustained response	3 months

TABLE 7 Categorisation of included study arms: sequential monotherapy without a target (*continued*)

Trial acronym or first author and year of publication	Target	Protocol	Frequency of assessments
		4. MTX was administered subcutaneously. For patients on subcutaneous MTX 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	
STREAM[55]		The following order of drugs was suggested to the treating rheumatologist: HCQ, SSZ, MTX and LEF	3 months
Fransen *et al.*, 2005[50]		No guideline to adapt treatment strategy was supplied	
van Hulst *et al.*, 2010[63]			3 months
FIN-RACo[46–49]		1. Prednisolone up to 10 mg was allowed in patients with continuously active disease, but simultaneous use of multiple DMARDs was not allowed. The decision to use prednisolone was made by the treating physician. The patients were treated continuously with one DMARD alone, with or without prednisolone and, if a more beneficial effect was needed, the dose was increased or the DMARD was changed 2. SSZ (2 g daily) was used as the initial drug in all patients and the dose was increased to 3 g daily at 3 months if clinically indicated 3. If an AE occurred, or if the clinical response was < 25% at 6 months, SSZ was replaced with MTX (7.5–15 mg weekly). As the third DMARD, azathioprine (2 mg/kg daily), auranofin, HCQ, injectable gold, penicillamine or podophyllotoxin could be used alternatively after azathioprine	Baseline and at months 1, 3, 4, 5, 6, 9, 12, 18 and 24

DAS, Disease Activity Score; MMP-3, matrix metalloproteinase 3; TNF, tumour necrosis factor.
a Bucillamine is similar to penicillamine.

TABLE 8 Categorisation of included study arms: steroid step-down, DMARD step-up combination

Trial acronym or first author and year of publication	Description of target	Protocol	Frequency of assessments
den Uyl *et al.*, 2013[69]	A DAS44 of < 1.6	60 mg/day prednisolone (tapered to 7.5 mg/day in 6 weeks), 7.5 mg/week of MTX and 1 g/day of SSZ (increased to 2 g/day after 1 week). MTX increased to 25 mg/week after 13 weeks of treatment if the DAS44 was ≥ 1.6	3 months
	A DAS44 of < 1.6	1. 30 mg/day of prednisolone, tapered to 7.5 mg/day in 9 weeks and 10 mg/week of MTX with stepwise increments in all patients to 25 mg/week in 9 weeks 2. Parenteral MTX after 13 weeks if the DAS44 is ≥ 1.6	3 months
CareRA[42]	A DAS28-CRP of < 3.2	15 mg of MTX weekly, 2 g of SSZ daily and a weekly step-down scheme of oral GCs (60 mg to 40 mg to 25 mg to 20 mg to 15 mg to 10 mg to 7.5 mg PDN)	Baseline, 4, 8 and 16 weeks. If a treatment adjustment was required at week 8, an optional visit was held at week 12
	A DAS28-CRP of < 3.2	15 mg of MTX weekly with a weekly step-down scheme of oral GCs (30 mg to 20 mg to 12.5 mg to 10 mg to 7.5 mg to 5 mg PDN)	
	A DAS28-CRP of < 3.2	15 mg of MTX weekly, 10 mg of LEF daily and a weekly step-down scheme of oral GCs (30 mg to 20 mg to 12.5 mg to 10 mg to 7.5 mg to 5 mg PDN)	

DAS28-CRP, Disease Activity Score, 28 joints with C-reactive protein concentration; PDN, prednisone.

Step-up disease-modifying antirheumatic drugs to biologics

In this classification the treatment protocols start patients on non-bDMARDs and outline increases in dose and/or combinations with other DMARDs, with the option of switching to bDMARDs as part of the sequence. The arms identified within this classification category are included in *Table 9*.

Step-up combinations not including to biologics

Similar to the previous set of treatment protocols, study arms in this category start patients on a non-bDMARD and subsequently allow increases in dose and/or combinations with other non-bDMARDs and steroids. The arms identified within this classification category are included in *Table 10*.

Combination disease-modifying antirheumatic drugs plus steroids

Patients are treated from the outset with two non-bDMARDs and steroids. Adjustments to treatments do not allow bDMARDs. The arms identified within this classification category are included in *Table 11*.

Disease-modifying antirheumatic drug and biologic combinations

Treatments for patients from the beginning of the protocol include both bDMARDs and non-bDMARDs in combination. The arms identified within this classification category are included in *Table 12*.

Triple disease-modifying antirheumatic drug therapy

Three non-bDMARDs are used in combination from the outset. The arms identified within this classification category are included in *Table 13*.

Even with this relatively large number of TTT treatment strategy classifications (which are designed to differ in terms of the treatment protocol, except for the control arms of studies), there is substantial variation.

TABLE 9 Categorisation of included study arms: step-up DMARDs, including to biologics

Trial acronym	Description of target	Protocol	Frequency of assessments
T-4 study57,[57]	A DAS28 of < 2.6	1. 1 g/day of SSZ plus oral 4 mg/week of MTX – the dosage of was not changed if the patient had responded compared with the previous visit otherwise	Variable, but approximately monthly
	A MMP-3 concentration of < 121 ng/ml for men and < 59.7 ng/ml for women	2. The dosage of oral MTX was increased in a stepwise manner to a maximum of 8 mg/week if patient had not responded. Change of therapy based on improvement in the number of tender joints (0–28), swollen joints (0–26) and concentration of CRP from pre-assessment values, without access to current DAS28 and MMP-3 values	
	A DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml for men and < 59.7 ng/ml for women	3. If the maximum tolerable dose of MTX that introduced a dose-dependent side effect was reached and the patient still did not fulfil a sustained response, TNF blockers were allowed. If patients on the administration of TNF blockers did not show improvement compared with the previous measurement, TNF blockers were changed to another biological agent, or the TNF blocker dose increased, or the interval for TNF administration was shortened. Maximum dosages were 1 g/day of SSZ, 20 mg/day of LEF, 300 mg/day of bucillamine,[a] 25 mg/week of gold sodium thiomalate, 3 mg/day of tacrolimus hydrate, 10 mg/kg bimonthly or 6 mg/kg monthly of IFX, 50 mg/week of ETN, 40 mg of ADA fortnightly and 8 mg/kg of TOC monthly. DMARDs including bucillamine,a gold sodium thiomalate, tacrolimus and LEF were given, as allowed by the rheumatologist at all times. Combination therapy with DMARDs other than MTX was allowed for two kinds of agents. Intra-articular GC (to a maximum of 10 mg of triamcinolone acetonide on a single visit) was permitted for persistently swollen and tender joints	
STREAM[55]	Remission (a DAS44 of < 1.6)	Treatment was started with 15 mg/week of oral MTX. If the DAS was ≥ 1.6 at a given time point: 1. There was an increase in MTX to 25 mg/week; 25 mg/week of MTX combined with 40 mg/2 weeks of ADA 2. 25 mg/week of MTX combined with 40 mg/week of ADA 3. A combination of 25 mg/week of MTX, 2000 mg/day of SSZ and 400 mg/day of HCQ 4. A combination of 25 mg/week of MTX, 2000 mg/day of SSZ, 400 mg/day of HCQ and 7.5 mg/day of PDN 5. 20 mg/day of LEF and 50 mg/week of intramuscular gold	3-monthly

continued

TABLE 9 Categorisation of included study arms: step-up DMARDs, including to biologics (*continued*)

Trial acronym	Description of target	Protocol	Frequency of assessments
		If the DAS was < 1.6 at one time point the treatment remained unchanged. If the DAS was < 1.6 at two consecutive time points the following actions were taken, depending on the stage of the treatment protocol: 1. 15 mg/week of MTX was decreased from 2.5 mg/2 weeks to 0 mg/week after 3 months 2. 25 mg/week of MTX was decreased from 2.5 mg/2 weeks to 10 mg/week after 3 months 3. 40 mg/2 weeks of ADA was stopped 4. 40 mg/week of ADA was decreased to 40 mg/2 weeks 5. HCQ was decreased from 200 mg/8 weeks to 0 mg If remission was sustained after 3 months, SSZ was decreased subsequently from 500 mg/4 weeks to 0 mg. If remission was sustained after 3 months: 1. MTX was decreased from 2.5 mg/2 weeks to 0 mg 2. 7.5 mg/day of PDN was decreased to 0 mg in 7 weeks 3. LEF was decreased to 10 mg/day If remission was sustained after 3 months: 1. LEF was stopped 2. Gold was decreased to 50 mg/2 weeks If DAS remained < 1.6, gold was decreased to 50 mg/4 weeks; if remission was sustained, gold was stopped. If at any time point the DAS was ≥ 1.6, the last effective treatment was restarted. In case of intolerance to a DMARD, the highest tolerated dose was used and, if the DAS was ≥ 1.6 at the next visit, the patient went on to the next step	
TEAR[58–60]	A DAS28-ESR of ≥ 3.2	Oral MTX, escalated to a dosage of 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12. Corticosteroid use at entry tapered. If the DAS28-ESR was ≥ 3.2 at week 14, patients were stepped up to MTX plus SSZ at a dosage of 500 mg twice daily, escalated (if tolerated) to 1000 mg twice daily at 6 weeks, plus HCQ at a dosage of 200 mg twice daily	

DAS, Disease Activity Score; DAS28-ESR, Disease Activity Score, 28 joints with erythrocyte sedimentation rate; MMP-3, matrix metalloproteinase 3; PDN, prednisone; TNF, tumour necrosis factor.
a Bucillamine is similar to penicillamine.

TABLE 10 Categorisation of included study arms: step-up combinations not including to biologics

Trial acronym or first author and year of publication	Description of target	Protocol	Frequency of assessments
BeSt[26–34]	Treatment adjustments were made every 3 months in an effort to obtain a DAS44 of ≤ 2.4. Remission was defined as a DAS44 of < 1.6	1. 15 mg/week of MTX, increased to 25–30 mg/week if the DAS44 was > 2.4. If response to therapy was still insufficient, SSZ was added, followed by the addition of 2. 400 mg/day of HCQ and then by PDN Patients whose disease failed to respond to the combination of these four drugs subsequently switched to MTX with IFX, MTX with ciclosporin and PDN, and finally to 20 mg/day LEF	3 months
TICORA[61]	A DAS44 of ≤ 2.4	Escalation of DMARDs in patients with persisting disease activity: 1. 500 mg of SSZ daily, increasing every week to a target dose of 40 mg/kg per day 2. 40 mg/kg per day of SSZ; 7.5 mg/week of MTX; 5 mg per week of folic acid; 200–400 mg/day of HCQ 3. Triple therapy with monthly increments of MTX by 2.5–5.0 mg per week (maximum 25 mg/week) 4. Triple therapy with weekly 500-mg increments of SSZ dose (maximum 5 g/day in divided doses if tolerated) 5. Addition of prednisolone in enteric-coated tablets, 7.5 mg daily 6. Change triple therapy to 2–5 mg/kg per day of ciclosporin; 25 mg/week of MTX; and 5 mg/week of folic acid. Change to DMARD (LEF or sodium aurothiomalate; dose NR, route of administration NR)	Monthly
FIN-RACo[46–49]	ACR remission	Combination therapy started with: 1. 500 mg of SSZ twice daily, 7.5 mg of MTX weekly, 300 mg of HCQ daily and 5 mg daily of prednisolone for 3 months 2. If the clinical improvement was < 50% in at least two of swollen joints, tender joints and ESR or CRP, then MTX and prednisolone increased to 10 mg weekly and 7.5 mg daily 3. The protocol allowed flexible subsequent dose adjustments to mimic clinical practice. The highest dose at 9 months and thereafter was 2 g daily of SSZ, 15 mg weekly of MTX, 300 mg daily of HCQ and 10 mg daily of prednisolone 4. If remission was achieved during the first year with the initial combination, the drug doses were tapered and prednisolone and MTX could even be discontinued at 9 and 18 months. SSZ (1 g daily) and HCQ (300 mg daily) had to be continued until the end of the study	Baseline and at months 1, 3, 4, 5, 6, 9, 12, 18 and 24

continued

TABLE 10 Categorisation of included study arms: step-up combinations not including to biologics (*continued*)

Trial acronym or first author and year of publication	Description of target	Protocol	Frequency of assessments
		5. If remission was achieved during the first year, but not with the initial combination, drug doses were gradually tapered to those of the second year 6. If the induced remission was lost, DMARD doses were increased with the intention of reaching remission. If one or several components of the combination had to be discontinued, a combination of three DMARDs was restarted by replacing SSZ and HCQ with auranofin (3–6 mg daily) and MTX with azathioprine (2 mg/kg daily). Other DMARDs could also be used as substitutes	
Saunders *et al.*, 2008[54]	A DAS28 of < 3.2	1. SSZ (target dosage 40 mg/kg/day in divided doses) 2. After 3 months, if the DAS28 remained > 3.2, MTX was added (7.5 mg/week, increased monthly to a maximum of 25 mg/week, as above). After the maximum tolerated dose of MTX was reached, 400 mg/day HCQ was added in patients with persistent disease activity	Monthly
CAMERA[35,36,67]	20%, 50% responses based on ESR, SJC, TJC and VAS of overall well-being	1. 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 2. The dosage was increased stepwise by 5 mg/week, to a maximum of 30 mg/week 3. If the maximum (tolerable) dose of MTX was reached and patients did not fulfil the criteria for sustained response 4. MTX was administered subcutaneously. For patients on subcutaneous MTX 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	

TABLE 10 Categorisation of included study arms: step-up combinations not including to biologics (*continued*)

Trial acronym or first author and year of publication	Description of target	Protocol	Frequency of assessments
Symmons *et al.*, 2005[9]	The goal was to control joint pain, stiffness and related symptoms and to suppress clinical and laboratory evidence of inflammation. CRP concentrations below twice the upper limit of normal	NSAIDs, intra-articular steroid injections (up to a maximum of one per month), DMARDs (antimalarials, SSZ, intramuscular gold, penicillamine, azathioprine, MTX, LEF) and low-dose steroids (≤ 7.5 mg daily) plus, if necessary, ciclosporin, parenteral steroids, medium-dose oral steroids (up to 10 mg daily) and cyclophosphamide	Every 4 months
TEAR[58–60]	A DAS28-ESR of ≥ 3.2	Oral MTX, escalated to a dosage of 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12. Corticosteroid use at entry tapered. If the DAS28-ESR was ≥ 3.2, patients were stepped up to triple therapy (MTX + SSZ + HCQ)	Every 6 weeks for 48 weeks, then every 12 weeks
Hodkinson *et al.*, 2015[51]	A SDAI of ≤ 11 (LDA)	15 mg/week of MTX, increased to 20 mg and then 25 mg	Monthly (3 months) then every 3 months
	A CDAI of ≤ 10 (LDA)	If this failed, triple therapy of 1000 mg/day of SSZ and 200 mg/day of chloroquine in combination with 25 mg/week of MTX was introduced	

CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score, 28 joints with erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; NR, not reported; PDN, prednisone; VAS, visual analogue scale.

TABLE 11 Categorisation of included study arms: combination DMARDs plus steroids

Trial acronym	Protocol		Frequency of assessments
BeSt[26–34]	Treatment adjustments were made every 3 months in an effort to obtain a DAS44 of ≤ 2.4. Remission was defined as a DAS44 of < 1.6	1. 7.5 mg/week of MTX, 2000 mg/day of SSZ and 60 mg/day of PDN (the last of which was tapered in 7 weeks to 7.5 mg/day). If DAS44 was > 2.4 2. MTX was augmented to 25–30 mg/week and, if the response was still insufficient, the combination was replaced by MTX with ciclosporin and PDN, followed by MTX with IFX, LEF monotherapy, gold with methylprednisolone, and finally by 2–3 mg/kg/day azathioprine with PDN In the case of a persistent DAS44 of > 2.4, first PDN was tapered to 0 mg after 28 weeks and then MTX was tapered to 0 mg after 40 weeks	3 months

PDN, prednisone.

TABLE 12 Categorisation of included study arms: DMARD biologic combination

Trial acronym	Description of target	Protocol	Frequency of assessments
BeSt[26–34]	Treatment adjustments were made every 3 months in an effort to obtain a DAS44 of ≤ 2.4. Remission was defined as a DAS44 of < 1.6	1. 25–30 mg/week of azathioprine with 3 mg/kg of azathioprine at weeks 0, 2 and 6 and every 8 weeks thereafter. After 3 months, if DAS44 was > 2.4: 2. IFX was increased to 6 mg/kg every 8 weeks. Extra DAS44 calculations for dose adjustments were performed every 8 weeks within 1 week before the next infusion of IFX. If the DAS44 was > 2.4 3. The dose of the next infusion was increased to 7.5 mg/kg every 8 weeks and then to 10 mg/kg every 8 weeks If patients still had a DAS44 of 2.4 while receiving MTX with 10 mg/kg of IFX, they switched to SSZ, then to LEF, then to the combination of MTX, ciclosporin, and PDN, then to gold with methylprednisolone, and, finally, to azathioprine with PDN. If three was a persistent good response of DAS44 of < 2.4 for at least 6 months, IFX was reduced from 10 mg/kg to 7.5 mg/kg to 6 mg/kg and then to 3 mg/kg every next infusion until stopped	3 months
Optimisation of Adalimumab study[52,53]	A DAS28 of < 2.6 in the DAS-targeted arm and a SJC of 0 in the SJC-targeted arm	1. There was no specified drug algorithm for any physician because many patients had tried two or more DMARDs before receiving ADA in routine care 2. Physicians were encouraged to make treatment changes in patients when the target was not achieved 3. The dose of ADA was not increased beyond subcutaneous 40 mg every 2 weeks, as that is the approved dose in Canada. Therefore, much of the targeted treatment was expected to be intensification of DMARDs, intra-articular steroid injections and oral or intramuscular steroids	0, 6, 12 and 18 months. Assessments at 2, 4 and 9 months were also recommended
	A SJC of 0	1. Physicians were encouraged to make treatment changes in patients when the target was not achieved 2. The dose of ADA 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 (DMARDs, intra-articular steroid injections and oral or intramuscular steroids)	

DAS, Disease Activity Score; PDN, prednisone.

TABLE 13 Categorisation of included study arms: triple DMARD from start

First author and year of publication	Description of target	Protocol	Frequency of assessments
Saunders *et al.*, 2008[54]	A DAS28 of < 3.2 (to correspond with a EULAR good response)	1. MTX (7.5 mg/week), SSZ (500 mg twice a day) and HCQ (200 mg daily) 2. The MTX dosage was escalated each month in 2.5- to 5-mg increments until good disease control was obtained (up to a maximum of 25 mg/week) or side effects occurred 3. Thereafter, if good disease control was not achieved (i.e. if the DAS28 remained > 3.2), SSZ was increased to 40 mg/kg/day in divided doses and, subsequently, if disease control remained inadequate, the dosage of HCQ was increased to 400 mg/day	Monthly

Tables 6–13 show that, within each classification group, study arms exhibit significant differences. These can be seen within each grouping in terms of the treatment target and the frequency of assessment. For example, within the group of study arms classified as 'step-up non-biologic combination therapy', the frequency of assessments was monthly in some studies (e.g. the TICORA trial,[61,63] Saunders *et al.*[54]) and every 3 months in others (e.g. BeSt[26–34]). Within the same classification group, treatment targets varied enormously. A DAS44 of ≤ 2.4 was used in two studies (BeSt[26–34,65,68] and TICORA[61,63]). A range of different measurement scales [ACR, SDAI, Clinical Disease Activity Index (CDAI), DAS28 and other multifaceted measures] and cut-off points (remission, other measures of response) were used in the other study arms.

Differences are also apparent in the details of the treatment protocols within each broad grouping. Study arm treatment protocols exhibit substantial variation in the study drugs used, the combinations in which they may be used, the doses used (both initially and when changing dose in response to assessment of treatment response), and the ordering of study drugs in the sequence of the protocol.

This variation would be present even if an alternative classification approach were to be adopted. For these reasons, it is not considered desirable to conduct analyses that synthesise results quantitatively across different sets of studies. The extent of variation between study arms would make interpretation of results difficult and potentially result in misleading conclusions.

Assessment of effectiveness

Population characteristics and treat-to-target characteristics

Trials examining early rheumatoid arthritis populations

Eleven trials reported on early RA populations (BeSt,[26–34,64–66] CAMERA,[35,36,67] CareRA,[38–43] COBRA-light,[44,45] FIN-RACo,[47–49,70] Hodkinson *et al.*,[51] Saunders *et al.*,[54] STREAM,[55] T-4 study,[56,57] TEAR[58–60] and U-Act-Early[62]). Population characteristics are presented in *Table 14*. The mean age of trial participants ranged from 46 to 62 years and trial arm samples ranged from 58% to 84% female and from 23.4% to 91.7% rheumatoid factor positive. Mean disease duration at baseline ranged from just < 2 weeks to just > 1 year. The mean DAS28 at baseline ranged from 4.4 to 6.9, indicating moderate to severe RA at baseline among the early RA population. The mean SJC (on 66 joints) ranged from 10.0 to 14.0 and the mean TJC (0–68 joints) ranged from 12.3 to 20.0, across all trial arms. The mean HAQ score at baseline ranged from 0.92 to 2.0.

Characteristics of the TTT features of the early RA trials are presented in *Table 15*. Targets included LDA [a DAS44 of ≤ 2.4 (BeSt[26–34,64–66]); a Disease Activity Score, 28 joints with C-reactive protein concentration (DAS28-CRP) of ≤ 3.2 (CareRA[38–43]); a SDAI of ≤ 11 (Hodkinson *et al.*[51]); a CDAI of ≤ 10 (Hodkinson *et al.*[51]);

TABLE 14 Population characteristics: trials reporting early RA populations

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n*/*N* (%)	Rheumatoid factor positive, *n*/*N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
BeSt[26–34,64–66]	Sequential monotherapy	126	54 (13)	86/126 (68)	84/126 (67)	2 (1–5) weeks[a,b] Symptom duration 23 (14–54) weeks[a]	DAS44, 4.5 (0.9)	NR	NR	NR	D-HAQ, 1.4 (0.7)
	Step-up combination therapy	121	54 (13)	86/121 (71)	77/121 (64)	2 (1–4) weeks[a,b] Symptom duration 26 (14–56) weeks[a]	DAS44, 4.5 (0.8)	NR	NR	NR	D-HAQ, 1.4 (0.6)
	Initial combination therapy with PDN	133	55 (14)	86/133 (65)	86/133 (65)	2 (1–4) weeks[a,b] Symptom duration 23 (15–53) weeks[a]	DAS44, 4.4 (0.9)	NR	NR	NR	D-HAQ, 1.4 (0.7)
	Initial combination therapy with IFX	128	54 (14)	85/128 (66)	82/128 (64)	3 (1–5) weeks[a,b] Symptom duration 23 (13–46) weeks[a]	DAS44, 4.3 (0.9)	NR	NR	NR	D-HAQ, 1.4 (0.7)
CAMERA[35,36,67]	Intensive strategy group	151	54 (14)	104/151 (69)	89/151 (66)	NR	5.6 (1.2), *n* = 102	14 (6)	15 (7)	51 (26)	1.2 (0.7)
	Conventional strategy group	148	53 (15)	97/148 (66)	77/148 (62)	NR	5.6 (1.0), *n* = 103	14 (6)	14 (7)	47 (25)	1.2 (0.7)

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n/N* (%)	Rheumatoid factor positive, *n/N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
CareRA: high-risk patients[40,42,43]	COBRA Classic	98	53.2 (11.9)	64/98 (65)	78/98 (80)	1.8 (3.1) weeks Symptom duration 33.8 (35.5) weeks	DAS28 (ESR), 5.4 (1.3); DAS28 (CRP), 5.0 (1.2)	11.9 (8.9); DAS28 joints 7.9 (6.0)	14.7 (9.5); DAS28 joints 9.5 (6.0)	59.5 (23.6)	1.2 (0.7)
	COBRA Slim	98	51.8 (131)	63/98 (64)	82/98 (84)	2.6 (3.3) weeks Symptom duration 33.2 (38.2) weeks	DAS28 (ESR), 5.2 (1.2); DAS28 (CRP), 4.9 (1.1)	10.8 (6.5); DAS28 joints 7.1 (4.6)	13.7 (8.2); DAS28 joints 8.5 (5.5)	56.5 (21.9)	0.98 (0.69)
	COBRA Avant-Garde	93[c]	51.2 (12.8)	64/93 (69)	70/93 (75)	3.1 (6.4) weeks Symptom duration[d] 44.3 (65.9) weeks	DAS28 (ESR), 5.0 (1.3); DAS28 (CRP), 4.7 (1.2)	10.6 (6.7); DAS28 joints[c,e] 7.0 (5.1)	14.1 (9.0); DAS28 joints[c,e] 8.2 (5.5)	57.5 (23.8)	1.0 (0.6)
CareRA: low-risk patients[40,43]	MTX-TSU	47	51.0 (14.0)	38/47 (81)	11/47 (23)	3.17 (6.62) weeks Symptom duration[f] 33.11 (62.21) weeks	DAS28 (ESR), 4.83 (1.68); DAS28 (CRP), 4.55 (1.63)	10.00 (6.98); SJC28[g] 6.89 (6.11)	14.06 (8.61); TJC28[g] 9.49 (7.46)	Pain (range 0–100) 52.09 (23.23); Nocturnal pain (yes)[g] 34/47 (72.3%)	0.99 (0.67)
	COBRA Slim	43	51.4 (14.4)	33/43 (77)	11/43 (26)	1.86 (2.70) weeks; Symptom duration[g] 34.42 (68.16) weeks	DAS28 (ESR), 4.88 (1.64); DAS28 (CRP), 4.50 (1.63)	10.93 (7.55); SJC28[g] 7.79 (6.0)	13.14 (10.70); TJC28[g] 8.51 (7.80)	Pain (range: 0 to 100) 48.23 (31.19) nocturnal pain (yes)[g] 21/43 (48.8%)	0.92 (0.85)
COBRA-light[44,45]	COBRA	81	53 (13)	54/81 (67)	47/81 (58)	16 (9–28) weeks[a]	5.67 (1.13)	13 (10–17)[a]	17 (12–24)[a]	NR	1.36 (0.66)
	COBRA-light	83	51 (13)	58/81 (70)	48/83 (58)	Median 17 (8–33) weeks[a]	5.45 (1.29)	11 (9–14)[a]	16 (10–23)[a]	NR	1.37 (0.71)

continued

TABLE 14 Population characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n*/*N* (%)	Rheumatoid factor positive, *n*/*N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
FIN-RACo[47–49,70]	Combination treatment	99 (97 in ITT)	47 (23–65)[h]	56 (58)	68 (70)	7.3 (2–22)[d]	NR	13 (6)	18 (8)	NR	NR
	Single-drug treatment	100 (98 in ITT)	48 (20–65)[h]	65 (66)	65 (66)	8.6 (2–23)[d]	NR	14 (7)	20 (10)	NR	NR
Hodkinson *et al.*, 2015[51]	SDAI arm	42	50.1 (13.4)[c]	34/42 (81)	36/42 (86)	Symptom duration 2.6 (3.1) years	6.1 (1.2)	11 (5.7)	12.5 (8.5)	66.7 (22.6)	HAQ-DI, 1.7 (0.8)
	CDAI arm	60	46.7 (13.0)[c]	50/60 (83)	54/60 (90)	Symptom duration 3.3 (4.2) years	6.3 (1.2)	10.0 (5.7)	12.3 (7.3)	59.2 (26.0)	HAQ-DI, 1.7 (0.7)
Saunders *et al.*, 2008[54]	Parallel triple therapy	49	55 (15)	37/49 (76)	34/49 (69)	10 (9)	6.8 (0.9)	12 (4)	18 (6)	71 (26)	1.9 (0.7)
	Step-up therapy	47	55 (11)	37/47 (79)	34/47 (72)	13 (12)	6.9 (0.9)	13 (5)	18 (6)	65 (22)	2.0 (0.7)
STREAM[55]	Aggressive group	42	48 (13)	24/42 (58)	20/42 (48)	6 (3–10)[a]	DAS44, 2.2 (0.5)	NR	NR	NR	0.50 (0.25–0.88)[a]
	Conventional care	40	46 (12)	32/40 (79)	13/40 (33)	6 (4–9)[a]	DAS44, 2.4 (0.7)	NR	NR	NR	0.69 (0.32–1.06)[a]
T-4 study[56,57]	Routine care	62	62 (12); *n* = 55	42/55 (76)	NR	1.5 (1.1) years; *n* = 55	4.4 (1.1); *n* = 55	NR	NR	NR	mHAQ score, 0.3 (0.4); *n* = 55
	DAS28-driven therapy	60	60 (11); *n* = 56	42/56 (77)	NR	1.3 (1.1) years; *n* = 56	4.6 (1.3); *n* = 56	NR	NR	NR	mHAQ score, 0.4 (0.6); *n* = 56
	MMP-3-driven therapy	60	62 (13); *n* = 53	44/53 (83)	NR	1.3 (1.2) years; *n* = 53	4.8 (1.3); *n* = 53	NR	NR	NR	mHAQ score, 0.4 (0.8); *n* = 53
	DAS28 and MMP-3-driven therapy	61	56 (13); *n* = 58	49/58 (84)	NR	1.3 (1.2) years; *n* = 58	4.6 (1.3); *n* = 58	NR	NR	NR	mHAQ score, 0.3 (0.4); *n* = 58

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n/N* (%)	Rheumatoid factor positive, *n/N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
TEAR[58–60]	Immediate ETN	244	50.7 (13.4)	181/244 (74)	216/244 (89)	3.5 (6.4)	DAS28-(ESR), 5.8 (1.1)	12.7 (5.8)	14.3 (6.6)	mHAQ pain score 5.3 (2.6); *n* = 243	mHAQ score, 1.1 (0.4); *n* = 227
	Immediate triple therapy	132	48.8 (12.7)	101/132 (77)	121/132 (92)	4.1 (7.2)	DAS28-(ESR), 5.8 (1.1)	12.1 (5.8)	14.1 (6.8)	mHAQ pain score 5.3 (2.5); *n* = 131	mHAQ score, 1.0 (0.4); *n* = 125
	Step-up ETN	255	48.6 (13.0)	176/255 (69)	232/255 (91)	2.9 (5.6)	DAS28-(ESR), 5.8 (1.1)	13.1 (6.2)	14.2 (6.9)	mHAQ pain score 5.2 (2.4)	mHAQ score, 1.0 (0.4); *n* = 237
	Step-up triple therapy	124	49.3 (12.0)	87/124 (70)	108/124 (87)	4.5 (7.6)	DAS28-(ESR), 5.9 (1.1)	13.1 (6.1)	14.6 (7.0)	mHAQ pain score 5.1 (2.5)	mHAQ score, 1.0 (0.4); *n* = 117
U-Act-Early[62]	TOC + MTX	106	53.0 (46.0–60.0)[a]	65/106 (61)	RF, 75 (71); CCP, 72 (68); both, 79 (75)	Symptom duration: 24.5 (16.0–41.5)[a] days	5.2 (1.1)	9 (6–15)[a] (44 joints)	10 (7–17)[a] (44 joints)	NR	1.1 (0.67)
	TOC + PBO–MTX	103	55.0 (47.0–63.0)[a]	78/103 (76)	RF, 68 (66); CCP, 67 (65); both, 77 (75)	Symptom duration: 25.5 (18.0–45.0)[a] days	5.3 (1.1)	11 (7–16)[a] (44 joints)	11 (7–18)[a] (44 joints)	NR	1.3 (0.66)
	MTX + PBO–TOC	108	53.5 (44.5–62.0)[a]	69/108 (64)	RF, 86 (80); CCP, 84 (78); both, 93 (86)	Symptom duration: 27.0 (15.0–46.0)[a] days	5.1 (1.2)	9 (5–15)[a] (44 joints)	10 (5.5–17)[a] (44 joints)	NR	1.1 (0.59)

CCP, cyclic citrullinated peptide; DAS, Disease Activity Score; DAS28-ESR, Disease Activity Score, 28 joints with erythrocyte sedimentation rate; D-HAQ, Dutch version of the Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; ITT, intention to treat; mHAQ, modified Health Assessment Questionnaire; MMP-3, matrix metalloproteinase 3; MTX-TSU, methotrexate tight step-up; NR, not reported; PDN, prednisone; RF, rheumatoid factor; SD, standard deviation; SJC28, swollen joint count, 28 joints; TJC28, tender joint count, 28 joints; VAS, visual analogue scale.

a Median (interquartile range).
b From diagnosis to inclusion.
c *n* = 94 in Verschueren *et al.*[42]
d Mean (range).
e Reported in Verschueren *et al.*[42]
f Median (range).
g Reported in Verschueren *et al.*[40]
h Calculated from age at symptom onset and symptom duration.

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
BeSt[26–34,64–66]	Comparison of different treatment protocols	Sequential monotherapy	126	A DAS44 of ≤ 2.4	1. 15 mg/week of MTX, increased to 25–30 mg/week if the DAS44 was > 2.4. Subsequent steps for patients with an insufficient response were: 2. 2000–3000 mg/day of SSZ monotherapy 3. 20 mg/day of LEF monotherapy 4. MTX with 3–10 mg/kg IFX every 8 weeks (intravenously) 5. 50 mg/week of gold (intramuscularly) with 120 mg of methylprednisolone (intramuscularly) 6. MTX with 2.5 mg/kg/day ciclosporin A and 7.5 mg/day PDN	Every 3 months
		Step-up combination therapy	121		1. 15 mg/week of MTX, increased to 25–30 mg/week if the DAS44 was > 2.4. If response to therapy was still insufficient, SSZ was added, followed by the addition of: 2. 400 mg/day of HCQ and then by PDN. Patients whose disease failed to respond to the combination of these four drugs subsequently switched to 3. MTX with IFX, MTX with ciclosporin and PDN, and finally to 20 mg/day LEF	
		Initial combination therapy with PDN	133		1. 7.5 mg/week of MTX, 2000 mg/day of SSZ and 60 mg/day of PDN (the last of which was tapered in 7 weeks to 7.5 mg/day). If the DAS44 was > 2.4 2. MTX was augmented to 25–30 mg/week and if the response was still insufficient, the combination was replaced by: 3. MTX with ciclosporin and PDN, followed by MTX with IFX, LEF monotherapy, gold with methylprednisolone and finally by 2–3 mg/kg/day azathioprine with PDN. In the case of a persistent DAS44 of > 2.4, first PDN was tapered to 0 mg/day after 28 weeks and then MTX was tapered to 0 mg/day after 40 weeks	

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		Initial combination therapy with IFX	128		1. 25–30 mg/week of MTX with 3 mg/kg of IFX at weeks 0, 2 and 6 and every 8 weeks thereafter. After 3 months, if DAS44 > 2.4: 2. IFX was increased to 6 mg/kg every 8 weeks. Extra DAS44 calculations for dose adjustments were performed every 8 weeks within 1 week before the next infusion of IFX. If the DAS44 was > 2.4: 3. The dose of the next infusion was increased to 7.5 mg/kg every 8 weeks and then to 10 mg/kg every 8 weeks. If patients still had a DAS > 2.4 while receiving MTX with 10 mg/kg of IFX, they switched to SSZ, then to LEF, then to the combination of MTX, ciclosporin and PDN, then to gold with methylprednisolone, and, finally, to azathioprine with PDN. If there is a persistent good response of the DAS44 of < 2.4 for at least 6 months, then: 4. IFX is reduced from 10 mg/kg to 7.5 mg/kg to 6 mg/kg and then to 3 mg/kg every next infusion until stopped	
CAMERA[35,36,67]	Other comparisons	Conventional strategy group	151	Response (> 20% improvement in SJC, > 20% improvement in any two of ESR, TJC and VAS general well-being), avoiding inadequate response (≤ 50% improvement from baseline for SJC and ≤ 50% improvement from baseline for two of ESR, TJC and VAS general well-being)	1. 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: 2. The dosage was increased stepwise by 5 mg/week to a maximum of 30 mg/week 3. If the maximum (tolerable) dose of MTX was reached and patients did not fulfil the criteria for sustained response MTX was administered subcutaneously. For patients on subcutaneous MTX having an inadequate response, ciclosporin was added to the MTX, while the dosage of MTX was reduced to 15 mg/week.	Every 3 months

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		Intensive strategy group	148	Response (decrease in SJC, if SJC unchanged, assessors' judgement looking at TJC, ESR and VAS general well-being), avoiding inadequate response (SJC ≥ 6, number of painful joints ≥ 3, ESR ≥ 28 mm/hour and a morning stiffness of ≥ 45 minutes)	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 4. 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	Every 4 weeks
CareRA: high-risk patients[40,42,43]	Comparison of different treatment protocols	COBRA Classic	98	DAS28-CRP ≤ 3.2	15 mg of MTX weekly, 2 g of SSZ daily and a weekly step-down scheme of oral GCs (60 mg to 40 mg to 25 mg to 20 mg to 15 mg to 10 mg to 7.5 mg of PDN), then: 1. Weekly increase of MTX dose to 20 mg 2. SSZ dose increase to 3 mg (then considered a strategy failure)	Screening: baseline, weeks 4, 8 and 16. If a treatment adjustment was required at week 8, an optional visit was held at week 12
		COBRA Slim	98		15 mg of MTX weekly with a weekly step-down scheme of oral GCs (30 mg to 20 mg to 12.5 mg to 10 mg to 7.5 mg to 5 mg of PDN), then: 1. Weekly increase of MTX dose to 20 mg 2. Addition of LEF 10 mg daily (then considered a strategy failure)	
		COBRA Avant-Garde	93[a]		15 mg of MTX weekly, 10 mg of LEF daily and a weekly step-down scheme of oral GCs (30 mg to 20 mg to 12.5 mg to 10 mg to 7.5 mg to 5 mg of PDN), then: 1. Weekly increase of MTX dose to 20 mg 2. LEF dose increase to 20 mg (then considered a strategy failure)	

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
CareRA: low-risk patients[40,43]	Comparison of different treatment protocols	MTX-TSU	47	A DAS28-CRP of ≤ 3.2	15 mg of MTX weekly, no oral steroids allowed, then: 1. MTX dose increase to 20 mg weekly 2. Addition of LEF 10 mg daily (then considered an efficacy failure)	Screening: baseline, weeks 4, 8 and 16. If a treatment adjustment was required at week 8, an optional visit was held at week 12
		COBRA Slim	43		15 mg of MTX weekly with a step-down scheme of daily oral GCs (30-20-12.5-10-7.5-5 mg of PDN). From week 28, GCs were tapered on a weekly basis by leaving out one daily dose each week over a period of 6 weeks until complete discontinuation, then: 1. MTX dose increase to 20 mg weekly 2. Addition of 10 mg of LEF daily (then considered an efficacy failure)	
COBRA-light[44,45]	Comparison of different treatment protocols	COBRA	81	A DAS44 of < 1.6	1. 60 mg/day of prednisolone, tapered to 7.5 mg/day in 6 weeks, 7.5 mg/week of MTX and 1 g/day of SSZ, increased to 2 g/day after 1 week 2. MTX increased to 25 mg/week after 13 weeks of treatment if the DAS44 was ≥ 1.6	Every 3 months
		COBRA-light	83		1. 30 mg/day of prednisolone, tapered to 7.5 mg/day in 9 weeks and 10 mg/week MTX with stepwise increments in all patients to 25 mg/week in 9 weeks 2. Parenteral MTX after 13 weeks if the DAS44 was ≥ 1.6	

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
FIN-RACo[47–49,70]	Comparison of different treatment protocols	Combination treatment	99 (97 in ITT)	Remission – a modified version of ACR 1981 defined remission (Pinals *et al.*[71]) – on any drug treatment, no swollen or tender joints (modified by excluding fatigue and duration definition)	1. Combination therapy started with: 2. 500 mg of SSZ twice daily, 7.5 mg of MTX weekly, 300 mg of HCQ daily and 5 mg of prednisolone daily for 3 months 3. If the clinical improvement was < 50% in at least two of SJC, TJC and ESR or CRP, the MTX and prednisolone increased to 10 mg weekly and 7.5 mg daily 4. The protocol allowed flexible subsequent dose adjustments to mimic clinical practice. The highest dose at 9 months and thereafter was 2 g daily of SSZ, 15 mg weekly of MTX, 300 mg daily of HCQ and 10 mg daily of prednisolone 5. If remission was achieved during the first year with the initial drug combination, the drug doses were tapered, and prednisolone and MTX could even be discontinued at 9 and 18 months. SSZ (1 g daily) and HCQ (300 mg daily) had to be continued until the end of the study 6. If remission was achieved during the first year but not with the initial drug combination, drug doses were gradually tapered to those of the second year 7. If the induced remission was lost, DMARD doses were increased with the intention of reaching remission 8. If one or several components of the combination had to be discontinued, a combination of three DMARDs was restarted by replacing SSZ and HCQ with auranofin (3–6 mg daily) and MTX with azathioprine (2 mg/kg daily). Other DMARDs could also be used as substitutes	Baseline and at months 1, 3, 4, 5, 6, 9, 12, 18 and 24

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		Single-drug treatment	100 (98 in ITT)		1. Prednisolone (up to 10 mg) was allowed in patients with continuously active disease (decision to use made by the treating physician), but simultaneous use of multiple DMARDs was not allowed. The patients were treated continuously with one DMARD alone, with or without prednisolone and, if a more beneficial effect was needed, the dose was increased or the DMARD was changed 2. SSZ (2 g daily) was used as the initial drug in all patients and the dose was increased to 3 g daily at 3 months, if clinically indicated 3. If an AE occurred, or if the clinical response was < 25% at 6 months, the SSZ was replaced with MTX (7.5–15 mg weekly) 4. As the third DMARD, azathioprine (2 mg/kg daily), auranofin, HCQ, injectable gold, penicillamine or podophyllotoxin could be used alternatively after azathioprine	
Hodkinson *et al.*, 2015[51]	Comparison of different targets	SDAI arm	42	A SDAI of ≤ 11 (LDA)	15 mg/week of MTX, then if not achieving a SDAI of ≤ 11: 1. Increased oral MTX to 20 mg and then to 25 mg 2. Triple therapy (1000 mg/day of SSZ, 200 mg/day of chloroquine, 25 mg/week of MTX) 3. LEF in combination with MTX. Low-dose oral corticosteroids (PDN 7.5 mg/day) were prescribed to all patients for the initial 6 months and were tapered and stopped after the 6-month visit if LDA was achieved	Monthly for the first 3 months then every 3 months until the end of 12 months

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		CDAI arm	60	A CDAI of ≤ 10 (LDA)	15 mg/week of MTX, then if not achieving a CDAI of ≤ 10: 1. Increased oral MTX to 20 mg, then 25 mg 2. Triple therapy (1000 mg/day of SSZ, 200 mg/day of chloroquine, of 25 mg/week MTX) 3. LEF in combination with MTX. Low-dose oral CSs (PDN 7.5 mg/day) were prescribed to all patients for the initial 6 months and were tapered and stopped after the 6-month visit if LDA was achieved	
Saunders *et al.*, 2008[54]	Comparison of different treatment protocols	Parallel triple therapy	47	A DAS28 of < 3.2	1. MTX (7.5 mg/week), SSZ (500 mg twice a day) and HCQ (200 mg daily). 5 mg/week folic acid was co-prescribed 4 days after MTX dosing 2. The MTX dosage was escalated each month in 2.5- to 5-mg increments until good disease control was obtained (up to a maximum of 25 mg/week) or side effects occurred 3. Thereafter, if good disease control was not achieved (i.e. if the DAS28 remained > 3.2), SSZ was increased to 40 mg/kg/day in divided doses; subsequently: 4. If disease control remained inadequate, the dosage of HCQ was increased to 400 mg/day. If there is persistent disease activity despite maximal drug therapy or drug-related toxicity, then alternative DMARDs or biologic agents could be used singly or in combination in order to control disease activity	Every 3 months by an independent, blinded assessor

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		Step-up therapy	49		1. SSZ (target dosage 40 mg/kg/day in divided doses) 2. After 3 months, if the DAS28 remained > 3.2, MTX was added (7.5 mg/week, co-prescribed with 5 mg/week of folic acid 4 days after MTX dosing, increased monthly to a maximum of 25 mg/week, as above) 3. After the maximum tolerated dose of MTX was reached, 400 mg/day of HCQ was added in patients with persistent disease activity	
STREAM[55]	TTT vs. usual care	Aggressive group	42	Remission (a DAS44 of < 1.6)	Treatment was started with 15 mg/week of oral MTX. If the DAS was ≥ 1.6 at a given time point: 1. Increase in MTX to 25 mg/week; 25 mg/week of MTX combined with 40 mg of ADA every 2 weeks 2. 25 mg/week of MTX combined with 40 mg/week of ADA 3. A combination of 25 mg/week of MTX, 2000 mg/day of SSZ and 400 mg/day of HCQ 4. A combination of 25 mg/week of MTX, 2000 mg/day of SSZ, 400 mg/day of HCQ and 7.5 mg/day of PDN 5. 20 mg/day of LEF (100 mg at days 1, 8 and 15) and 50 mg/week of intramuscular gold If the DAS was < 1.6 at one time point, the treatment remained unchanged. If the DAS was < 1.6 at two consecutive time points, the following actions were taken: 1. 15 mg/week of MTX was decreased from 2.5 mg every 2 weeks to 0 mg/week after 3 months 2. 25 mg/week of MTX was decreased from 2.5 mg every 2 weeks to 10 mg/week after 3 months 3. 40 mg of ADA every 2 weeks was stopped 4. 40 mg/week of ADA was decreased to 40 mg every 2 weeks 5. HCQ was decreased from 200 mg every 8 weeks to 0 mg	Every 3 months

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
					If remission was sustained after 3 months, SSZ was decreased subsequently from 500 mg every 4 weeks to 0 mg. If remission was sustained after 3 months: 1. MTX was decreased from 2.5 mg every 2 weeks to 0 mg 2. 7.5 mg/ day of PDN was decreased to 0 mg in 7 weeks 3. LEF was decreased to 10 mg/day If remission was sustained after 3 months 1. LEF was stopped 2. Gold was decreased to 50 mg every 2 weeks If DAS remained < 1.6 and gold was decreased to 50 mg every 4 weeks; if remission was sustained, gold was stopped. If at any time point the DAS was ≥ 1.6 the last effective treatment was restarted. In case of intolerance to a DMARD, the highest tolerated dose was used and, if the DAS was ≥ 1.6 at the next visit, the patient went on to the next step	
		Conventional care	40	Not prompted to make treatment decisions based on DAS. The treating physician could only change therapy if the DAS was > 2.4 at the 3-month assessment	The rheumatologist had access to the DAS, but was not prompted to make treatment decisions based on the DAS. The following order of drugs was suggested to the treating rheumatologist: HCQ (or MTX after 2005 with 25 patients recruited), SSZ, MTX and LEF	

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
T-4 study[56,57]	TTT vs. usual care; comparison of different targets	Routine care	62	No target	All groups received 1 g/day of SSZ. Change of therapy in the routine care group was based on the treating physician's clinical judgement according to the improvement in the number of tender joints (0–28), swollen joints (0–26) and value of serum CRP from pre-assessment values, without access to current DAS28 and MMP-3 values	Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56
		DAS28-driven therapy	60	A DAS28 of < 2.6	1. 1 g/day of SSZ plus 4 mg/week of MTX:[b] the dosage was not changed if the patient had responded compared with the previous visit; otherwise: 2. The dosage was increased in a stepwise manner to a maximum of 8 mg/week[c] if patient had not responded. Change of therapy based on improvement in the number of tender joints (0–28), swollen joints (0–26) and value of CRP from pre-assessment values, without access to current DAS28 and MMP-3 values 3. If the maximum tolerable dose of MTX that introduced a dose-dependent side effect was reached and the patient still did not fulfil sustained response, 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 TNF blocker dose increased, or the interval for TNF administration was shortened. DMARDs including bucillamine,[c] gold sodium thiomalate, tacrolimus and LEF were given, as allowed, by the rheumatologist at all times. Combination therapy with DMARDs other than MTX was allowed for two kinds of agents. Intra-articular GC (to a maximum of 10 mg of triamcinolone acetonide on a single visit) was permitted for persistently swollen and tender joints	
		MMP-3-driven therapy	60	A MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women		
		DAS28 and MMP-3-driven therapy	61	A DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml for men or 59.7/< ng/ml for women		

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
TEAR[58–60]	Comparison of different targets; comparison of different treatment protocols	Immediate ETN	244	No target	Oral MTX, escalated to 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12, plus subcutaneous 50 mg/week of ETN. Corticosteroid use at entry tapered	Every 6 weeks during the first 48 weeks and every 12 weeks thereafter (joint assessments)
		Immediate triple therapy	132		Oral MTX, escalated to 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12, plus 500 mg twice daily of SSZ, escalated (if tolerated) to 1000 mg twice daily at 6 weeks, plus 200 mg twice daily of HCQ. Corticosteroid use at entry tapered	
		Step-up ETN	255	A DAS28-ESR of < 3.2	Oral MTX, escalated to 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12 plus an ETN PBO. Corticosteroid use at entry tapered. If DAS28-ESR was ≥ 3.2 at week 24, patients were stepped up to MTX plus subcutaneous 50 mg/week of ETN	
		Step-up triple therapy	124		Oral MTX, escalated to 20 mg/week or to a lower dosage if treatment resulted in no active tender/painful or swollen joints by week 12 plus a triple-therapy PBO. Corticosteroid use at entry tapered. If DAS28-ESR was ≥ 3.2 at week 24, patients were stepped up to MTX plus 500 mg twice daily of SSZ, escalated (if tolerated) to 1000 mg twice daily at 6 weeks, plus 200 mg twice daily of HCQ	

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
U-Act-Early[62]	Comparison of different treatment protocols	TOC + MTX	105	A DAS28 of < 2.6 and a SJC28 of ≤ 4	1. 8 mg/kg of TOC (maximum 800 mg) every 4 weeks; the number of infusions could differ depending on achievement of sustained remission, at which the point infusions were tapered down in dose according to protocol and eventually discontinued. MTX started at 10 mg per week orally and increased stepwise every 4 weeks by 5 mg to a maximum of 30 mg per week, until remission or dose-limiting toxicity. Patients received 5 mg of folic acid orally twice per week 2. If remission was not achieved at the maximum dose or maximum tolerated dose of MTX, 200 mg of HCQ twice per day orally for 3 months was added to the regimen 3. If remission was not achieved after HCQ step-up, the initial treatment regimens ended and standard of care therapy was started at the discretion of the treating physician, typically MTX combined with a TNF inhibitor 4. If sustained remission was achieved, the dose of MTX was reduced stepwise by 5 mg every 4 weeks until 10 mg, then discontinued as the next step; 4 weeks thereafter, TOC was tapered to 4 mg/kg, and after 3 months of 4 mg/kg per 4 weeks, TOC was discontinued, provided sustained remission persisted	There was no fixed number of weeks or visits per patient. SJC, TJC, pain, general health, ESR and CRP assessed at baseline and every 4 weeks thereafter up to 104 weeks including baseline

continued

TABLE 15 Treat-to-target characteristics: trials reporting early RA populations (*continued*)

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		TOC + PBO–MTX	103		1. 8 mg/kg of TOC (maximum 800 mg) every 4 weeks; the number of infusions could differ depending on achievement of sustained remission, at which point the infusions were tapered down in dose according to the protocol and eventually discontinued. The same scheme was followed for PBO–MTX as the TCO + MTX arm. Patients received 5 mg of folic acid orally twice per week 2. If remission was not achieved at the maximum dose or maximum tolerated dose of PBO–MTX, 200 mg of HCQ twice per day orally for 3 months was added to the regimen 3. If remission was not achieved after HCQ step-up, the initial treatment regimens ended and MTX was started in place of PBO–MTX and stepped up in accordance the protocol 4. If remission was not achieved after switching to the active MTX treatment and stepping up, standard of care therapy was initiated, typically MTX combined with a TNF inhibitor 5. If sustained remission was achieved, the dose of PBO–MTX was reduced stepwise by 5 mg every 4 weeks until 10 mg, then discontinued as the next step; 4 weeks thereafter, TOC was tapered to 4 mg/kg, and after 3 months of 4 mg/kg per 4 weeks, TOC was discontinued, provided sustained remission persisted	

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
		MTX + PBO–TOC	108		1. MTX started at 10 mg per week orally and increased stepwise every 4 weeks by 5 mg to a maximum of 30 mg/week, until remission or dose-limiting toxicity. The same scheme was followed for PBO–TOC as the TCO + MTX arm. Patients received 5 mg of folic acid orally twice per week 2. If remission was not achieved at the maximum dose or maximum tolerated dose of PBO–TOC, 200 mg of HCQ twice per day orally for 3 months was added to the regimen 3. If remission was not achieved after HCQ step-up, the initial treatment regimens ended and TOC was started in place of PBO–TOC and stepped up according to the protocol 4. If remission was not achieved after switching to the active TOC treatment and stepping up, standard of care therapy was initiated, typically MTX combined with a TNF inhibitor 5. If sustained remission was achieved, the dose of MTX was reduced stepwise by 5 mg every 4 weeks until 10 mg, then discontinued as the next step; 4 weeks thereafter, PBO–TOC was tapered to 4 mg/kg and after 3 months of 4 mg/kg per 4 weeks, PBO–TOC was discontinued, provided sustained remission persisted	

DAS, Disease Activity Score; DAS28-ESR, Disease Activity Score, 28 joints with erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; ITT, intention to treat; MMP-3, matrix metalloproteinase 3; MTX-TSU, methotrexate tight step-up; PDN, prednisone; SJC28, swollen joint count, 28 joints; TNF, tumour necrosis factor; VAS, visual analogue scale.

a $n = 94$ in Verschueren *et al.*[42]

b This small dose of MTX is unique to Japanese patients and much higher doses are required in other populations.

c Bucillamine is similar to penicillamine.

a DAS28 of < 3.2 (Saunders *et al.*[54]); a Disease Activity Score, 28 joints with erythrocyte sedimentation rate (DAS28-ESR) of < 3.2 (TEAR[58–60])], remission [a DAS44 of < 1.6 (COBRA-light[44,45] and STREAM[55]); modified ACR 1981 definition (FIN-RACo[46–49]); a DAS28 of < 2.6 (T-4 study[56,57] and Optimisation of Adalimumab study[52,53]); a DAS28 of < 2.6 and a SJC (28 joints) of ≤ 4 (U-Act-Early[62])] response [defined by thresholds of SJC, TJC, erythrocyte sedimentation rate (ESR) and general well-being visual analogue scale (VAS) (CAMERA[35,36,67])]: and matrix metalloproteinase 3 (MMP-3) concentration (< 121 ng/ml for men or < 59.7 ng/ml for women; T-4 study[56,57]). Treatment protocols for attaining the target varied considerably across studies in terms of the number of steps in the treatment protocol and the treatments used at each step, the only similar ones being in the COBRA Classic arms of the CareRA[40,42,43] and COBRA-light[44,45] trials (which were similar, but not exactly alike). Assessments were made every 3 months or less in all trials with an early RA population.

Trials examining established rheumatoid arthritis populations

Three trials[9,50,52,53] reported on established RA populations (i.e. BROSG trial,[9] Fransen *et al.*[50] and the Optimisation of Adalimumab study[52,53]). Population characteristics are presented in *Table 16*. The mean age of trial participants ranged from 51.5 to 60.8 years, and trial arm samples ranged from 62% to 83.5% female and from 62% to 93.5% rheumatoid factor positive. The mean disease duration at baseline ranged from 4 to 12.6 years. The mean DAS28 at baseline ranged from 4.5 to 5.8, indicating moderate to severe RA at baseline among the established RA population. The mean SJC (on 66 joints) ranged from 10.5 to 11.1 and mean TJC (0–68 joints) ranged from 11.3 to 13.5, across all trial arms. The mean HAQ score at baseline ranged from 1.25 to 1.6.

Characteristics of the TTT features of the established RA trials are presented in *Table 17*. Targets included LDA (DAS28 of ≤ 3.2[50]), remission (DAS28 of < 2.6[52,53]), SJC of 0,[52,53] control of joint pain, stiffness and related symptoms, and suppression of clinical and laboratory evidence of inflammation, plus CRP below twice the upper limit of normal.[9] Two[9,50] of the three trials examining an established RA population (BROSG[9] trial and Fransen *et al.*[50]) did not employ a specific treatment protocol for reaching the target. The Optimisation of Adalimumab study[52,53] used the same treatment protocol for both the DAS28 of < 2.6- and the SJC of 0-targeted arms. Only the Fransen *et al.*[50] trial had assessments every 3 months or less (0, 4, 12 and 24 weeks), whereas the BROSG[9] trial had assessments every 4 months and the Optimisation of Adalimumab study[52,53] had assessments every 6 months (although visits every 2 months until 6 months and then every 3 months until 12 months were recommended for the two targeted arms).

Trials examining both early and established rheumatoid arthritis populations

Two trials[61,63] examined both early and established RA populations combined (TICORA[61] and van Hulst *et al.*[63]). Population characteristics are presented in *Table 18*. The mean age of trial participants ranged from 51 to 60 years, and trial arm samples ranged from 60% to 71% female and 73% to 79% rheumatoid factor positive. The mean disease duration at baseline ranged from 19 months to 8.9 years. The mean DAS28 at baseline ranged from 3.9 to 4.2 (and DAS44 ranged from 4.6 to 4.9). The mean SJC (on 66 joints) ranged from 11 to 12 and the mean HAQ score at baseline ranged from 1.1 to 2.0.

The characteristics of the TTT features of the trials with populations containing both patients with early RA and those with established RA are presented in *Table 19*. LDA targets were used by both trials (a DAS44 of ≤ 2.4[61] and a DAS28 of ≤ 3.2[63]) (with no target in the usual-care arms). The van Hulst *et al.*[63] trial did not employ a specific treatment protocol for reaching the target. The TICORA[61] trial used a specific treatment protocol for the intensive management arm, but not for the routine management arm. Both trials had assessments every 3 months.

Effectiveness of treat to target compared with usual care

Heterogeneity in the treatment protocols used, and outcomes reported, precluded statistical meta-analysis and, therefore, the findings of the trials examining TTT compared with usual care were combined and examined narratively by outcome. Where it was possible, some comparisons were examined using forest plots, with odds ratios (ORs) and confidence intervals (CIs) calculated.

TABLE 16 Population characteristics: trials reporting established RA populations

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n*/*N* (%)	Rheumatoid factor positive, *n*/*N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
BROSG trial[9]	Symptomatic treatment (shared care)	233	60.4 (11.1) [61.8 (27.1–61.8)][a]	159/233 (68)	NR	12.6 (6.7) years	NR	28 joint count: 4.5 (4.5); *n* = 228	28 joint count: 5.7 (6.3); *n* = 228	41.7 (23.1); *n* = 221	1.25 (0.68); *n* = 233
	Aggressive therapy (hospital)	233	60.8 (11.3) [62.5 (30.1–87.4)][a]	158/233 (68)	NR	12.5 (6.8) years	NR	28 joint count: 3.9 (3.8); *n* = 233	28 joint count: 4.6 (5.4); *n* = 232	42.6 (23.2); *n* = 230	1.31 (0.72); *n* = 233
Fransen *et al.*, 2005[50]	DAS28	205	Main sample, *n* = 205: 57 (11), 58 (52–65)[b]	Main sample, 138/205 (67)	Main sample, *n* = 205: 172 (84)	Main sample, *n* = 205: 6 (3–14) years[b]	Subsample, *n* = 61: 4.6 (1.2)	NR	NR	NR	NR
			Subsample, *n* = 61: 57 (10), 57 (51–65)[b]	Subsample: 38/61 (62)	Subsample, *n* = 61: 53 (87)	Subsample, *n* = 61: 4 (2–10) years[b]					
	Usual care	179	Main sample, *n* = 179: 59 (13), 58 (50–70)[a]	Main sample: 132/179 (74)	Main sample, *n* = 179: 132 (74)	Main sample, *n* = 179: 7 (3–14) years[b]	Subsample, *n* = 81: 4.5 (1.2)	NR	NR	NR	NR
			Subsample *n* = 81: 59 (12), 58 (51–68)[b]	Subsample: 62/81 (77)	Subsample, *n* = 81: 55 (68)	Subsample, *n* = 81: 5 (2–12) years[b]					
Optimisation of Adalimumab study[52,53]	Routine care	109	56.0 (12.9)	91/109 (84)	NR	NR	5.7 (1.0)	10.6 (6.0)	11.3 (6.9)	NR	1.6 (0.6)
	DAS28 target	100	55.3 (13.7)	82/100 (82)	NR	NR	5.7 (1.1)	11.1 (5.3)	13.0 (7.9)	NR	1.4 (0.7)
	SJC target	99	51.5 (13.2)	77/99 (78)	NR	NR	5.8 (1.3)	10.5 (5.7)	13.5 (7.3)	NR	1.5 (0.6)

NR, not reported; SD, standard deviation.
a Mean (range).
b Median (interquartile range).

TABLE 17 Treat-to-target characteristics: trials reporting established RA populations

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
BROSG trial[9]	Other comparisons	Symptomatic treatment (shared care)	233	To control joint pain, stiffness and related symptoms	Managed predominantly in the primary care setting. NSAIDs, intra-articular steroid injections (up to a maximum of one per month), DMARDs (antimalarials, SSZ, intramuscular gold, penicillamine, azathioprine, MTX and LEF) and low-dose steroids (≤ 7.5 mg daily). Non-drug modalities, such as physiotherapy referral, were also used as the GP felt appropriate. DMARD therapy was monitored using the standard guidelines in current use in the five centres	Seen at home every 4 months by a rheumatology specialist nurse and annually by the rheumatologist, encouraged to visit the GP if developed any new or deteriorating symptoms
		Aggressive therapy (hospital)	233	To control joint pain, stiffness and related symptoms and to suppress clinical and laboratory evidence of inflammation. CRP concentrations below twice the upper limit of normal	Managed predominantly in the hospital clinic setting. Symptomatic treatment group drugs plus, if necessary, ciclosporin, parenteral steroids, medium-dose oral steroids (up to 10 mg daily) and cyclophosphamide	Every 4 months (or more often if clinically indicated)
Fransen *et al.*, 2005[50]	TTT vs. usual care	DAS28	205	A DAS28 of ≤ 3.2 (for subsample of 142 patients with DAS assessment)	Systematic monitoring of disease activity by assessment of DAS28 by the treating rheumatologist. The aim was to reach a DAS28 of ≤ 3.2 (LDA) by changing DMARD treatment if the score was > 3.2	0, 4, 12 and 24 weeks
		Usual care	179	No target	No systematic monitoring of disease activity was done and no guideline to adapt treatment strategy was supplied	
Optimisation of Adalimumab study[52,53]	TTT vs. usual care; comparison of different targets	RC	109	No target	No treatment protocol	0, 6, 12 and 18 months
		DAS28 target	100	A DAS28 of < 2.6	1. There was no specified drug algorithm for any physician, as many patients had tried two or more DMARDs before receiving ADA in RC 2. Physicians were encouraged to make treatment changes in patients when the target was not achieved 3. The dose of ADA was not increased beyond 40 mg subcutaneous every 2 weeks, as that is the approved dose in Canada. Therefore much of the targeted treatment was expected to be intensification of DMARDs, intra-articular steroid injections and oral or intramuscular steroids	0, 6, 12 and 18 months. Assessments at 2, 4 and 9 months were also recommended
		SJC target	99	SJC of 0		

DAS, Disease Activity Score; GP, general practitioner; RC, routine care.

TABLE 18 Population characteristics: trials that included populations of patients with early and established RA

Trial acronym or first author and year of publication	Treatment arm	Number of participants	Characteristic								
			Mean age, years (SD)	Female, *n*/*N* (%)	Rheumatoid factor positive, *n*/*N* (%)	Mean disease duration (months) (SD)	Mean DAS28 at baseline (SD) (ESR or CRP where stated)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	Mean pain score (100-mm VAS) (SD)	Mean HAQ score (SD)
TICORA[61]	Intensive management	55	51 (15)	39/55 (71)	41/55 (75)	19 (16)	DAS44: 4.9 (0.9)	12 (4) (0–44)	NR	62 (20)	2.0 (0.8)
	Routine management	55	54 (11)	38/55 (69)	40/55 (73)	20 (16)	DAS44: 4.6 (1.0)	11 (4) (0–44)	NR	59 (20)	1.9 (0.7)
van Hulst *et al.*, 2010[63]	Intervention group	144	59 (13)	87/144 (60)	105/144 (75)	8.9 (0–32) years[a]	4.2 (1.3)	NR	NR	NR	1.3 (0.7)
	Usual-care group	104	60 (13)	71/104 (68)	80/144 (79)	5.8 (0–40) years[a]	3.9 (1.3)	NR	NR	NR	1.1 (0.7)

NR, not reported; SD, standard deviation.
a Median (range).

TABLE 19 Treat-to-target characteristics: trials that included populations of patients with early and established RA

Trial acronym or first author and year of publication	Type of comparison	Treatment arm	Number of participants	Target	Treatment protocol	Frequency of assessment
TICORA[61]	TTT vs. usual care	Intensive management	55	A DAS44 of ≤ 2.4	Escalation of DMARDs in patients with persisting disease activity: 1. 500 mg daily of SSZ, increasing every week to target dose of 40 mg/kg per day 2. 40 mg/kg per day of SSZ, 7.5 mg/week of MTX, 5 mg per week of folic acid, 200–400 mg/day of HCQ (< 6.5 mg/kg per day) 3. Triple therapy with monthly increments of MTX by 2.5–5.0 mg per week (maximum 25 mg per week) 4. Triple therapy with weekly 500-mg increments of SSZ dose (maximum 5 g per day in divided doses if tolerated) 5. Addition of prednisolone in enteric-coated tablets, 7.5 mg daily 6. Change triple therapy to 2–5 mg/kg per day ciclosporin, 25 mg/week of MTX and 5 mg/week of folic acid 7. Change to alternative DMARD (LEF or sodium aurothiomalate)	Every 3 months
		Routine management	55	No target	Clinical decision-making not aided by formal composite measures of disease activity DMARD 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 corticosteroid were given with the same restrictions as those in the intensive group	
van Hulst *et al.*, 2010[63]	TTT vs. usual care	Intervention group	144	A DAS28 of ≤ 3.2	No protocol: DAS28 provided on paper to the rheumatologist. Rheumatologist advised to aim for their patients to reach a DAS28 of ≤ 3.2	Every 3 months (more if needed)
		Usual-care group	104	No target	No protocol	

Trials examining early rheumatoid arthritis populations

Table 20 summarises the TTT outcomes for the comparison of TTT with usual care for the early RA population. Details of treatment adaptations and dose of drugs given are summarised in *Appendix 4, Table 51*. Both trials (i.e. STREAM[55] and T-4 study[57]) reported the proportion of patients meeting the target for at least one of the study arms (although the T-4 study reported only the number and proportion of patients meeting the DAS28 target and not the MMP-3 target or the combined DAS28 and MMP-3 target). The number meeting the target was 38% in the DAS28 of < 2.6 arm of the T-4 study.[57] The number meeting the target in the STREAM trial was slightly higher in the conventional care group (65%) than in the aggressive group (54%) at 1 year and then slightly higher in the aggressive group (66%) than in the conventional care group (49%) at 2 years, although the statistical significance of these comparisons was not reported [our calculated OR is 1.66 (95% CI 0.67 to 4.12) at 1 year and 0.52 (95% CI 0.21 to 1.28) at 2 years]. Neither trial reported the proportion of patients attaining LDA at follow-up. In the STREAM trial, the proportion of patients in remission was slightly higher in the usual-care arm (65%) than in the TTT arm (54%) at 1 year and slightly higher in the TTT arm (66%) than the usual-care arm (49%) at 2 years, although the statistical significance of these comparisons was not reported.[55] In the T-4 study, the proportion of patients attaining DAS28 remission was highest in the combined DAS28 and MMP-3 target group (56%; OR 0.21, 95% CI 0.10 to 0.47) vs. routine care], still significantly higher in the DAS28 of < 2.6 target group (38%; OR 0.43, 95% CI 0.19 to 0.95) vs. routine care] than the MMP-3 target group (13%), which in turn was significantly lower than in the routine care arm (21%;[57] OR 1.72, 95% CI 0.66 to 4.52). Visualised data in *Figure 5* show some evidence of a benefit of TTT on remission at 1 year, when some targets may be more beneficial than others.

Specific disease activity outcomes are summarised in *Table 21*. In the T-4 study,[57] the mean decrease in DAS28 score between baseline and 56 weeks was significantly greater in one of the three TTT arms {the DAS28-targeted arm: –2.5 [standard deviation (SD) 3.1]} than in the usual care arm [–1.3 (SD 2.7)], although there was no significant difference between either of the other arms (the MMP-3-targeted arm or the combined DAS28 and MMP-3-targeted arm) and the usual-care arm. Nor in the STREAM trial[55] was there any difference in the DAS44 score between the TTT arm and the usual-care arm at 2 years. In neither study was there any significant difference in mean change from baseline in HAQ score/modified Health Assessment Questionnaire (mHAQ) score between the targeted arm and the usual-care arm (measured at 2 years in the STREA trial[55] and at 56 weeks in the T-4 study[57]). In the T-4 study,[57] the mean change in erosion score from baseline to 56 weeks was significantly better in the combined DAS28 and MMP-3 target group [in which erosion score was reduced by –0.8 (SD 4.8)] than in the routine care group [in which the erosion score increased by 0.8 (SD 1.4)], but differences in the change in erosion score between either of the other arms (the DAS28-targeted arm or MMP-3-targeted arm) and usual care were not significant. Similarly, the increase in joint space narrowing (JSN) score at 56 weeks was significantly lower in the combined DAS28 and MMP-3 target group [0.3 (SD 2.1)] than in the routine care group [1.4 (SD 2.7)]. In addition, in the T-4 study,[57] the mean change in Sharp/van der Heijde score (SHS) from baseline to 56 weeks was better in the combined DAS28 and MMP-3 target group [a reduction in total score of –0.6 (SD 5.9)] than in the routine care group [an increase in total score [2.0 (SD 2.1)]. In the STREAM trial, however, there was no significant difference in the proportion of patients without erosions at baseline who developed new erosions over the course of the trial, or in the median increase in SHS from baseline at 2 years.[55] SJC, TJC, EULAR response, ACR response and quality of life were not reported in any trial comparing TTT with usual care in an early RA population.

In summary, among trials examining an early RA population, there is no clear evidence either in favour of or against the clinical effectiveness of a TTT approach, in comparison with usual care, overall. There is some evidence to suggest that TTT may be more effective than usual care in terms of remission at 1 year. The STREAM[55] trial found usual care to be more effective at 1 year, but TTT to be more effective at 2 years, in terms of the proportion of patients meeting the target and attaining remission. The T-4 study[57] found usual care to be more effective than the MMP-3 target, but the combined DAS28 and MMP-3-targeted arm to be more effective than usual care, in terms of the proportion of patients attaining remission. There were mixed findings in relation to DAS28/DAS44 (the T-4 study[57] found greater benefit for the DAS28-targeted arm than for usual care, but no difference between the MMP-3 or combined targeted arms and usual care;

TABLE 20 Comparison of TTT vs. usual care: early RA population

Trial name or acronym	Treatment arm	*n*[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)			OR (95% CI) for remission
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)	
STREAM[55]	Aggressive group	42	2 years	1 year	41/42 (98)	Remission (DAS44 of < 1.6)	22[b] (54)	NR	22[b] (54) (DAS44 of < 1.6)	1.66 (0.67 to 4.12)
	Conventional care	40		1 year	38/40 (95)	No target	21[b] (65)[c]	NR	21[b] (65) (DAS44 of < 1.6)	
	Aggressive group	42		2 years	41/42 (98)	Remission (DAS44 of < 1.6)	27[b] (66)	NR	27[b] (66) (DAS44 of < 1.6)	0.52 (0.21 to 1.28)
	Conventional care	40		2 years	38/40 (95)	No target	19[b] (49)[c]	NR	19[b] (49) (DAS44 of < 1.6)	
T-4 study[56,57]	Routine care	62	56 weeks	56 weeks	55/62 (89) available for analysis	No target	NA	NR	13/62 (21) (DAS28 of < 2.6);[d,e] 9/62 (15) (SDAI of ≤ 3.3)[d]	–
	DAS28-driven therapy	60		56 weeks	56/60 (93) available for analysis	A DAS28 of < 2.6	23/60 (38%)	NR	23/60 (38) (DAS28 of < 2.6);[d] 19/60 (32) (SDAI of ≤ 3.3)[f]	0.43 (0.19 to 0.95)[g]
	MMP-3-driven therapy	60		56 weeks	53/60 (8%) available for analysis	A MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women	NR	NR	8/60 (13) (DAS28 of < 2.6);[d,h] 8/60 (13) (SDAI of ≤ 3.3)	1.72 (0.66 to 4.52)[g]
	DAS28 and MMP-3-driven therapy	61		56 weeks	58/61 (95) available for analysis	A DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women	NR	NR	34/61 (56) (DAS28 of < 2.6);[e,h] 28/61 (46) (SDAI of ≤ 3.3)[d,f]	0.21 (0.10 to 0.47)[g]

NA, not applicable; NR, not reported.
a Randomised.
b Calculated.
c This refers to the proportion of control arm participants meeting the target set for patients in the intervention arm.
d $p < 0.05$.
e $p < 0.0005$.
f $p < 0.001$.
g Compared with usual care.
h $p < 0.0001$.

FIGURE 5 Forest plot for TTT vs. usual care in the early RA population on remission at 1 year. M–H, Mantel–Haenszel.

TABLE 21 Disease activity outcomes: comparison of TTT vs. usual care – early RA population

					Outcome								
Trial name or acronym	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
STREAM[55]	Aggressive group	42	2 years	2 years	NR	1.4 (0.7)	NR	NR	NR	NR	0.09 (0.50)[b,c]	New erosions in 5 out of 39 (13%) patients without erosions at baseline SHS: 0 (0–1.0)[c,d]	NR
	Conventional care	40		2 years	NR	1.7 (0.8)	NR	NR	NR	NR	0.25 (0.59)[b,c]	New erosions in 8 out of 34 (24%) patients without erosions at baseline SHS: 0.25 (0–2.5)[c,d]	NR
T-4 study[56,57]	Routine care	62	56 weeks	56 weeks	–1.3 (2.7);[c,e] $n = 55$	NR	NR	NR	NR	NR	0.0 (0.7)[c] (mHAQ); $n = 55$	SHS: erosion score, 0.8 (1.4)[c,f] JSN score: 1.4 (2.7)[c,g] Total score: 2.0 (2.1)[c,h]	NR
	DAS28-driven therapy	60		56 weeks	–2.5 (3.1);[c,e] $n = 56$	NR	NR	NR	NR	NR	0.0 (1.0)[c] (mHAQ); $n = 56$	SHS: erosion score, 0.2 (3.1)[c] JSN score: 1.4 (2.8)[c,i] Total score: 1.6 (4.3)[c,f]	NR
	MMP-3-driven therapy	60		56 weeks	–1.3 (2.4);[c] $n = 53$	NR	NR	NR	NR	NR	–0.1 (0.8)[c] (mHAQ); $n = 53$	SHS: erosion score, 0.0 (2.0)[c] JSN score: 0.7 (2.0)[c] Total score: 0.7 (2.4)[c]	NR

Trial name or acronym	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	DAS28 and MMP-3-driven therapy	61		56 weeks	–2.0 (2.2);[c] $n = 58$	NR	NR	NR	NR	NR	0.0 (0.6)[c] (mHAQ); $n = 58$	SHS: erosion score, –0.8 (4.8)[c,f] JSN score: 0.3 (2.1)[c,g,i] Total score: –0.6 (5.9)[c,f,h]	NR

NR, not reported.
a Randomised.
b Mean (SD).
c Change from baseline.
d Median (interquartile range).
e $p < 0.05$.
f $p < 0.005$.
g $p < 0.05$ (routine care vs. combined DAS28 and MMP-3-targeted arm).
h $p < 0.001$.
i $p < 0.05$ (DAS28-targeted arm vs. combined DAS28 and MMP-3-targeted arm).

the STREAM[55] trial also found no difference), and in relation to joint erosion (the T-4 study[57] found greater benefit for the combined target arm than with usual care in terms of SHS, but no difference between the DAS28- or MMP-3-targeted arms and usual care; the STREAM[55] trial also found no difference). There was no difference between TTT arms and usual care on HAQ score (assessed in the STREAM trial[55] and the T-4 study[57]).

Impact of target among trials comparing treat to target with usual care in an early rheumatoid arthritis population Among trials with early RA populations that used a remission target (DAS44 of < 1.6[55] and DAS28 of < 2.6[57]), there was mixed evidence in terms of the proportion of patients meeting the target and the proportion attaining remission (the STREAM trial[55] found usual care to be more effective at 1 year, but TTT to be more effective at 2 years) and DAS28/DAS44 (the T-4 study[57] found TTT to be more effective than usual care, but the STREAM trial[55] found no difference), with no difference on HAQ score[55,57] or joint erosion.[55]

The one trial examining a MMP-3 normalisation target in an early RA population found evidence in favour of usual care in terms of the proportion of patients attaining remission,[57] but no difference between the MMP-3 normalisation-targeted arm and usual care on HAQ score progression.[57]

The one trial examining a combined remission and MMP-3 normalisation target in an early RA population found evidence in favour of TTT in terms of the proportion of patients attaining remission and joint erosion,[57] but no difference between the combined DAS28 remission and MMP-3 normalisation-targeted arm and usual care on HAQ score progression.[57]

In summary, comparing trials by target, there is no clear evidence in favour of any specific target being more effective than usual care in an early RA population.

Trials examining established rheumatoid arthritis populations

Table 22 summarises the TTT outcomes for the comparison of TTT with usual care for the established RA population. Details of treatment adaptations and doses of drugs given are summarised in *Appendix 4, Table 65*. In the Fransen *et al.*[50] trial, the proportion of patients who met the study target at 24 weeks was significantly greater in the DAS28-targeted arm (31%) than in the usual-care arm (16%), as was the proportion who attained LDA at 24 weeks (remission was not reported). In the Optimisation of Adalimumab study there were no significant differences between the usual-care arm and each of the two targeted arms at 6, 12 or 18 months in terms of the proportion of patients meeting the target (for both a DAS28 of < 2.6 and SJC of 0), attaining LDA or attaining remission.[52,53] The data depicted in *Figure 6* show some evidence of a benefit of TTT on LDA at 6 months, in that some targets may be more beneficial than others. This became more evident at 12 and 18 months, certainly for the DAS28-targeted arm compared with routine care [OR 0.74 (95% CI 0.42 to 1.31) at 12 months and OR 0.34 (95% CI 0.19 to 0.61) at 18 months].

Table 23 summarises the disease activity outcomes for the comparison of TTT with usual care for the established RA population. There were no significant differences in mean DAS28 at 6, 12 or 18 months between either of the targeted arms and the routine care arm in the Optimisation of Adalimumab study,[52,53] nor between the targeted and usual-care arms of the Fransen *et al.*[50] trial at 24 weeks. Similarly, there were no significant differences in mean SJC or TJC at 6, 12 or 18 months between either of the targeted arms and the routine care arm in the Optimisation of Adalimumab study[52,53] (the Fransen *et al.*[50] trial did not report SJC or TJC). The proportion of patients with a good or moderate EULAR response was significantly different across the three arms of the Optimisation of Adalimumab study, with higher proportions in the DAS28-targeted arm (63.0%) and SJC-targeted arm (53.5%) than in the usual-care arm at 18 months, but not at 6 or 12 months.[52,53] There were no significant differences in mean change from baseline in the HAQ score at 6, 12 or 18 months between either of the targeted arms and the routine care arm in the Optimisation of Adalimumab study[52,53] (the Fransen *et al.*[50] trial did not report HAQ scores). The DAS44, ACR 20/50/70 responses, joint erosion and quality of life were not reported by either trial examining TTT compared with usual care in an established RA population.

TABLE 22 Treat-to-target outcomes: comparison of TTT vs. usual care – established RA population

Trial name or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n/N* (%) (randomised phase)	Definition of study target	Number (%)			OR (95% CI) for remission
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)	
Fransen *et al.*, 2005[50]	DAS28	205	24 weeks	4 weeks	NA	A DAS28 of ≤ 3.2	NR	NR	NR	–
	Usual care	179		4 weeks	NA	No target	NR	NR	NR	–
	DAS28	205		12 weeks	NA	A DAS28 of ≤ 3.2	NR	NR	NR	–
	Usual care	179		12 weeks	NA	No target	NR	NR	NR	–
	DAS28	205		24 weeks	189/205 (82)	A DAS28 of ≤ 3.2	19/61 (31)[b]	19/61 (31) (DAS28 of ≤ 3.2)[b]	NR	0.42 (0.19 to 0.94)
	Usual care	179		24 weeks	159/179 (89)	No target	13/81 (16)[b,c]	13/81 (16) (DAS28 of ≤ 3.2)[b]	NR	
Optimisation of Adalimumab study[52,53]	Routine care	109	18 months	6 months	NA	No target	17% (DAS28 of < 2.6);[c] 22% (SJC = 0)[c]	28% (DAS28 of < 3.2)	17% (DAS28 of < 2.6)	–
	DAS28 target	100		6 months	NA	A DAS28 of < 2.6	24%	33% (DAS28 of < 3.2)	24% (DAS28 of < 2.6)	0.81 (0.45 to 1.45)[d]
	SJC target	99		6 months	NA	A SJC of 0	24%	30% (DAS28 of < 3.2)	16% (DAS28 of < 2.6)	0.91 (0.50 to 1.66)[d]
	Routine care	109		12 months	NA	No target	21% (DAS28 of < 2.6);[c] 23% (SJC = 0)[c]	32% (DAS28 of < 3.2)	21% (DAS28 of < 2.6)	–
	DAS28 target	100		12 months	NA	A DAS28 of < 2.6	28%	39% (DAS28 of < 3.2)	28% (DAS28 of < 2.6)	0.74 (0.42 to 1.31)[d]
	SJC target	99		12 months	NA	A SJC of 0	26%	31% (DAS28 of < 3.2)	26% (DAS28 of < 2.6)	1.04 (0.58 to 1.86)[d]

continued

TABLE 22 Treat-to-target outcomes: comparison of TTT vs. usual care – established RA population (*continued*)

Trial name or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)			OR (95% CI) for remission
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)	
	Routine care	109		18 months	52/109 (47.7)	No target	16% (DAS28 of < 2.6);[c] 21% (SJC = 0)[c]	23% (DAS28 of < 3.2)	16% (DAS28 of < 2.6)	–
	DAS28 target	100		18 months	73/100 (73)	A DAS28 of < 2.6	38%	47% (DAS28 of < 3.2)	38% (DAS28 of < 2.6)	0.91 (0.50 to 1.66)[d]
	SJC target	99		18 months	77/99 (77.8)	A SJC of 0	26%	27% (DAS28 of < 3.2)	22% (DAS28 of < 2.6)	0.79 (0.42 to 1.49)[d]

NA, not applicable; NR, not reported.
a Randomised.
b $p = 0.028$.
c This refers to the proportion of control arm participants meeting the target set for patients in the intervention arm.
d Compared with usual care.

Study or subgroup	Usual/routine care Events	Total	Targeted therapy/group Events	Total	OR M–H, fixed, 95% CI
Usual care vs. DAS28-driven therapy, 24 weeks					
Fransen 2005[50]	13	81	19	61	0.42 (0.19 to 0.94)
Routine care vs. DAS28 target, 6 months					
Optimisation of Adalimumab study; Pope 2013[52]	31	109	33	100	0.81 (0.45 to 1.45)
Routine care vs. SJC-0 target, 6 months					
Optimisation of Adalimumab study; Pope 2013[52]	31	109	30	99	0.91 (0.50 to 1.66)

FIGURE 6 Forest plot for TTT vs. usual care in the established RA population on LDA at 6 months. M–H, Mantel–Haenszel.

TABLE 23 Disease activity outcomes: comparison of TTT vs. usual care – established RA population

Trial name or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
Fransen *et al.*, 2005[50]	DAS28	205	24 weeks	24 weeks	–0.40 (1.0)[b,c]	NR	NR	NR	NR	NR	NR	NR	NR
	Usual care	179		24 weeks	–0.14 (1.2)[b,c]	NR	NR	NR	NR	NR	NR	NR	NR
Optimisation of Adalimumab study[52,53]	Routine care	109	18 months	6 months	3.26[d]	NR	–6.4 (0.7)[c,d]	–7.8 (0.9)[c,d]	Good/moderate response: 57%	NR	–0.47 (0.06)[c,d]	NR	NR
	DAS28 target	100		6 months	3.72[d]	NR	–7.6 (0.8)[c,d]	–9.0 (1.0)[c,d]	Good/moderate response: 62%	NR	–0.44 (0.06)[c,d]	NR	NR
	SJC target	99		6 months	3.49[d]	NR	–6.9 (0.7)[c,d]	–7.6 (0.9)[c,d]	Good/moderate response: 63%	NR	–0.45 (0.05)[c,d]	NR	NR
	Routine care	109		12 months	3.12[d]	NR	–6.5 (0.7)[c,d]	–8.4 (0.9)[c,d]	Good/moderate response: 51%	NR	–0.57 (0.06)[c,d]	NR	NR
	DAS28 target	100		12 months	3.38[d]	NR	–8.3 (0.8)[c,d]	–9.4 (1.0)[c,d]	Good/moderate response: 61%	NR	–0.47 (0.06)[c,d]	NR	NR
	SJC target	99		12 months	3.18[d]	NR	–7.2 (0.7)[c,d]	–7.8 (0.9)[c,d]	Good/moderate response: 51%	NR	–0.39 (0.06)[c,d]	NR	NR
	Routine care	109		18 months	3.27[d]	NR	–6.5 (0.8)[c,d]	–8.0 (1.0)[c,d]	Good/moderate response: 36%[e]	NR	–0.49 (0.07)[c,d]	NR	NR
	DAS28 target	100		18 months	3.40[d]	NR	–8.3 (0.8)[c,d]	–9.3 (1.0)[c,d]	Good/moderate response: 63%[e]	NR	–0.51 (0.07)[c,d]	NR	NR
	SJC target	99		18 months	3.16[d]	NR	–6.4 (0.8)[c,d]	–7.4 (1.0)[c,d]	Good/moderate response: 54%[e]	NR	–0.41 (0.06)[c,d]	NR	NR

NR, not reported; SEM, standard error of the mean.
a Randomised.
b Mean (SD).
c Change from baseline.
d Mean.
e $p = 0.018$ (chi-squared test).

In summary, among trials examining an established RA population, there is no clear evidence either in favour of or against the clinical effectiveness of a TTT approach, in comparison with usual care, overall. There is some evidence to suggest that TTT may be more effective than usual care in terms of LDA at 6 months. There was evidence in favour of a TTT approach compared with usual care in the Fransen *et al.* trial[50] in terms of the proportion of patients meeting the target and attaining LDA, but no difference between TTT and usual care in the Optimisation of Adalimumab study[52] in terms of the proportion of patients meeting the target and attaining LDA and remission. There was evidence in favour of a TTT approach compared with usual care in terms of EULAR response in the Optimisation of Adalimumab study[52] (both the DAS28- and SJC-targeted arms were found to be more effective than usual care in terms of attaining a good or moderate EULAR response at 18 months, although there was no difference at 6 or 12 months). There was, however, no difference between TTT and usual care in terms of DAS28 in the Fransen *et al.*[50] trial and the Optimisation of Adalimumab study,[52] nor in terms of SJC, TJC or HAQ response in the Optimisation of Adalimumab study.[52]

Impact of target among trials comparing treat to target with usual care in an established rheumatoid arthritis population The one trial examining a LDA target (DAS28 of ≤ 3.2), in an established RA population, found evidence in favour of TTT in terms of the proportion of patients meeting the target and the proportion attaining remission.[50]

The one trial examining a remission target (DAS28 of < 2.6) in an early RA population found evidence in favour of TTT in terms of EULAR good/moderate response,[52] but no difference between the DAS28 remission-targeted arm and usual care on the proportion of patients meeting the target, the proportion of patients attaining LDA,[52] the proportion of patients attaining remission, DAS28, SJC, TJC or HAQ score progression.[52]

The one trial examining a SJC of zero target in an early RA population found evidence in favour of TTT in terms of EULAR good/moderate response,[52] but no difference between the SJC of zero-targeted arm and usual care on the proportion of patients meeting the target, the proportion of patients attaining LDA, the proportion of patients attaining remission, DAS28, SJC, TJC or HAQ score progression.[52]

In summary, when the evidence is examined by target there is evidence in favour of TTT [using a LDA target (DAS28 of ≤ 3.2)], compared with usual care in an established RA population.[50] However, the evidence is mixed with regard to remission (DAS28 of < 2.6) and SJC (SJC of 0) targets,[52] although only one trial used each of these targets and this related only to one outcome reported in the case of the LDA target.[50] The remission and SJC targets impacted on the same outcomes in the same way, although findings were from the same (single) trial.[52]

Trials examining both early and established rheumatoid arthritis populations

Table 24 summarises the TTT outcomes for the comparison of TTT with usual care for the trials with populations containing both patients with early RA and those with established RA. Details of treatment adaptations and dose of drugs given are summarised in *Appendix 4, Table 53*. Neither the TICORA[61] nor the van Hulst *et al.*[63] trial reported the proportion of patients meeting the study target or the proportion of patients attaining LDA, and the van Hulst *et al.*[63] trial did not report the proportion of patients attaining remission. In the TICORA trial, the proportion of patients who attained remission at 18 months was significantly greater in the intensive management arm (65%) than in the routine management arm (16%).[61]

Table 25 summarises the disease activity outcomes for the comparison of TTT with usual care for the trials with populations containing both patients with early RA and those with established RA. In the van Hulst *et al.*[63] trial there was no significant difference in mean DAS28 between the intervention group and usual-care group at 3, 6, 9, 12, 15 or 18 months, or in the mean change from baseline in DAS28 at 18 months. The TICORA[61] trial did not report the DAS28. At 3, 6, 9, 12, 15 and 18 months, the mean DAS44 was significantly lower in the intensive management arm than the routine management arm. In addition, there was a significantly greater mean change from baseline in the DAS44 in the intensive management arm [–3.5 (SD 1.1)] than in the routine management arm [–1.9 (SD 1.4)] of the TICORA trial at 18 months.[61] The DAS44 was not reported in the van Hulst *et al.* trial.[63] There was a significantly greater mean change from baseline in the SJC in the intensive

TABLE 24 Treat-to-target outcomes: comparison of TTT vs. usual care – trials with a combined early and established RA population

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)
TICORA[61]	Intensive management	55	18 months	18 months	53/55 (96)	A DAS44 of ≤ 2.4	NR	NR	36 (65)[b] (EULAR remission – a DAS44 of < 1.6)
	Routine management	55		18 months	50/55 (91)	No target	NR	NR	9 (16)[b] (EULAR remission – a DAS44 of < 1.6)
van Hulst *et al.*, 2010[63]	Intervention group	144	18 months	18 months	138/144 (96)	A DAS28 of ≤ 3.2	NR	NR	NR
	Usual-care group	104		18 months	92/104 (88)	No target	NR	NR	NR

NR, not reported.
a Randomised.
b $p < 0.0001$.

TABLE 25 Disease activity outcomes: comparison of TTT vs. usual care – trials with a combined early and established RA population

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
TICORA[61]	Intensive management	55	18 months	3 months	NR	2.67 (1.38)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Routine management	55		3 months	NR	3.65 (1.40)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Intensive management	55		6 months	NR	2.29 (1.43)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Routine management	55		6 months	NR	3.32 (1.70)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Intensive management	55		9 months	NR	2.07 (1.30)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Routine management	55		9 months	NR	3.08 (1.48)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Intensive management	55		12 months	NR	1.77 (1.13)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Routine management	55		12 months	NR	2.78 (1.46)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Intensive management	55		15 months	NR	1.50 (0.96)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Routine management	55		15 months	NR	2.66 (1.36)[b,c]	NR	NR	NR	NR	NR	NR	NR
	Intensive management	55		18 months	NR	1.33 (0.96);[b,c] change from baseline –3.5 (1.1)[b,d,e]	–11 (5)[d,e,f]	–20 (9)[d,e,g]	Good response: 45 (82%)[b,h]	ACR 20: 50 (91%)[b,h] ACR 50: 46 (84%)[b,h] ACR 70: 39 (71%)[b,h]	–0.97 (0.8)[d,e,i]	SHS: erosion score, 0.5 (0–3.4)[e,j,k] JSN score: 3.25 (1.1–7.5)[e,j] Total score: 4.5 (1 to 9.9)[e,j,m]	SF-12 Physical Summary: 9.3 (12.0)[d,e,l] SF-12 Mental Health Summary: 10.9 (16.0)[d,e]

continued

TABLE 25 Disease activity outcomes: comparison of TTT vs. usual care – trials with a combined early and established RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Routine management	55		18 months	NR	2.68 (1.25);[b,c] –1.9 (1.4)[b,d,e]	–8 (5)[d,e,f]	–12 (12)[d,e,g]	Good response: 24 (44%)[b,h]	ACR 20: 35 (64%)[b,h] ACR 50: 22 (40%)[b,h] ACR 70: 10 (18%)[b,h]	–0.47 (0.9)[b,e,i]	SHS: erosion score, 3 (0.5–8.5)[e,j,k] JSN score: 4.5 (1.5–9.0)[e,j] Total score: 8.5 (2.0 to 15.5)[e,j,m]	SF-12 Physical Summary: 4.0 (11.0)[d,e] SF-12 Mental Health Summary: 6.0 (18.0)[d,e]
van Hulst *et al.*, 2010[63]	Intervention group	144	18 months	3 months	4.06 (3.84 to 4.28)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Usual-care group	104		3 months	3.87 (3.66 to 4.11)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention group	144		6 months	3.87 (3.65 to 4.08)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Usual-care group	104		6 months	3.60 (3.35 to 3.87)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention group	144		9 months	3.68 (3.45 to 3.86)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Usual-care group	104		9 months	3.40 (3.17 to 3.64)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention group	144		12 months	3.74 (3.54 to 3.98)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Usual-care group	104		12 months	3.53 (3.28 to 3.80)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention group	144		15 months	3.61 (3.37 to 3.81)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Usual-care group	104		15 months	3.39 (3.13 to 3.66)[c,n]	NR	NR	NR	NR	NR	NR	NR	NR
	Intervention group	144		18 months	3.55 (3.33 to 3.76);[c,n] –0.66[e,o]	NR	–3.11[e,o]	–2.10[e,o]	Good response 21.5% Moderate response 22.9% No response 55.6%	NR	–0.19 (NR)[e,o]	NR	NR
	Usual-care group	104		18 months	3.24 (2.99 to 3.49);[c,n] –0.69[e,o]	NR	–1.52[e,o]	1.24[f,o]	Good response 18.3% Moderate response 26.9% No response 54.8%	NR	–0.15 (NR)[e,o]	NR	NR

NR, not reported; SF-12, Short Form questionnaire-12 items.
a Randomised.
b $p < 0.0001$.
c Converted from graphical data.
d Mean (SD).
e Change from baseline.
f $p = 0.0028$.
g $p = 0.0003$.
h Number (%).
i $p = 0.0025$.
j Median (interquartile range).
k $p = 0.002$.
l $p = 0.021$.
m $p = 0.02$.
n Mean (95% CI).
o Mean.

management arm [–11 (SD 5)] than in the routine management arm [–8 (SD 5)] at 18 months in the TICORA trial; however, there was no significant difference in mean change from baseline in the SJC between the intervention group and usual-care group at 18 months in the van Hulst *et al.* trial.[63] There was a significantly greater mean change from baseline in the TJC in the intensive management arm [–20 (SD 5)] than in the routine management arm [–12 (SD 12)] at 18 months in the TICORA trial; however, there was no significant difference in mean change from baseline in the TJC between the intervention group and usual-care group at 18 months.[61]

In the TICORA[61] trial at 18 months, the proportion of patients who attained a EULAR good response was significantly greater in the intensive management arm (82%) than in the routine management arm (44%); however, in the van Hulst *et al.* trial[63] at 18 months, the proportion of patients who attained a EULAR good response, a moderate response and no response were similar in the intervention group and usual-care group (statistical significance not reported). In the TICORA trial,[61] the proportions of patients who attained an ACR 20, ACR 50 and ACR 70 at 18 months were significantly greater in the intensive management arm (90%, 84% and 71%, respectively) than in the routine management arm (64%, 40% and 18%, respectively); in the van Hulst *et al.* trial,[63] however, ACR response was not reported. In the TICORA trial,[61] at 18 months, mean change in the HAQ score from baseline was a significantly greater in the intensive management arm [–0.97 (SD 0.8)] than in the routine management arm [–0.47 (SD 0.9)];[61] in the van Hulst *et al.* trial,[63] however, there was no significant difference at 18 months in mean change from baseline in HAQ score between the intervention group and usual-care group.

In the TICORA[61] trial, median increase from baseline in the SHS erosion score and total SHS were significantly lower in the intensive management arm [SHS erosion score: 0.5, interquartile range (IQR) 0–3.4; total SHS: 4.5, IQR 1–9.9] than in the routine management arm (SHS erosion score: 3, IQR 0.5–8.5; total SHS: 8.5, IQR 2.0–15.5), but no significant difference in SHS JSN score between the arms was found at 18 months. Erosion was not reported in the van Hulst *et al.* trial.[63] Mean change from baseline in the Short Form questionnaire-36 items (SF-36) Physical Summary score was significantly greater in the intensive management arm [9.3 (SD 12.0)] than in the routine management arm [4.0 (SD 11.0)]. Furthermore, at 18 months, there was no significant difference in mean change from baseline in the SF-36 Mental Health Summary score between the TTT and usual-care arms.[61] Quality of life was not reported in the van Hulst *et al.* trial.[63]

We identified an abstract also relating to the TICORA trial (i.e. Porter *et al.*[72]); however, there is a discrepancy between the data reported in the abstract and those reported in the Grigor *et al.*[61] paper in terms of EULAR good response, EULAR remission, ACR 20, ACR 70, CRP and SHS erosion score. We used the data from the Grigor *et al.*[61] paper in our synthesis.

In summary, among trials with populations including both patients with early RA and those with established RA, there is no clear evidence either in favour of or against the clinical effectiveness of a TTT approach in comparison with usual care. TICORA,[61] which was the only trial in the systematic review that was rated as having a low risk of bias, demonstrated evidence in favour of a TTT approach in terms of the proportion of patients attaining remission. There was also evidence in favour of a TTT approach rather than usual care in terms of ACR 20/50/70 response in the TICORA[61] trial. The evidence, however, was equivocal for DAS28/DAS44 score, SJC, TJC, EULAR response and HAQ score progression, with the TICORA[61] trial reporting TTT to be more effective than usual care and the van Hulst *et al.*[63] trial reporting no difference between TTT and usual care. In terms of joint erosion and quality of life, evidence from the TICORA[61] trial was ambiguous, with some subscales showing benefit for TTT over usual care and some demonstrating no difference.

Impact of target among trials comparing treat to target with usual care in a population containing both patients with early rheumatoid arthritis and those with etablished rheumatoid arthritis Both trials examining populations including both patients with early RA and those with established RA[61,63] examined a LDA target (DAS44 of ≤ 2.4[61] or DAS28 of ≤ 3.2[63]). Thus, the findings described and summarised above relate only to a LDA target for this comparison and this population group.

Comparison of different targets

Heterogeneity in the treatment protocols used, and outcomes reported, precluded statistical meta-analysis and, therefore, the findings of the trials comparing different targets were combined and examined narratively by outcome.

Trials examining early rheumatoid arthritis populations

Table 26 summarises the TTT outcomes for the comparison of different targets for the early RA population. Details of treatment adaptations and doses of drugs given are summarised in *Appendix 4, Table 54*. Only one of the three trials (i.e. TEAR[58]) reported the proportion of patients meeting the target (while Hodkinson *et al.*[51] and the T-4 study[57] did not). This was lower for both DAS28 of < 3.2-targeted arms combined (28%) than for the immediate ETN and immediate triple-therapy arms without a target (41% and 43%, respectively) at 24 weeks.[58] Similar proportions of patients attained LDA and remission in the Hodkinson *et al.* trial,[51] whereas in the TEAR trial a significantly greater proportion of patients in each of the immediate ETN (41%) and immediate triple-therapy (43%) arms attained LDA according to DAS28 criteria than both step-up arms combined at 24 weeks (28%); however, the proportions of participants attaining remission at 102 weeks were not significantly different between the two DAS28 < 3.2 targeted arms and the two immediate therapy arms without a target.[58] In the T-4 study, the proportion of patients attaining DAS28 remission was highest in the combined DAS28 and MMP-3-targeted group (56%). The proportion of patients attaining DAS28 remission was significantly higher than in the DAS28 of < 2.6 target group (38%) or the MMP-3 target group (13%), the proportion in this last group being significantly lower than in the routine care arm (21%).[57]

Table 27 summarises the disease activity outcomes for the comparison of different targets for the early RA population. There were no significant differences in DAS28 or decrease in DAS28 between arms with different targets in any of the three trials to examine the comparison of different targets in an early RA population. In the TEAR trial,[58] the mean SJC was slightly higher in the two targeted step-up arms [4.4 (SD 3.1) and 4.4 (SD 2.8) for step-up the ETN and step-up triple-therapy arms, respectively] than in either immediate treatment arm with no target [2.2 (SD 3.9) and 2.3 (SD 3.3) for the immediate ETN and immediate triple-therapy arms, respectively] at 102 weeks (although the statistical significance between groups was not reported). In the Hodkinson *et al.* trial,[51] however, there was no significant difference in the mean SJC at 12 months between the SDAI- and CDAI-targeted arms. There was little difference in the mean TJC between the two DAS28-targeted (step-up) arms and the two immediate treatment arms with no target, at 102 weeks, in the TEAR trial.[58] In addition, there was no significant difference in the mean TJC at 12 months between the SDAI- and CDAI-targeted arms in the Hodkinson *et al.* trial.[51]

There was no significant difference in the proportion of patients between the CDAI- and SDAI-targeted arms with EULAR good response at 12 months in the Hodkinson *et al.* trial[51] (the T-4 study[57] and TEAR trial[58] did not report EULAR response). In the TEAR trial,[58] the proportion of patients achieving ACR 20/50/70 response at 6 months was significantly higher in the immediate treatment arms with no target (56.28%, 32.14% and 11.13%, respectively, and 55.88%, 31.33% and 7.97%, respectively, for the immediate ETN and immediate triple-therapy arms) thanin the two DAS28-targeted (step-up) arms (40.12%, 19.51% and 2.84%, respectively, and 39.32%, 17.53% and 3.62%, respectively, for the step-up ETN and step-up triple-therapy arms). There was no significant difference in ACR 20/50/70 response between the two DAS28-targeted (step-up) arms and the immediate treatment arms with no target at 2 years. ACR response was not reported in the Hodkinson *et al.*[51] trial or the T-4 study.[56,57] There were no significant differences in the mean HAQ score or change in HAQ score between arms with different targets in the Hodkinson *et al.* trial,[51] T-4 study[57] or TEAR trial[58] at 1 or 2 years.

In the T-4 study,[57] mean change from baseline in the SHS JSN score and total SHS were significantly lower in the combined DAS28 and MMP-3-targeted group [0.3 (SD 2.1) and –0.6 (SD 5.9), respectively] than in the DAS28-targeted group [1.4 (SD 2.8) and 1.6 (SD 4.3), respectively] at 56 weeks. There was no significant difference between the DAS28-targeted, MMP-3-targeted and combined DAS28 and MMP-3-targeted arms in the mean change from baseline in SHS erosion score at 56 weeks. Similarly, in the TEAR

TABLE 26 Treat-to-target outcomes: comparison of different targets – early RA population

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)
Hodkinson *et al.*, 2015[51]	SDAI arm	42	12 months	12 months	41/42 (98)	A SDAI of ≤ 11 (LDA)	NR	13(32) (DAS28[b])	14 (34) (DAS28[b])
	CDAI arm	60		12 months	57/60 (95)	A CDAI of ≤ 10 (LDA)	NR	17 (30) (DAS28[b])	19 (33) (DAS28[b])
T-4 study[56,57]	Routine care	62	56 weeks	56 weeks	55/62 (89) available for analysis	No target	NA	NR	13/62 (21) (DAS28 of < 2.6)[c,d] 9/62 (15) (SDAI of ≤ 3.3)[e]
	DAS28-driven therapy	60		56 weeks	56/60 (93) available for analysis	A DAS28 of < 2.6	23/60 (38)	NR	23/60 (38) (DAS28 of < 2.6)[f] 19/60 (32) (SDAI of ≤ 3.3)[g]
	MMP-3-driven therapy	60		56 weeks	53/60 (88) available for analysis	A MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women	NR	NR	8/60 (13) (DAS28 of < 2.6)[h] 8/60 (13) (SDAI of ≤ 3.3)
	DAS28 and MMP-3-driven therapy	61		56 weeks	58/61 (95) available for analysis	A DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women	NR	NR	34/61 (56) (DAS28 of < 2.6) 28/61 (46) (SDAI of ≤ 3.3)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)
TEAR[58–60]	Immediate ETN	244	102 weeks	24 weeks	See below	No target	100/244 (41)	100/244 (41) (DAS28-ESR of ≤ 3.2)	NR
	Immediate triple therapy	132		24 weeks	See below		65/152 (43)	65/152 (43) (DAS28-ESR of ≤ 3.2)	NR
	Step-up ETN	255		24 weeks	See below	A DAS28-ESR of < 3.2	105/376 (28)	105/376 (28)[i] (DAS28-ESR of ≤ 3.2)	NR
	Step-up triple therapy	124		24 weeks	See below				NR
	Immediate ETN	244		102 weeks	168/244 (69) (159 with DAS28)	No target	90/159 (57)[d]	NR	90/159 (57)[j] (DAS28-ESR of ≤ 2.6)
	Immediate triple therapy	132		102 weeks	82/132 (62) (76 with DAS28)		45/76 (59)[d]	NR	45/76 (59)[j] (DAS28-ESR of ≤ 2.6)
	Step-up ETN	255		102 weeks	182/255 (71) (166 with DAS28)	A DAS28-ESR of < 3.2	88/166 (53)[d]	NR	88/166 (53)[j] (DAS28-ESR of ≤ 2.6)
	Step-up triple therapy	124		102 weeks	81/124 (65) (75 with DAS28)		42/75 (57)[d]	NR	42/75 (57)[j] (DAS28-ESR of ≤ 2.6)

NA, not applicable; NR, not reported.
a Randomised.
b No further details reported.
c Treatment arms not reported.
d Assuming proportion of completers with DAS28.
e $p < 0.05$ vs. DAS28-driven therapy group.
f $p < 0.0005$ vs. DAS28 and MMP-3-driven therapy group.
g $p < 0.05$ vs. DAS28 and MMP-3-driven therapy group.
h $p < 0.005$ vs. MMP-3-driven therapy group.
i $p < 0.001$ vs. DAS28 and MMP-3-driven therapy group.
j $p < 0.0001$ vs. DAS28 and MMP-3-driven therapy group.

TABLE 27 Disease activity outcomes: comparison of different targets – early RA population

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
Hodkinson *et al.*, 2015[51]	SDAI arm	42	12 months	12 months	3.0 (1.2)	NR	1.3 (2.6)	1.4 (2.4)	EULAR good response: 23 (56%)	NR	HAQ-DI: 1.0 (0.7)	NR	NR
	CDAI arm	60		12 months	3.3 (1.2)	NR	1.4 (2.4)	1.7 (2.5)	EULAR good response: 29 (51%)	NR	HAQ-DI: 1.0 (0.7)	NR	NR
T-4 study[56,57]	Routine care	62	56 weeks	56 weeks	–1.3 (2.7);[b] $n = 55$	NR	NR	NR	NR	NR	0.0 (0.7)[b] (mHAQ); $n = 55$	SHS erosion score: 0.8 (1.4)[b,c] JSN score: 1.4 (2.7)[b,d] Total score: 2.0 (2.1)[b,c]	NR
	DAS28-driven therapy	60		56 weeks	–2.5 (3.1);[b] $n = 56$	NR	NR	NR	NR	NR	0.0 (1.0)[b] (mHAQ); $n = 56$	SHS erosion score: 0.2 (3.1)[b] JSN score: 1.4 (2.8)[b,e] Total score: 1.6 (4.3)[b,f]	NR
	MMP-3-driven therapy	60		56 weeks	–1.3 (2.4);[b] $n = 53$	NR	NR	NR	NR	NR	–0.1 (0.8)[b] (mHAQ); $n = 53$	SHS erosion score: 0.0 (2.0)[b] JSN score: 0.7 (2.0)[b] Total score: 0.7 (2.4)[b]	NR
	DAS28 and MMP-3-driven therapy	61		56 weeks	–2.0 (2.2);[b] $n = 58$	NR	NR	NR	NR	NR	0.0 (0.6)[b] (mHAQ); $n = 58$	SHS erosion score: –0.8 (4.8)[b,c] JSN score: 0.3 (2.1)[b,d,e] Total score: –0.6 (5.9)[b,f,g]	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
TEAR[58–60]	Immediate ETN	244	102 weeks	6 months	NR	NR	NR	NR	NR	ACR 20: 56.28%[h,i] ACR 50: 32.14%[h,i] ACR 70: 11.13%[h,i]	NR	NR	NR
	Immediate triple therapy	132		6 months	NR	NR	NR	NR	NR	ACR 20: 55.88%[h,i] ACR 50: 31.33%[h,i] ACR 70: 7.97%[h,i]	NR	NR	NR
	Step-up ETN	255		6 months	NR	NR	NR	NR	NR	ACR 20: 40.12%[h,i] ACR 50: 19.51%[h,i] ACR 70: 2.84%[h,i]	NR	NR	NR
	Step-up triple therapy	124		6 months	NR	NR	NR	NR	NR	ACR 20: 39.32%[h,i] ACR 50: 17.53%[h,i] ACR 70: 3.62%[h,i]	NR	NR	NR
	Immediate ETN	244		2 years	NR	NR	NR	NR	NR	ACR 20: 51.10%[h] ACR 50: 37.18%[h] ACR 70: 20.52%[h]	NR	NR	NR
	Immediate triple therapy	132		2 years	NR	NR	NR	NR	NR	ACR 20: 45.97%[h] ACR 50: 31.27%[h] ACR 70: 10.66%[h]	NR	NR	NR
	Step-up ETN	255		2 years	NR	NR	NR	NR	NR	ACR 20: 49.11%[h] ACR 50: 32.44%[h] ACR 70: 15.77%[h]	NR	NR	NR
	Step-up triple therapy	124		2 years	NR	NR	NR	NR	NR	ACR 20: 47.92%[h] ACR 50: 37.15%[h] ACR 70: 11.43%[h]	NR	NR	NR

continued

TABLE 27 Disease activity outcomes: comparison of different targets – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Immediate ETN	244		102 weeks	3.0 (1.4); *n* = 159 (DAS28-ESR)	NR	2.2 (3.9); *n* = 159	3.3 (5.5)	NR	NR	mHAQ: 1.0 (0.3); *n* = 15	SHS erosion score: 3.6 (7.4); *n* = 159 JSN score: 3.7 (9.8); *n* = 159 Total SHS: 7.0 (16.6); *n* = 159	NR
	Immediate triple therapy	132		102 weeks	2.9 (1.5); *n* = 76 (DAS28-ESR)	NR	2.3 (3.3); *n* = 76	2.6 (4.5); *n* = 76	NR	NR	mHAQ: 1.0 (0.3); *n* = 73	SHS erosion score: 3.3 (3.9); *n* = 76 JSN score: 3.9 (10.6); *n* = 76 Total SHS: 7.3 (13.3); *n* = 76	NR
	Step-up ETN	255		102 weeks	3.0 (1.4); *n* = 166 (DAS28-ESR)	NR	4.4 (3.1); *n* = 166	3.6 (5.8); *n* = 166	NR	NR	mHAQ: 0.9 (0.3); *n* = 154	SHS erosion score: 3.0 (3.9); *n* = 166 JSN score: 2.1 (4.4); *n* = 166 Total SHS: 4.8 (7.2); *n* = 166	NR
	Step-up triple therapy	124		102 weeks	2.8 (1.3); *n* = 75 (DAS28-ESR)	NR	4.4 (2.8); *n* = 75	2.6 (4.4); *n* = 75	NR	NR	mHAQ: 0.9 (0.3); *n* = 71	SHS erosion score: 3.3 (4.4); *n* = 75 JSN score: 2.6 (5.0); *n* = 75 Total SHS: 6.2 (8.9); *n* = 75	NR

NR, not reported.
a Randomised.
b Change from baseline.
c $p < 0.005$.
d $p < 0.05$ (routine care group vs. combined DAS28 and MMP-3-targeted group).
e $p < 0.001$.
f $p < 0.05$ (DAS28-targeted group vs. combined DAS28 and MMP-3-targeted group).
g $p < 0.005$.
h Converted from graphical data.
i $p < 0.0001$, groups 1 and 2 vs. groups 3 and 4.

trial, there was no significant difference in mean SHS erosion score, SHS JSN score or total SHS between both DAS28-targeted (step-up) arms and either immediate treatment arm with no target at 102 weeks.[58]

The DAS44 and quality of life were not reported in any trial examining TTT compared with usual care in an early RA population.

In summary, there was mainly no difference in the clinical effectiveness of different targets on the proportion of patients meeting the target,[58] attaining LDA[51,58] and attaining remission.[51] Only the T-4 study[57] (early RA) found differences between targets: the DAS28 of < 2.6 target was more effective than the MMP-3 target, and the combined DAS28 of < 2.6 and MMP-3 target was more effective than both the DAS28 of < 2.6 target and the MMP-3 target, in terms of the proportion of patients in remission. There was no difference in the clinical effectiveness of different targets on DAS28/DAS44,[51,57,58] TJC,[51,58] EULAR response[51] and HAQ response.[51,57,58] Findings in other outcomes were equivocal. In terms of SJC, a LDA target (DAS28 of < 3.2) was found to be more effective than immediate treatment with no target in the TEAR trial;[58] however, there was no difference between the two LDA-targeted arms (a CDAI of ≤ 10 and a SDAI of ≤ 11) in the Hodkinson *et al.* trial.[51] In terms of ACR 20/50/70 response, the immediate treatment arm was more effective than the LDA arm in the TEAR trial[58] at 6 months; however, there were no differences between targets in the TEAR trial[58] at 2 years. In terms of joint erosion, the T-4 study[57] found the combined target arm to be more effective than the DAS28 of < 2.6-targeted arm on SHS JSN score and total score; however, there was no difference between the combined target arm, DAS28 of < 2.6 arm and MMP-3 normalisation arm on the SHS erosion score,[57] and no difference between the DAS28 of < 3.2 arm and the immediate treatment arm with no target on SHS erosion score, JSN score and total score in the TEAR trial.[58]

Trials examining established rheumatoid arthritis populations

Table 28 summarises the TTT outcomes for the comparison of different targets for the established RA population. Details of treatment adaptations and dose of drugs given are summarised in *Appendix 4, Table 55*. Only one trial with an established RA population made comparisons between different treatment targets. The Optimisation of Adalimumab study found no differences between arms with different targets in terms of the proportions of patients meeting the target, attaining LDA or attaining remission.[52,53]

Table 29 summarises the TTT outcomes for the comparison of different targets for the established RA population. The one trial that compared different targets in an established RA population was the Optimisation of Adalimumab study.[52,53] There were no significant differences in mean DAS28 at 6, 12 or 18 months between the DAS28 of < 2.6- and SJC of 0-targeted arms.[52,53] The proportion of patients with a good or moderate EULAR response was significantly different across the three trial arms, with a slightly higher proportion in the DAS28 of < 2.6-targeted arm (63.0%) than the SJC of 0-targeted arm (53.5%).[52,53] There were no significant differences in mean change from baseline in HAQ score at 6, 12 or 18 months between the DAS28 of < 2.6- and SJC of 0-targeted arms.[52,53] DAS44, ACR 20/50/70 responses, joint erosion and quality of life were not reported in the Optimisation of Adalimumab study.[52,53]

In summary, there was no difference in the clinical effectiveness of different targets on the proportion of patients meeting the target, attaining LDA and attaining remission.[52] In addition, there was mainly no difference in the clinical effectiveness of different targets on disease activity outcomes.[52] Only the Optimisation of Adalimumab study[52] demonstrated the benefit of a DAS28 of < 2.6 target over a SJC of 0 target and this was only for the proportion of patients with a EULAR moderate/good response.

Comparison of different treatment protocols

Heterogeneity in the treatment protocols used and outcomes reported precluded statistical meta-analysis. Because of the heterogeneity in treatment protocols, the data from trials in the comparison of different treatment protocols were not narratively combined and examined by outcome as with the previous two comparisons; instead, results are reported separately by trial.

TABLE 28 Treat-to-target outcomes: comparison of different targets – established RA population

Trial name	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)
Optimisation of Adalimumab study[52,53]	Routine care	109	18 months	6 months	NA	No target	NR (17) (DAS28 of < 2.6); NR (22) (SJC = 0)	NR (28) (DAS28 of < 3.2)	NR (17) (DAS28 of < 2.6)
	DAS28 target	100		6 months	NA	A DAS28 of < 2.6	24%	NR (33) (DAS28 of < 3.2)	NR (24) (DAS28 of < 2.6)
	SJC target	99		6 months	NA	A SJC of 0	24%	30% (DAS28 of < 3.2)	NR (16) (DAS28 of < 2.6)
	Routine care	109		12 months	NA	No target	NR (21) (DAS28 of < 2.6); NR (22.9) (SJC = 0)	NR (32) (DAS28 of < 3.2)	NR (21) (DAS28 of < 2.6)
	DAS28 target	100		12 months	NA	A DAS28 of < 2.6	28%	NR (39) (DAS28 of < 3.2)	NR (28) (DAS28 of < 2.6)
	SJC target	99		12 months	NA	A SJC of 0	26%	NR (31) (DAS28 of < 3.2)	NR (26) (DAS28 of < 2.6)
	Routine care	109		18 months	52/109 (48)	No target	NR (16) (DAS28 of < 2.6); NR (21.1) (SJC = 0)	NR (23) (DAS28 of < 3.2)	NR (16) (DAS28 of < 2.6)
	DAS28 target	100		18 months	73/100 (73)	A DAS28 of < 2.6	NR (38.0)	NR (47) (DAS28 of < 3.2)	NR (38) (DAS28 of < 2.6)
	SJC target	99		18 months	77/99 (78)	A SJC of 0	NR (26.3)	NR (27) (DAS28 of < 3.2)	NR (22) (DAS28 of < 2.6)

NA, not applicable; NR, not reported.
a Randomised.

TABLE 29 Disease activity outcomes: comparison of different targets – established RA population

Trial name	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
Optimisation of Adalimumab study[52,53]	Routine care	109	18 months	6 months	3.26[b]	NR	–6.4 (0.7)[c,d]	–7.8 (0.9)[c,d]	Good/moderate response: 56.9%	NR	–0.47 (0.06)[c,d]	NR	NR
	DAS28 target	100		6 months	3.72[b]	NR	–7.6 (0.8)[c,d]	–9.0 (1.0)[c,d]	Good/moderate response: 62.0%	NR	–0.44 (0.06)[c,d]	NR	NR
	SJC target	99		6 months	3.49[b]	NR	–6.9 (0.7)[c,d]	–7.6 (0.9)[c,d]	Good/moderate response: 62.5%	NR	–0.45 (0.05)[c,d]	NR	NR
	Routine care	109		12 months	3.12[b]	NR	–6.5 (0.7)[c,d]	–8.4 (0.9)[c,d]	Good/moderate response: 51.4%	NR	–0.57 (0.06)[c,d]	NR	NR
	DAS28 target	100		12 months	3.38[b]	NR	–8.3 (0.8)[c,d]	–9.4 (1.0)[c,d]	Good/moderate response: 61.0%	NR	–0.47 (0.06)[c]	NR	NR
	SJC target	99		12 months	3.18[b]	NR	–7.2 (0.7)[c,d]	–7.8 (0.9)[c,d]	Good/moderate response: 50.5%	NR	–0.39 (0.06)[c,d]	NR	NR
	Routine care	109		18 months	3.27[b]	NR	–6.5 (0.8)[c,d]	–8.0 (1.0)[c,d]	Good/moderate response: 35.8%[e]	NR	–0.49 (0.07)[c,d]	NR	NR
	DAS28 target	100		18 months	3.40[b]	NR	–8.3 (0.8)[c,d]	–9.3 (1.0)[c,d]	Good/moderate response: 63.0%[e]	NR	–0.51 (0.07)[c,d]	NR	NR
	SJC target	99		18 months	3.16[b]	NR	–6.4 (0.8)[c,d]	–7.4 (1.0)[c,d]	Good/moderate response: 53.5%[e]	NR	–0.41 (0.06)[c,d]	NR	NR

NR, not reported; SEM, standard error of the mean.
a Randomised.
b Mean.
c Mean (SEM).
d Change from baseline.
e $p = 0.018$ (chi-squared test).

Trials examining early rheumatoid arthritis populations

Appendix 5, *Table 75* summarises the TTT outcomes for the comparison of different treatment protocols for the early RA population. All seven trials reported the proportion of patients meeting the target. In the BeSt trial, significantly higher proportions of patients met the target in the initial combination therapy with prednisone (PDN) (71%) and initial combination therapy with IFX (74%) arms than in the sequential monotherapy arm (53%) at 12 months.[30] However, at the 7- and 8-year follow-ups, the numbers meeting the target were similar across the four arms.[28,29] In CareRA trial, the proportion of patients meeting the target was not significantly different between the COBRA Classic, COBRA Slim and COBRA Avant-Garde arms among the high-risk patients,[42,43] nor between the methotrexate tight step-up (MTX-TSU) and COBRA Slim arms[40,43] at 16 or 52 weeks. In COBRA-light, there was no significant difference in the proportion meeting the target between the different treatment protocol arms at 13 weeks and 6 or 12 months.[44,45] In the FIN-RACo trial, the proportion of participants meeting the target was significantly higher in the combination treatment arm (37%) than in the single-drug arm (18%) at 2[46] and 11 years[47] (37% and 19%, respectively), but not at 5 years (29% and 22%, respectively).[47] In the Saunders *et al.*[54] trial, the proportions of patients meeting the target in the step-up therapy and parallel triple-therapy arms at 12 months were not significantly different. In the TEAR trial, the proportion of patients meeting the target was similar for the step-up ETN (52.9%) and step-up triple-therapy (56.5%) arms at 12 weeks, but lower for both the step-up etanercept and step-up triple-therapy arms combined (28%) than the immediate etanercept and immediate triple-therapy arms (41% and 43%, respectively) at 24 weeks.[58] There was no significant difference in patients attaining the LDA target among arms using different treatment protocols in the high- or low-risk patient populations in the CareRA trial at 52 weeks.[43] In the U-Act-Early trial, a significantly greater proportion of patients met the target in the TOC plus MTX (86%) and TOC plus PBO–MTX (88%) arms than the MTX plus PBO–TOC arm (77%) at 104 weeks.[62]

Five trials reported the proportion of patients with LDA at follow-up in each arm. In the BeSt trial, significantly higher proportions of patients attained LDA in the initial combination therapy with PDN (71%) and initial combination therapy with IFX (74%) arms than in the sequential monotherapy arm (53%) at 12 months,[30] but at 7- and 8-year follow-up the proportions attaining LDA were similar across the four arms. In the CareRA trial, the proportion of patients attaining LDA was not significantly different between the COBRA Classic, COBRA Slim and COBRA Avant-Garde arms among the high-risk patients,[42,43] nor between the MTX-TSU and COBRA Slim arms among the low-risk patients[40,43] at 16 and 52 weeks. In the Saunders *et al.*[54] trial, there was no significant difference between the proportions of patients attaining LDA in the step-up therapy and parallel triple-therapy arms at 12 months. In the TEAR trial, a significantly greater proportion of patients in each of the immediate ETN (41%) and immediate triple-therapy (43%) arms attained LDA according to DAS28 criteria than both step-up arms combined at 24 weeks (28%).[58]

All seven trials reported the proportion of patients attaining remission at follow-up in each arm. In the BeSt trial, the proportions of patients attaining remission in the four arms were not significantly different at 7 or 8 years.[28,29] Among the high-risk patients in the CareRA trial, the proportions of patients attaining remission at 4, 8, 16 and 52 weeks were similar among the different treatment protocol arms.[42,43] Similarly, among the low-risk patients in the CareRA trial, the proportion of patients attaining remission at 16 and 52 weeks was not significantly different between the COBRA Slim and MTX-TSU arms.[40,43] We noted some discrepancies between the data reported in an abstract and the full text for the CareRA trial. In the De Cock *et al.*[38] abstract, the percentage of patients attaining remission is different from that reported in the Verschueren *et al.*[42] paper for the COBRA Classic and COBRA Avant-Garde arms among the high-risk patients. We have used data from the full text[42] in our synthesis. In the COBRA-light trial, there was no significant difference between the different treatment protocol arms in the proportion of patients attaining remission at 13 weeks and at 6 or 12 months.[44,45] In the FIN-RACo trial, the proportion of participants attaining remission was significantly higher in the combination treatment arm than in the single-drug arm at 2[46] (37% vs. 18%) and 11 years[47] (37% vs. 19%), but not at 5 years (29% vs. 22%).[47] In the Saunders *et al.*[54] trial, there was no significant difference between the proportions of patients attaining remission in the step-up therapy and parallel triple-therapy arms at 12 months. In the TEAR trial, the proportions of participants attaining remission at 102 weeks were not significantly different between the step-up etanercept, step-up triple-therapy,

immediate etanercept and immediate triple-therapy arms.[59] In the U-Act-Early trial, the proportion of patients attaining remission at 104 weeks was significantly greater in the TOC plus MTX (86%) arm and TOC plus PBO–MTX (88%) arm than in the MTX plus PBO–TOC arm (77%).[62]

The disease activity outcomes for the trials comparing different treatment protocols for the early RA population are summarised in *Appendix 5*, *Table 73*.

In the BeSt trial, the proportion of patients who attained ACR 20 and ACR 70 response was greater in the initial combination therapy with PDN and initial combination therapy with IFX arms than in the sequential monotherapy and step-up combination therapy arms at 3, 6 and 12 months; however, the statistical significance of this comparison was not reported.[30] The Dutch version of the Health Assessment Questionnaire (D-HAQ) mean score was significantly lower in the initial combination with PDN and initial combination with IFX arms than in the sequential monotherapy and step-up combination therapy arms at 3, 6 and 9 months, and significantly lower in the initial combination with PDN and initial combination with IFX arms than in the sequential monotherapy arm at 12 months.[30] At 5 years, the mean HAQ scores were significantly lower in the initial combination therapy with IFX arm than in the three other arms, and also in the initial combination with PDN arm than in the sequential monotherapy and step-up combination therapy arms.[31] Similarly, at 7 years, HAQ scores were significantly lower in the initial combination with IFX arm than in the sequential monotherapy and step-up combination therapy arms.[29] In addition, at 8 years, the mean HAQ scores were significantly lower in the initial combination therapy with IFX arm than in the step-up combination therapy arm.[28] There were no significant differences between HAQ scores at 10 years.[64] The SHS erosion score and total SHS at 12 months were significantly lower in the initial combination with PDN [0.9 (SD 1.9) and 2.0 (SD 3.6), respectively] and initial combination with IFX arms [0.7 (SD 2.1) and 1.3 (SD 4.0), respectively] than in the sequential monotherapy [3.5 (SD 8.2) and 7.1 (SD 15.4), respectively] and step-up combination therapy arms [2.6 (SD 4.7) and 4.3 (SD 6.5), respectively)] .[30] However, there were no differences among the arms in median change in SHS or mean SHS estimates corrected for baseline SHS at 10 years.[64] The mean improvement from baseline in the SF-36 Physical Components score at 3 and 6 months was significantly greater in the initial combination therapy with PDN (11.2 and 12.5, respectively) and the initial combination therapy with IFX (9.6 and 12.4, respectively) arms than in the sequential monotherapy (5.8 and 8.0, respectively) and the step-up combination therapy (3.9 and 8.5, respectively) arms, with no significant differences between groups in SF-36 Mental Components score at 3 or 6 months and no significant differences between groups in either SF-36 score at 12 months[30] or 2 years.[26] DAS28, DAS44, SJC, TJC and EULAR response were not reported in the BeSt trial.

In the CareRA trial, there was no significant difference in change from baseline in DAS28-CRP between the COBRA Classic, COBRA Slim and COBRA Avant-Garde arms among the high-risk patients[42] and in the MTX-TSU and COBRA Slim arms among the low-risk patients[40] at 16 or 52 weeks.[43] There were no significant differences in the proportion of patients with a EULAR good response and EULAR moderate response between the COBRA Classic, COBRA Slim and COBRA Avant-Garde arms among the high-risk patients[42] and between the MTX-TSU and COBRA Slim arms among the low-risk population[40] at 16 or at 52 weeks.[43] We noted some discrepancies between the data reported in an abstract and the full text. In the De Cock *et al.*[38] abstract, the percentage of patients with a good EULAR response is different from the percentage reported in the Verschueren *et al.*[42] paper in all high-risk arms. We have used data from the full texts in our synthesis. Among the high-risk patients, similar proportions of patients in the COBRA Classic, COBRA Slim and COBRA Avant-Garde arms had a clinically meaningful HAQ response and a HAQ of 0 at 16 weeks.[42] Among the low-risk patients, the proportion of patients who had a HAQ score of 0 at 16 weeks was significantly greater in the MTX-TSU arm (51.2%) than in the COBRA Slim arm (23.4%), although there were no significant differences between arms in mean HAQ change at 16 or 52 weeks[40,43] or in the proportion of patients with clinically meaningful HAQ change at 16 weeks.[40] The change in SHS was not significantly different between arms using different treatment protocols in the high- and low-risk populations at 52 weeks.[43] The DAS44, SJC, TJC, ACR 20/50/70 response and quality of life were not reported in the CareRA trial.

In the COBRA-light trial, there was no significant difference in mean DAS28 at 12 months between the COBRA and COBRA-light arms. There was no significant difference in mean DAS44 scores, change from baseline in DAS44 or change from baseline in the Disease Activity Score, 44 joints with C-reactive protein concentration (DAS44-CRP) between the COBRA and COBRA-light arms at 6 or 12 months.[44,45] There was no significant difference in SJC or TJC at 12 months between the COBRA and COBRA-light arms.[45] There was no significant difference in the proportion of patients attaining a EULAR good response or EULAR non-response between the COBRA and COBRA-light arms at 13 weeks or 6 months.[44] There was no significant difference in the proportion of patients with ACR 70 in the COBRA and COBRA-light arms at 12 months.[45] There was no significant difference in mean HAQ scores between the COBRA and COBRA-light arms at 3, 6 or 12 months.[44,45] The difference in change in SHS erosion score between the COBRA [0.18 (SD 0.4)] and COBRA-light [0.30 (SD 0.8)] arms at 12 months approached statistical significance ($p = 0.05$).[45] There were no significant differences in mean SHS JSN scores or total SHSs at 12 months between the COBRA and COBRA-light arms.[45] Quality of life was not reported in the COBRA-light trial.

In the FIN-RACo trial,[46–49] there was a significant treatment effect over time (baseline to 11-year follow-up) for DAS28 in the combination treatment arm compared with the single-drug arm, although the difference between arms at 11 years was not statistically significant.[49] There was no significant difference in mean change from baseline in the SJC between the combination treatment and single-drug treatment arms at 2 years, or in median SJC at 11 years.[49] There was no significant difference in mean change from baseline in the TJC between the combination treatment and single-drug arms at 2 years,[46] or in median TJC at 11 years.[49] There was no significant difference between the combination treatment and single-drug arms in the proportion of patients meeting ACR 20 response criteria at 6 months or 2 years;[46] however, the proportion of patients who met ACR 50 response criteria at 2 years was significantly greater in the combination treatment arm than in the single-drug arm.[46] There was no significant difference between the combination treatment and single-drug arms in the mean HAQ score at 2,[46] 5[47] or 11[49] years, the mean change from baseline in Stanford HAQ score at 2 years[46] or the proportion of patients with a HAQ score of 0 or a HAQ score of > 1 at 11 years.[47] There was a significantly lower median number of eroded joints (2 eroded joints, IQR 0–5 eroded joints) and a significantly lower median Larsen score (4, IQR 0–4) in the combination treatment arm than in the single-drug arm (4 eroded joints, IQR 2–7 eroded joints; Larsen score 12, IQR 4–20) at 2 years.[46] There was also a significantly greater mean increase from baseline in Larsen score in the single-drug arm (27, 95% CI 22 to 33) than in the combination treatment arm (17, 95% CI 12 to 26) at 11 years,[49] with no significant difference in the proportion of patients in both treatment arms having no erosive changes in large joints at this time point. The DAS44, EULAR response and quality of life were not reported in the FIN-RACo trial.

In the Saunders *et al.*[54] trial, there was no significant difference in mean change from baseline in DAS28 between the parallel triple-therapy and step-up therapy arms at 12 months. There was no significant difference in the proportion of patients with a EULAR good response between the parallel triple-therapy and step-up therapy arms at 12 months. There was no significant difference in the proportion of patients meeting the criteria for ACR 20/50/70 response between the parallel triple-therapy and step-up therapy arms at 12 months. There was no significant difference in mean change from baseline in HAQ score between the parallel triple-therapy and step-up therapy arms at 12 months. There was no significant difference in mean change from baseline in SHS erosion score, SHS JSN score or total SHS between the parallel triple-therapy and step-up therapy arms at 12 months. There was no significant difference in mean change from baseline in Short Form questionnaire-12 items (SF-12) score between the parallel triple-therapy and step-up therapy arms at 12 months. The DAS44, SJC and TJC were not reported in the Saunders *et al.*[54] trial.

In the TEAR trial, there were no significant differences in the DAS28-ESR between the immediate ETN, immediate triple-therapy, step-up ETN and step-up triple-therapy arms at 102 weeks.[58] The mean SJC was slightly higher in the step-up ETN [4.4 (SD 3.1)] and step-up triple-therapy [4.4 (SD 2.8)] arms than in the immediate ETN [2.2 (SD 3.9)] and immediate triple-therapy [2.3 (SD 3.3)] arms at 102 weeks, although the statistical significance between groups was not reported.[58] The mean TJC was similar in the immediate ETN, immediate triple-therapy, step-up ETN and step-up triple-therapy arms at 102 weeks.[58] The proportion

of patients achieving ACR 20/50/70 response at 6 months was significantly higher in the immediate ETN (56.28%, 32.14% and 11.13%, respectively) and immediate triple-therapy (55.88%, 31.33% and 7.97%, respectively) arms than in the step-up ETN (40.12%, 19.51% and 2.84, respectively) and step-up triple-therapy (39.32%, 17.53% and 3.62, respectively) arms.[58] There was no significant difference in ACR 20/50/70 response between the four different treatment arms at 2 years (although there was a significant effect of drug, in favour of ETN over triple-therapy in terms of ACR 70 response at 2 years).[58] There was no significant difference in mean mHAQ scores between the immediate ETN, immediate triple-therapy, step-up ETN and step-up triple-therapy arms at 102 weeks.[58] There was no significant difference in mean SHS erosion score, SHS JSN score or total SHS between the immediate ETN, immediate triple-therapy, step-up ETN and step-up triple-therapy arms at 102 weeks.[58] The DAS44, EULAR response and quality of life were not reported in the TEAR trial.[58]

There were no significant differences in the DAS28 change from baseline across the study arms in the U-Act-Early trial at 24, 52 or 104 weeks.[62] Patients in the MTX plus PBO–TOC arm had a significantly higher mean SJC [3.0 (SD 4.4)] and TJC [3.7 (SD 4.8)] than in the TOC plus MTX arm [1.0 (SD 2.1) and 2.8 (SD 4.9), respectively] and the TOC plus PBO–MTX arm [1.6 (SD 2.8) and 3.0 (SD 3.9), respectively] at 24 weeks, but there were no significant differences between the arms with different treatment protocols at 52 or 104 weeks.[62] A significantly greater proportion of patients in the TOC plus MTX (89%) and TOC plus PBO–MTX (87%) arms attained a EULAR good response at 24 weeks than in the MTX plus PBO–TOC arm (49%). In addition, the proportion of patients who attained a EULAR moderate response at 24 weeks was significantly greater in the MTX plus PBO–TOC arm (32%) than in the TOC plus MTX (5%) and TOC plus PBO–MTX (11%) arms.[62] The proportion of patients who attained a EULAR good response at 52 weeks was significantly greater in the TOC plus PBO–MTX arm (88%) than in the TOC plus MTX (75%) arm or in the MTX plus PBO–TOC (72%) arm; however, at 104 weeks there were no significant differences between arms receiving different treatment protocols.[62] The proportions of patients who attained ACR 20/50/70/90 responses at 24 weeks and an ACR 90 response at 52 weeks was significantly greater in the TOC plus MTX and TOC plus PBO–MTX arms than in the MTX plus PBO–TOC arm; however, there were no significant differences across arms in terms of ACR 20/50/70/90 at 104 weeks.[62] The three groups were significantly different on mean HAQ score at 24 weeks, with a lower score in the TOC plus MTX arm [0.50 (SD 0.55)] than in the TOC plus PBO–MTX arm [0.63 (SD 0.66)] or the MTX plus PBO–TOC [0.65 (SD 0.54)] arm, with no significant differences at 52 or 104 weeks.[62] There was a significantly smaller mean increase in SHS in the TOC plus MTX arm [0.50 (SD 1.50)] than in the MTX plus PBO–TOC arm [0.96 (SD 2.87)] at 52 weeks, and a significantly smaller mean increase in SHS in the TOC plus MTX arm [1.18 (SD 3.92)] and the TOC plus PBO–MTX arm [1.45 (SD 4.27)] than in the MTX plus PBO–TOC arm [1.53 (SD 2.42)] at 104 weeks.[62] The DAS44 and quality of life were not reported in the U-Act-Early trial.[62]

Other comparisons

Trials examining early rheumatoid arthritis populations

The CAMERA[35,36,67] trial employed a conventional strategy group and an intensive strategy group, which used (different) compound improvement-based targets, different frequencies of assessment and the same treatment protocol. The CAMERA[35,36,67] trial did not report the proportions of patients attaining the target or attaining LDA at 1- or 2-year follow-up points (*Table 30*). The proportions of patients attaining remission at 1 and 2 years were significantly higher in the intensive strategy group (35% and 50%, respectively) than in the conventional strategy group (14% and 37%, respectively).[36]

The mean SJC and TJC were slightly lower in the intensive strategy group than in the conventional strategy group at 6 months, 1 and 2 years, although the statistical significance of these comparisons was not reported (*Table 31*).[36] The proportion of patients with a good EULAR response was a significantly higher in the intensive strategy group (48%) than in the conventional strategy group (25%) and the proportion of patients with no EULAR response was significantly smaller in the intensive strategy group (12%) than in the conventional strategy group (32%), with no significant difference between groups in the proportion of patients with a moderate EULAR response at 6 months.[67] The proportion of patients who attained an ACR

TABLE 30 Treat-to-target outcomes: early RA population – other comparisons

Trial acronym	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criterion)	Attaining remission (criterion)
CAMERA[35,36,67]	Intensive strategy group	151	2 years	1 year	NA	Clinical response (see *Table 15*)	NR	NR	53/151 (35)[b] (≥ 1 period of remission)[c]
	Conventional strategy group	148		1 year	NA	Clinical and laboratory response (see *Table 15*)	NR	NR	21/148 (14)[b] (≥ 1 period of remission)[c]
	Intensive strategy group	151		2 years	92/151 (61)	Clinical response (see *Table 15*)	NR	NR	76/151 (50)[d] (≥ 1 period of remission)[c]
	Conventional strategy group	148		2 years	113/148 (76)	Clinical and laboratory response (see *Table 15*)	NR	NR	55/148 (37)[d] (≥ 1 period of remission)[c]

NA, not applicable; NR, not reported.
a Randomised.
b $p < 0.001$.
c Remission was defined as: a SJC = 0 and two or more of a TJC of ≤ 3, an ESR of ≤ 20 mm/1st hour and a VAS general well-being of ≤ 20 mm.
d $p = 0.029$.

TABLE 31 Disease activity outcomes: early RA population – other comparisons

					Outcome								
Trial acronym	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
CAMERA[35,36,67]	Intensive strategy group	151	2 years	6 months	NR	NR	3.76[b,c]	4.83[b,c]	Good 67 (48%);[d] moderate 55 (40%); none 16 (12%);[d] $n = 151$	NR	0.82[b,c]	NR	NR
	Conventional strategy group	148		6 months	NR	NR	7.44[b,c]	7.93[b,c]	Good 34 (25%);[d] moderate 58 (43%); none 43 (32%);[d] $n = 148$	NR	0.92[b,c]	NR	NR
	Intensive strategy group	151		1 year	NR	NR	3.11;[b,c] –11 (8)[e]	3.96;[b,c] –11 (7)[e]	NR	ACR 50: 87/151 (58%)[f]	0.78;[b,c] –0.44 (0.59)[e]	NR	NR
	Conventional strategy group	148		1 year	NR	NR	5.29;[b,c] –9 (7)[e]	5.74;[b,c] –8 (8)[e]	NR	ACR 50: 64/151 (43%)[f]	0.83;[b,c] –0.39 (0.66)[e]	NR	NR
	Intensive strategy group	151		2 years	NR	NR	6.87;[b,c] –11 (8)[e]	4.87;[b,c] –0 (9)[e]	NR	ACR 50: 69/148 (46%)	0.82;[b,c] –0.41 (0.64)[e]	NR	NR
	Conventional strategy group	148		2 years	NR	NR	6.87;[b,c] –11 (8)[e]	4.39;[b,c] –9 (8)[e]	NR	ACR 50: 67/148 (45%)	0.78;[b,c] –0.42 (0.76)[e]	NR	NR

NR, not reported.
a Randomised.
b Mean.
c Converted from graphical data.
d $p = 0.001$.
e Change from baseline.
f $p = 0.018$.

50 response at 1 year was significantly greater in the intensive strategy group (58%) than in the conventional strategy group (43%), although there was no significant difference in the proportion of patients with an ACR 50 response at 2 years between the intensive strategy group and the conventional strategy group.[36] There were similar mean changes from baseline in HAQ score in the intensive strategy group and the conventional strategy group at 1 and 2 years.[36] The Disease Activity Score (DAS), joint erosion and quality of life were not reported.

Trials examining established rheumatoid arthritis populations

The BROSG[9] trial had two arms: intensive management, which used a DAS44 of ≤ 2.4 target and employed a seven-step treatment protocol based on the target, and in which patients were seen in a hospital setting; and a routine management arm, which had no target and patients were seen in the community as well as in the clinic, with treatment escalation based on clinical opinion. The BROSG trial did not report the proportions of patients attaining the target or attaining LDA or remission (*Table 32*). By the end of the trial (3 years' follow-up), 77.1% of patients in the aggressive therapy arm had some change in disease suppressive treatment, compared with 55.9% in the symptomatic treatment arm (significance not reported).[9]

The mean SJC, TJC and HAQ scores were similar in the symptomatic treatment arm and aggressive therapy arm at 3 years in the BROSG trial (*Table 33*).[9] No other disease activity outcomes were reported.

Adverse events

Comparison of treat to target with usual care

Trials examining early rheumatoid arthritis populations Two studies compared TTT with usual care in the early RA population (*Table 34*). In the STREAM trial,[55] there were significantly more AEs at 2 years in the aggressive group (62) than in the conventional care group (35). However, there was no significant difference between the TTT and usual-care arms in the proportion of patients who experienced any AE at 2 years.[55] The proportion of patients with any AE was similar in the routine care and targeted arms of the T-4 study at 56 weeks.[57] The proportion of patients with SAEs was not significantly different between the usual-care and TTT arms in the T-4 study, and was similar in terms of number of deaths and withdrawals as a result of AEs at 56 weeks.[57]

Appendix 5, *Table 74* summarises the specific AEs reported in trials of TTT compared with usual care in the early RA population. There was no difference in the proportion of patients with serious infection between any of the TTT arms and usual care in the T-4 study at 56 weeks.[57] No other specific AEs were reported in the T-4 study[57] or STREAM trial.[55]

In summary, among trials examining an early RA population, there was no difference in the proportion of patients experiencing any AE,[55,57] SAE,[57] death,[57] withdrawals as a result of AEs[57] or specific AEs;[57] however, more events (any AE) were experienced in the TTT arm than in the usual-care arm in the STREAM trial.[55]

Impact of target among trials comparing treat to target with usual care in an early rheumatoid arthritis population

Among trials with early RA populations that used a remission target (a DAS44 of < 1.6[55] and a DAS28 of < 2.6[57]), there was mixed evidence in terms of the proportion of patients with any AE, with no difference in the proportion of patients with a SAE,[57] deaths,[57] withdrawals as a result of AEs[57] and specific AEs (serious infection[57]). The STREAM[55] trial found fewer AEs in the usual-care arm at 2 years, but no difference between arms in the proportions of patients with any AE at 2 years. The T-4 study[57] also found no difference between the remission-targeted arm and usual care at 56 weeks in the proportions of patients with any AE.

One trial, the T-4 study,[57] examining a MMP-3 normalisation target in an early RA population, found no difference between the MMP-3 normalisation-targeted arm and usual care at 56 weeks in the proportions

TABLE 32 Treat-to-target outcomes: established RA population – other comparisons

Trial	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Definition of study target	Number (%)		
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)
BROSG trial[9]	Symptomatic treatment (shared care)	233	3 years	3 years	197/233 (85)	To control joint pain, stiffness and related symptoms	NR	NR	NR
	Aggressive therapy (hospital)	233		3 years	202/233 (87)	To control joint pain, stiffness and related symptoms, and to suppress clinical and laboratory evidence of inflammation CRP concentration below twice the upper limit of normal	NR	NR	NR

NR, not reported.
a Randomised.

TABLE 33 Disease activity outcomes: established RA population – other comparisons

Trial	Treatment arm	Number of participants[a]	Duration of randomised phase	Follow-up time point	Outcome								
					Mean DAS28 (SD)	Mean DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
BROSG trial[9]	Symptomatic treatment (shared care)	233	3 years	3 years	NR	NR	28 joint count: 3.2 (3.8)	28 joint count: 5.0 (5.9)	NR	NR	1.40 (0.73)	Larsen score: 78.6 (39.4)[b] Eroded joint count 13.1 (7.8);[b] $n = 171$	NR
	Aggressive therapy (hospital)	233		3 years	NR	NR	28 joint count: 2.7 (2.9)	28 joint count: 4.4 (5.7)	NR	NR	1.45 (0.76)	Larsen score 77.9 (42.4)[b] Eroded joint count 13.4 (8.2);[b] $n = 176$	NR

NR, not reported.
a Randomised.
b Mean (SD).

TABLE 34 Adverse events: comparison of TTT vs. usual care

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AE, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawal as a result of AEs[a]
Early RA population							
STREAM[55]	Aggressive group	NR	2 years	59% patients had 62 AEs[c]	Five SAEs, including one patient hospitalised once and one hospitalised twice for drug-related SAEs	None reported	0
	Conventional care	NR	2 years	42% patients had 35 AEs[c]	Three SAEs, including one patient hospitalised once for a drug-related SAE	None reported	0
T-4 study[56,57]	Routine care	61	56 weeks	41/NR (67)	Malignancy, *n* = 1 (1.6); serious infection, *n* = 0 (0)	0 (0)	6
	DAS28-driven therapy	59	56 weeks	49/NR (81)	Death, *n* = 0 (0); malignancy, *n* = 0 (0); serious infection, *n* = 0 (0)	0 (0)	3
	MMP-3-driven therapy	59	56 weeks	46/NR (78)	Malignancy, *n* = 0 (0); serious infection, *n* = 1 (1.7)	2 (3.4)	6
	DAS28 and MMP-3-driven therapy	61	56 weeks	42/NR (69)	Malignancy, *n* = 1 (1.6); serious infection, *n* = 0 (0)	0 (0)	2
Established RA population							
Fransen *et al.*, 2005[50]	DAS28	205	24 weeks	NR	NR	NR	NR
	Usual care	179	24 weeks	NR	NR	NR	NR
Optimisation of Adalimumab study[52,53]	Routine care	100	18 months	NR	NR	NR	10 (10)
	DAS28 target	109	18 months	NR	NR	NR	12 (9.08)[d]
	SJC target	99	18 months	NR	NR	NR	4 (4)

continued

TABLE 34 Adverse events: comparison of TTT vs. usual care (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AE, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawal as a result of AEs[a]
Combined early and established population							
TICORA[61]	Intensive management	55	18 months	32/55 (58) patients had 46 AEs	NR	1/55 (2)	20/129 (16), new DMARD courses were stopped because of toxic effects
	Routine management	55	18 months	42/55 (76) patients had 85 AEs	NR	3/55 (5)	38/89 (43), new DMARD courses were stopped because of toxic effects
van Hulst *et al.*, 2010[63]	Intervention group	AEs NR	NR	NR	NR	NR	NR
	Usual-care group	AEs NR	NR	NR	NR	NR	NR

NR, not reported.
a Refers to numbers of patients, unless otherwise specified.
b Defined in the trial as a SAE.
c $p = 0.034$.
d Data from the flow chart, discrepant with text (which reports 10%).

of patients with any AE, the proportion of patients with a SAE, death, withdrawals as a result of AEs and specific AEs (serious infection).

Similarly, the T-4 study,[57] examining a combined remission and MMP-3 normalisation target in an early RA population, found no difference between the MMP-3 normalisation-targeted arm and usual care at 56 weeks in the proportions of patients with any AE, the proportion of patients with a SAE, deaths, withdrawals as a result of AEs and specific AEs (serious infection).

In summary, comparing trials by target on AEs, there is no clear evidence in favour of any target being more or less safe than usual care in an early RA population.

Trials examining established rheumatoid arthritis populations *Table 34* summarises the AEs among trials of patients with established RA comparing TTT with usual care. The proportions of patients with any AE or a SAE or who died were not reported in either the Fransen *et al.*[50] trial or the Optimisation of Adalimumab study.[52] In the Optimisation of Adalimumab study, the proportion of patients who withdrew because of AEs was lower in the SJC-targeted arm(4%) than in the routine care arm (10%), although statistical significance was not reported.[52]

Appendix 6, *Table 75* summarises the specific AEs reported in trials of TTT compared with usual care in an early RA population. The Fransen *et al.*[50] trial reported that the proportion of patients with dermatological AEs (rash or itching) was significantly greater in the usual-care arm (11%) than in the TTT arm (4%). In addition, the proportion of patients who at 24 weeks were reported to have experienced a gastrointestinal AE was significantly greater in the usual-care arm (9%) than in the TTT arm (4%). Specific AEs were not reported in the Optimisation of Adalimumab study.[52,53]

In summary, the findings of trials examining established RA populations suggest that TTT may be more beneficial to patients than usual care in terms of AE outcomes. A smaller proportion of patients withdrew because of AEs[52] and experienced specific AEs (dermatological and gastrointestinal AEs[50]) in the TTT arm than in the usual-care arm.

Impact of target among trials comparing treat to target with usual care in an established rheumatoid arthritis population

One trial, Fransen *et al.*,[50] examining a LDA target (DAS28 of ≤ 3.2) in an established RA population, found evidence in favour of TTT in terms of specific AEs at 24 weeks (dermatological and gastrointestinal AEs).

One trial, the Optimisation of Adalimumab study,[52] examining a remission target in an established RA population, found no difference in the number and proportion of patients who withdrew from the trial because of AEs between the remission-targeted arm (DAS of < 2.6) and the usual-care arm, although the statistical significance of this comparison was not reported.

The one trial, the Optimisation of Adalimumab study,[52] examining a SJC of 0 target in an established RA population found evidence in favour of TTT in terms of withdrawals as a result of AEs, although the statistical significance of this comparison was not reported.

In summary, there is evidence in favour of the safety of TTT, using a LDA target, compared with usual care in an established RA population,[50] but of a difference between targeted arms and usual care with regard to remission (DAS28 of < 2.6) and SJC (SJC of 0) targets,[52] although only one trial used each of these targets and this related to only one outcome reported in the case of the LDA target.[50] The remission target and SJC target impacted on the same outcomes in the same way, although findings were from the same (single) trial (i.e. the Optimisation of Adalimumab study[52]).

Trials examining both early and established rheumatoid arthritis populations *Table 34* summarises the AEs among trials with a population of patients with early and established RA comparing TTT with usual care. In the TICORA trial,[61] the proportion of patients who experienced any AE was greater in the

usual-care arm (76% experienced 85 AEs) than in the TTT arm (58% experienced 46 AEs; statistical significance not reported), and at 18 months the proportion in each arm who had died was similar to that in the TTT arm. AEs were not reported for the van Hulst *et al.* trial.[63]

Appendix 6, *Table 76* summarises the specific AEs reported in trials of TTT compared with usual care in the early RA population. The TICORA[61] trial reported only numbers of AEs and not the numbers and/or proportions of patients with AEs. There were slightly more dermatological, gastrointestinal and infectious AEs in the usual-care arm than in the TTT arm, although the statistical significance of this comparison was not reported. Specific AEs were not reported in the van Hulst *et al.* trial.[63]

In summary, the one trial[61] reporting on AE outcomes in a population including both patients with early RA and those with established RA reported mixed findings in terms of AE outcomes. The TICORA trial,[61] which was the only trial rated as being at a low risk of bias, reported that a smaller proportion of patients reported any AE and specific AEs (dermatological, gastrointestinal and infectious AEs, significance not reported) in the TTT arm than in the usual-care arm; however, there was no difference in the number of deaths between the TTT and usual-care arms.[61]

Impact of target among trials comparing treat to target with usual care in a population containing both early and established rheumatoid arthritis patients

The one trial[61] reporting on AE outcomes in a population including both patients with early RA and those with established RA examined a LDA target (DAS44 of ≤ 2.4). Thus, the findings described and summarised above relate only to a LDA target for this comparison and this population group.

Comparison of different targets

Trials examining early rheumatoid arthritis populations The Hodkinson *et al.*[51] trial did not report AEs. In the two trials comparing different targets in an early RA population, the T-4 study[57] and TEAR[58] (*Table 35*), the proportions of patients with AEs or SAEs and of deaths and withdrawals due to AEs were similar across arms of different targets, including a DAS28 of < 2.6; a MMP-3 concentration of < 121 ng/ml for men and < 59.7 ng/ml for women; a DAS28 of < 2.6 and a MMP-3 concentration of < 121 ng/ml for men or < 59.7 ng/ml for women; no target; and a DAS28-ESR of < 3.2.

Appendix 5, *Table 72* summarises the specific AEs reported in trials comparing different targets in the early RA population. The T-4 study[57] reported no difference in the proportion of patients with serious infection between the DAS28-, MMP-3- and combined DAS28 and MMP-3-targeted arms at 56 weeks. No significant differences in the number of specific AEs were reported in the TEAR trial at 102 weeks.[58]

In summary, among trials comparing different targets in an early RA population, different targets made no difference to the proportions of patients with any AE,[57,58] SAEs,[57,58] deaths,[57,58] withdrawals as a result of AEs[57,58] and specific AEs.[57,58]

Trials examining established rheumatoid arthritis populations *Table 35* summarises the AEs among trials of patients with established RA comparing different targets. In the Optimisation of Adalimumab study,[52] the proportion of patients who withdrew because of an AE was greater in the DAS28 of < 2.6-targeted arm (9%) than in the SJC-targeted arm (4%), although statistical significance was not reported. The proportions of patients with any AE, a SAE or who died were not reported. No specific AEs were reported.

Comparison of different treatment protocols

Trials examining early rheumatoid arthritis populations *Tables 73* and *74* in *Appendix 5* examine AEs among trials of patients with early RA comparing different treatment protocols.

TABLE 35 Adverse events: comparison of different targets

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AE in source, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawal as a result of AEs[a]
Early RA population							
Hodkinson *et al.*, 2015[51]	SDAI arm	AEs NR	NR	NR	NR	NR	NR
	CDAI arm	AEs NR	NR	NR	NR	NR	NR
T-4 study[56,57]	Routine care	61	56 weeks	41 (67.2)	Death, *n* = 0 (0); malignancy, *n* = 1 (1.6); serious infection, *n* = 0 (0)	0 (0)	6
	DAS28-driven therapy	59	56 weeks	49 (81.4)	Death, *n* = 0 (0); malignancy, *n* = 0 (0); serious infection, *n* = 0 (0)	0 (0)	3
	MMP-3-driven therapy	59	56 weeks	46 (78.0)	Death, *n* = 2 (3.4); malignancy, *n* = 0 (0); serious infection, *n* = 1 (1.7)	2 (3.4)	6
	DAS28 and MMP-3-driven therapy	61	56 weeks	42 (68.9)	Death, *n* = 0 (0); malignancy, *n* = 1 (1.6); serious infection, *n* = 0 (0)	0 (0)	2
TEAR[58–60]	Immediate ETN	244	102 weeks	193 (79.1)	35 (14.3)	1	12 (4.9): SAE, *n* = 8; AE, *n* = 3; death, *n* = 1
	Immediate triple therapy	132	102 weeks	101 (76.5)	18 (13.6)	1	7 (5.3): SAE, *n* = 2; AE, *n* = 4; death, *n* = 1
	Step-up ETN	255	102 weeks	187 (73.3)	32 (12.5)	2	9 (3.5): SAE, *n* = 2; AE, *n* = 5; death, *n* = 2
	Step-up triple therapy	124	102 weeks	92 (74.2)	16 (12.9)	0	4 (3.2): SAE, *n* = 2; AE, *n* = 2; death, *n* = 0
Established RA population							
Optimisation of Adalimumab study[52,53]	Routine care	100	18 months	NR	NR	NR	10 (10)
	DAS28 target	109	18 months	NR	NR	NR	12 (9.08)[c]
	SJC target	99	18 months	NR	NR	NR	4 (4)

NR, not reported.
a Refers to numbers of patients unless otherwise specified.
b Defined in the trial as a SAE.
c Data from flow chart, discrepant with text (which reports 10%).

In the BeSt trial, the proportions of patients across the four arms (varying in treatment protocol) who had experienced any AE or a SAE were similar at 1 year[30] and 5 years.[31] Similar proportions of patients died in each arm at 5[31] and 10 years,[33] although this proportion was slightly greater in the two initial combination therapy arms (15.8% and 15.6%), than in the sequential monotherapy and step-up combination therapy arms (12.7% and 12.4%, respectively; statistical significance not reported). Withdrawals as a result of AEs were not reported. Similar proportions of patients had specific AEs in each treatment arm of the BeSt trial at 1 year (see *Appendix 5*, *Table 74*; significance not reported).[30] The proportion of patients with specific AEs were not significantly different across treatment arms at 5 years.[31]

Among the high-risk patients in the CareRA trial, the proportions of patients with any AE at 16 weeks were significantly higher in the COBRA Classic (61.2%) and COBRA Avant-Garde (69.9%) arms than in the COBRA Slim (46.9%) arm.[42] Similar numbers of SAEs were reported in the three trial arms and similar proportions of deaths and withdrawals as a result of AEs across all arms were reported at 16 weeks.[42] Among the low-risk patients, there were no significant differences in the proportion of patients with any AE across arms at 16 weeks, with no SAEs in either arm.[40]

The proportion of patients with any AE was not significantly different between arms using different treatment protocols in the high- and low-risk populations of the CareRA trial at 52 weeks; however, the mean number of AEs per patient differed significantly across groups in the high-risk population of the CareRA trial, with a higher mean number of AEs per patient in the COBRA Classic [1.9 (SD 2.0)] and COBRA Avant-Garde [1.9 (SD 1.6)] arms than in the COBRA Slim arm [1.3 [SD 1.4)] at 52 weeks.[43] The number of therapy-related SAEs was similar across arms in the high- and low-risk populations of the CareRA trial at 52 weeks.[43] There were no deaths in either arm of the low-risk population and similar proportions of patients died in the high-risk population. There were no withdrawals as a result of AEs in the high- or low-risk population of the CareRA trial.[43]

Specific AEs were reported only in terms of numbers of events in the CareRA trial for the high-risk patients at week 16 and for the high- and low-risk patients at week 52 (rather than the proportion of patients experiencing each AE), and the statistical significance of comparisons across groups was not reported at 16 weeks. There were more dermatological AEs in the COBRA Classic and COBRA Avant-Garde arms than in the COBRA Slim arm at 16 weeks among the high-risk patients.[42] Among the low-risk patients, there were similar proportions of patients with gastrointestinal and infectious AEs at 16 weeks.[40] The numbers of dermatological, ophthalmological and infectious AEs were similar across trial arms in the high- and low-risk populations; however, there were more gastrointestinal AEs in the COBRA Avant-Garde arm (67) than in the COBRA Classic (45) and COBRA Slim (48) arms among the high-risk population at 52 weeks.[43] No other specific AEs were reported.

In the COBRA-light trial, similar proportions of patients had any AE ($\geq$ 1) across the COBRA and COBRA-light arms at 6 months.[44] Twice as many patients in the COBRA-light arm as in the COBRA arm experienced a SAE (6 vs. 3) at 6 months[44] and 12 months (9 vs. 16),[45] although the statistical significance was not reported. Numbers of withdrawals as a result of AEs across arms were similar at 6 months.[44] In terms of specific AEs, in the COBRA-light trial, the proportion of patients who had dermatological AEs at 6 months was slightly greater in the COBRA-light arm (43%) than in the COBRA arm (37%), although statistical significance was not reported.[44] All other specific AEs were similar across trial arms.

In the FIN-RACo[46] trial, the proportion of patients who had any AE or SAEs were similar in the combination treatment and single-drug arms at 2 years, with no deaths or withdrawals as a result of AEs in either arm at 2 years. There were no significant differences in the proportions of patients with specific AEs in the combination treatment and single-drug arms at 2 years.

In the Saunders *et al.*[54] trial, AEs were reported only in terms of number of AEs rather than as number and/or proportion of patients with AEs. Similar numbers of AEs were reported in the parallel triple-therapy and

step-up therapy arms at 12 months, with similar numbers of drug withdrawals and no withdrawals from the trial in either arm. Numbers of specific AEs were similar in the parallel triple-therapy and step-up therapy arms.

In the TEAR trial,[58] AEs were reported only in terms of numbers of AEs rather than as number and/or proportion of patients with AEs. Similar proportions of patients experienced any AE, a SAE, death or withdrawal as a result of AEs or specific AEs in the four trial arms (immediate ETN, immediate triple therapy, step-up ETN and step-up triple therapy) at 102 weeks.

The proportion of patients with any AE was not significantly different between arms using different treatment protocols in the U-Act-Early trial at 104 weeks.[62] The proportion of patients with a SAE was not significantly different between arms at 104 weeks, and there were no deaths in either arm.[62] There was no significant difference in withdrawals as a result of AEs across groups in the U-Act-Early trial.[62] The proportion of patients with specific AEs was similar across arms at 104 weeks.[62]

Other comparisons

Trials examining early rheumatoid arthritis populations There were similar proportions of patients with any AE in the intensive strategy group and conventional strategy group in the CAMERA trial (*Table 36*).[36] More SAEs (graded as severe by the rheumatologist) were reported in the intensive strategy arm ($n = 35$) than in the conventional strategy arm ($n = 10$), although the statistical significance of this comparison was not reported.[35] Likewise, there was a greater proportion of withdrawals as a result of AEs in the intensive strategy arm (18%) than in the conventional strategy arm (7%), although the statistical significance was not reported.[36] In terms of specific AEs (see *Appendix 6*, *Table 75*), a significantly greater proportion of patients in the intensive strategy group experienced dermatological AEs (53.7%), gastrointestinal AEs (66.4%), central nervous system AEs (59.1%), hepatic AEs (55.0%) and haematological AEs (25.5%) than in the conventional strategy group (40.0%, 53.6%, 38.6%, 35.0% and 10.7%, respectively) at 2 years.[35]

Trials examining established rheumatoid arthritis populations AEs were not reported for the BROSG trial.[9]

Discussion

This section focuses on the main outcomes of the proportion of patients meeting the target, attaining LDA and attaining remission. Overall, across populations, there is no clear evidence either in favour of or against the clinical effectiveness of a TTT approach, in comparison with usual care, in terms of the proportion of patients meeting the target, attaining LDA or attaining remission. However, there does seem to be some limited support for TTT among the early RA population, in terms of remission, among the established RA

TABLE 36 Adverse events: early RA population – other comparisons

				AE, *n*/*N* (%)			
Trial acronym	Treatment arm	Safety population, *n*	Follow-up time point	Any AE[a]	Any SAE[a,b]	Death	Withdrawal as a result of AEs[a]
CAMERA[35,36,67]	Intensive strategy group	149	2 years	142 (95)	35 severe AEs reported[c]	NR	27/151 (18)
	Conventional strategy group	140	2 years	126 (90)	10 severe AEs reported[c]	NR	11/148 (7)

NR, not reported.
a Refers to numbers of patients unless otherwise specified.
b Defined in the trial as a SAE.
c Graded as severe according to the rheumatologist.

population, in terms of LDA, and among trials that included populations of patients with both early and established RA, in terms of remission. Similarly, there is no clear evidence either in favour of or against the clinical effectiveness of a TTT approach, in comparison with usual care, in terms of the DAS28/DAS44 response, SJC, TJC, EULAR response, HAQ score, erosion and quality of life across populations, when overall findings are considered;[50,52,55,57,61,63] however, there does seem to be some limited support for TTT on some clinical outcomes. Similarly, comparing trials by target, there is no clear evidence in favour of any target being more or less effective than usual care across population groups, as measured by the proportion of patients meeting the target, attaining LDA and attaining remission. There is also no clear evidence in favour of one particular target over all others in relation to DAS28/DAS44 response, SJC, TJC, EULAR response, HAQ score, erosion and quality of life across populations, when overall findings are considered. Specifically, we found no difference in the clinical effectiveness of different targets on DAS28/DAS44,[51,57,58] TJC[51,58] and HAQ score response[51,58] among the trials reviewed and equivocal evidence for SJC,[51,58] EULAR response,[51,52] ACR 20/50/70 response[58] and joint erosion.[57,58] All trials comparing different targets were rated as being at high risk of bias.

Adverse events appear to have been experienced differently by different population groups in the comparison of TTT with usual care. Among trials examining an early RA population, evidence was mixed, favouring the usual-care arm. Among trials examining established RA populations, the evidence favoured the TTT arm and was mixed in the only trial reporting on these outcomes in a population containing both early and established RA patients (i.e. the TICORA trial[61]), slightly favouring TTT.

Overall, when the evidence comparing trials by target on AEs is considered across all population groups, there is no clear evidence in favour of any target being more or less safe than usual care, or more or less safe than any other target. Caution is warranted, however, in interpreting these findings, given the small number of studies reporting AE data in each population group. In addition, the same AEs were not considered in all studies and AEs were recorded/reported seemingly erratically in the original papers, with little systematic consideration of AEs. Future trials should systematically record and report on an agreed range of AEs, to build the evidence base of AEs within TTT. This is an important issue to address, given that the intensity of TTT as a treatment plan is typically greater than that usual care.

The quality of the included studies will have inevitably had an impact on the findings of our review. The risk of bias, as assessed with the Cochrane risk-of-bias instrument,[24] was rated as being high in six RCTs and three cluster RCTs, and unclear in five RCTs; this was generally because of the judgements for allocation concealment, blinded outcome assessment and attrition domains. Only one RCT (i.e. the TICORA trial[61]) was rated as being at low risk of bias.

In trials rated as being at high or unclear risk of bias, findings were generally equivocal or demonstrated no difference between arms. The one trial rated as being at low risk of bias,[61] which compared TTT against usual care in a population that included both patients with early RA and those with established RA, by the criterion of this review (patients with a disease duration of < 5 years) demonstrated evidence that was generally in favour of a TTT approach, with favourable results in terms of the proportion of patients attaining remission, DAS44 response, change in SJC and TJC, EULAR good response, ACR 20/50/70 response, HAQ score progression, change in joint erosions (as measured by the SHS erosion score and total SHS) and SF-36 Physical Summary score (and no difference between TTT and usual care in terms of SHS JSN score and SF-36 Mental Health Summary score).[61]

There are, however, some elements of the design of the TICORA trial[61] that require consideration in interpreting findings. The TTT arm had more intensive assessments, more frequent visits and a higher dose of steroids than the usual-care arm; therefore, it is unclear whether the effects on outcomes were because of TTT or the increased assessment or escalation of therapy. The issue of unbalanced steroid use also applies to the FIN-RACo trial,[46–49] in which more patients in the intensive treatment arm received prednisolone; as a result, it is difficult to untangle the effects of TTT from the effects of the steroid. Future trials are needed in which TTT is the only variable that differs between arms and in which all other aspects of care are held constant, as far as is practicable. In addition, the STREAM trial,[55] which appears frequently in the current

review because of the large number of outcomes it contributed, had a small sample size and uneven distribution of some baseline variables, such as rheumatoid factor (which was also relatively low at baseline).

The current systematic review is the most comprehensive review to date to examine the clinical effectiveness of TTT. We have synthesised findings on TTT compared with usual care and a comparison of different targets. Synthesis of different treatment protocols was precluded (even in terms of a narrative integration of findings) by heterogeneity and lack of comparability between treatment protocols, although we have provided a comprehensive summary of the findings of trials that compare different treatment protocols. The current review is also the only systematic review to examine findings by population, which is important in this context as the recommendations for TTT differ slightly for early and established RA patients, as the treatment prognosis and implications of TTT may be different in these populations.[17,18] Another strength of the current review is the focus on RCTs, which reduces the impact of selection bias on the review findings.

The main limitation of the current review is the small number of trials within each comparison, in each population group. Trials showed much heterogeneity in targets, treatment protocols, frequency of contact, outcomes and follow-up time points, even within the same population group, in each comparison. Risk of bias was rated to be high in the majority of included trials. Another consideration is that many trials used a DAS28 of < 2.6 to assess clinical remission as an outcome; however, doubts have been raised as to whether or not this is true remission, as it is now known that active disease and radiological progression can be present in patients with a DAS28 of < 2.6.[73–78]

The systematic reviews by Schoels *et al.*[23] (initial review) and Stoffer *et al.*[79] (update of the Schoels *et al.* review), designed to inform the international task force recommendations for treating to target,[17,18] both concluded that TTT was more effective than usual care. Similarly, Jurgens *et al.*[21] examined the effectiveness of TTT on remission rates and found results in favour of TTT, Schipper *et al.*[80] compared the effectiveness of TTT with usual care on mean change in DAS28 and found TTT to be more effective than usual care and Bakker *et al.*[81] found evidence of the effectiveness of TTT in terms of remission, but did not synthesise the evidence (findings were reported individually by study). The Knevel *et al.*[82] review, which also analysed RCTs and non-randomised studies, found no evidence to recommend one particular target over others, similar to the findings of the current review. The Knevel *et al.*[82] review also reported no particular benefit of TTT among patients with established RA, but an overall benefit of TTT among early RA patients. It is unclear whether or not the reviews by Schoels *et al.*,[23] Stoffer *et al.*[79] and Knevel *et al.*[82] reported on all outcomes reported in all included studies; the current review provides an explicit and comprehensive overview of all measured outcomes. All five previous reviews examined data from RCTs and non-randomised studies together, whereas the current review focused on RCTs only, to reduce the possibility of selection bias.

Although the search strategy for this assessment report was comprehensive, the possibility of a publication bias cannot be discounted. It was not possible to undertake a formal assessment of publication bias, as there were too few trials per comparison to assess funnel plot asymmetry.

From the evidence reviewed here, we consider that the evidence for TTT is mixed but, in early RA, there does seem to be some limited support for TTT, particularly in terms of the numbers of patients achieving remission. This is particularly true if the TICORA trial,[61] which was the only trial in the review rated as being at low risk of bias, is interpreted as providing evidence relevant to the early RA population (inclusion criterion for the TICORA trial was disease duration of < 5 years). We also found no clear evidence to support the clinical effectiveness of one particular target over others. There is also no clear evidence of a greater likelihood of AEs in a TTT approach compared with usual care (or of the use of one target in particular), suggesting that such an approach is no more harmful (and may, indeed, be less harmful, as some of the evidence suggests). Caution is warranted in interpreting this conclusion, however, as there were only small numbers of trials within each comparison, in each population group, and there was much heterogeneity in terms of targets, treatment protocols, frequency of contact, outcome and follow-up time points. In addition, only one trial (i.e. the TICORA trial[61]) was rated as being at low risk of bias; the rest were rated as being unclear or high

risk of bias, mainly because of the lack of blinding in outcome assessment and attrition bias (and, in addition, elements of design make the attribution of the TICORA trial's[61] findings to TTT less clear).

According to the current review findings, there is a weak basis for recommending TTT in the routine care of RA and TTT does not appear to confer any significant harms, although AEs were not examined in a consistent way across trials. Despite this uncertainty, it is not immediately clear that additional research on TTT should be conducted because there are many different aspects to the TTT concept. If such research is to be conducted, there should be a focus on well-conducted trials comparing TTT with usual care and/or different TTT targets, which are adequately blinded (in terms of participants, study personnel and outcome assessment), with low rates of attrition and adequate allocation concealment, designed to control for all other variables than TTT/different targets, reporting on the proportion of patients meeting the target and being in remission.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

The objective of this review was to identify and evaluate studies exploring the cost-effectiveness of TTT strategies in the treatment of RA.

Identification of studies

Electronic databases

Studies were identified by searching the following electronic databases on the 14 January 2016:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (via Ovid) 1948 to present
- EMBASE (via OvidSP) 1980 to present
- Web of Science Science Citation Index Expanded (via Thomson Reuters) from 1900 to present
- Web of Science Conference Proceedings Index (via Thomson Reuters) from 1990 to present
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO*host*) 1982 to present
- NHS Economic Evaluation Database (via The Cochrane Library) 1995 to 2015
- American Economic Association's electronic bibliography (via Ovid) from 1886 to present.

Sensitive keyword strategies using free text and, where available, subject headings or thesaurus terms for RA and TTT were combined in the electronic database searches. Searches in MEDLINE, EMBASE, Web of Science and CINAHL were limited by study design by combining the results with economic- and cost-related search terms (see *Appendix 2* for full search strategies). Date limits or language restrictions were not used on any of the database searches.

Inclusion and exclusion criteria

Studies were selected according to predetermined inclusion and exclusion criteria. Studies were included if they reported the cost-effectiveness of TTT strategies in RA estimating the health-related benefits in terms of quality-adjusted life-years (QALYs) gained; life-years gained; DAS; SHS; percentage of patients achieving remission; percentage of patients achieving LDA; percentage of patients achieving treatment response; change in patient utility (VAS or SF-36 scores); or any other clinical measure of disease progression/activity or health-related quality of life. Studies that did not report costs but in which the treatment protocols were described in sufficient detail to allow the incremental cost between treatment arms to be assumed or approximated were also included. Papers not published in the English language were excluded.

One reviewer (AR) independently screened all titles and abstracts. When there was uncertainty in the decision, a second reviewer (MDS) was used and a consensus through discussion was obtained. Full papers were obtained for any titles/abstracts that were considered relevant or where the title/abstract information was not sufficient to make a decision.

Quality assessment strategy

The quality of the economic evaluation studies that met the inclusion criteria was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[83,84] The use of this checklist ensures a consistent approach to assessing the quality of each economic evaluation. This can be found in *Appendix 5*.

Results of the cost-effectiveness review

The systematic searches identified 1231 potentially relevant citations. Of the titles and abstracts screened, two relevant full-text papers were retrieved and assessed in detail. A PRISMA flow diagram describing the process of identifying relevant literature can be found in *Appendix 4*.

Two eligible studies were found to be relevant: Vermeer *et al.*[85] and van den Hout *et al.*[86] Vermeer *et al.*[85] conducted an economic evaluation of TTT compared with usual care in patients in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry: the DREAM remission induction cohort (TTT) and the Nijmegen early-RA-inception cohort. Adult patients with an ACR classification criterion for RA, with symptom duration of < 1 year and who had had no previous DMARDs were included.

The TTT strategy included regular assessment of patients (weeks 0, 8, 12, 20, 24, 36 and 52, and every 3 months thereafter) against the target of remission (DAS28< 2.6). A treatment protocol of DMARD monotherapy, followed by a step-up to combination DMARD therapy, followed by anti-tumour necrosis factor (TNF), was adopted. The usual-care group did not have the DAS28 released to the treating rheumatologist. Treatment was not provided in accordance with a protocol, but left to the discretion of the rheumatologist. In general, patients were treated with step-up or sequential monotherapy with cDMARDs and/or a biologic, notably anti-TNF.

The costs used were those applicable in 2011 in the Netherlands. Results were expressed in terms of cost per remission and cost per QALY using 2-year follow-up data and an extended analysis using 3-year follow-up for a smaller proportion of patients with available data.

The authors found that TTT was associated with an incremental cost of €3591 per remission at 2 years and after 3 years was dominant (cost saving and more patients in remission). Similarly, at 2 years the cost per QALY for TTT compared with usual care was €19,410 and it was dominant at 3 years (more QALYs, cost saving). This suggests that TTT has higher costs in the short term (as the strategy requires more intensive drug therapy and more frequent assessment of patients), but it is more effective and, in the longer term, this greater effectiveness offsets some of the initial extra costs and may more than offset them. For example, patients in remission are less likely to progress to costly biologic therapies or require hospitalisation. However, it may be the case that TTT simply delays rather than avoids these cost-incurring events completely. This would become apparent only with longer follow-up.

van den Hout *et al.*[86] conducted an economic evaluation as part of the BeSt study.[26–34] This was a randomised trial of patients ($n = 508$) with early-onset RA randomised to (1) DMARD monotherapy, (2) step-up combination therapy (including to treatment with IFX), (3) DMARD and steroid combination therapy stepped up (including to treatment with IFX) or (4) initial IFX and DMARD combination therapy. DASs were measured every 3 months and used to change treatments according to the protocol the patient was randomised to. Costs and utilities were measured over 2 years to allow cost per QALY estimates to be made from a Dutch perspective. Productivity costs were included using both friction cost and human capital approaches.

The primary analysis used British tariffs to generate utility scores for the EuroQol-5 Dimensions (EQ-5D) and the friction cost method for costing productivity losses. The most effective strategy in terms of QALYs generated was strategy 4, but the additional cost meant that this was unlikely to be considered cost-effective: the incremental cost-effectiveness ratio (ICER) compared with the next most effective strategy was €130,000. Strategy 2 was most likely to be cost-effective for willingness-to-pay values up to €74,000 per QALY and strategy 3 for willingness-to-pay values between €74,000 and €130,000 per QALY. These general findings did not change in sensitivity analysis, except when the human capital approach to valuing productivity losses was taken. Then, strategy 4 became highly cost-effective.

Independent economic assessment

Methods

We considered how economic modelling could best be undertaken to be of use to decision-makers in relation to TTT strategies. As noted above, TTT does not represent a specific intervention or technology, but is a term that encompasses a range of different treatment strategies. Various aspects of TTT – the setting of a treatment target, frequent assessment of that target, changes to therapy informed by patient performance against the target and protocols for switching or amending drug therapy according to patient performance – have been tested in clinical trials but not in a consistent manner.

As all trials vary in terms of the aspects of TTT they test, one means of providing generalisable results is to pool similar studies together. In *Chapter 3*, *Assessment of characteristics of individual study arms*, an illustrative grouping of studies was provided on the basis of the treatment protocols used to adjust drug therapies according to the patient assessments. A similar approach to this was taken in the economic modelling undertaken to help inform the NICE clinical guideline in RA.[4] The NICE guideline considered the optimal use of non-bDMARDs and steroids in patients with early RA. Trial arms were categorised by treatment protocol and a similar approach was taken here for studies identified as TTT trials. It can be seen that, even within studies that used treatment protocols that were broadly similar within TTT approaches, there remains substantial heterogeneity. The precise details of the treatment protocols differ: cDMARDs used are different, doses vary and the timings with which treatment changes are made also are different. There are also differences between studies in terms of the frequency of assessment and the treatment target. For these reasons it was not considered feasible to pool study arms together in the assessment of clinical effectiveness. Those same concerns remain valid when considering the appropriate method for assessing cost-effectiveness.

There are additional issues to be considered in relation to cost-effectiveness methods. To conduct an economic evaluation, even within the follow-up period of any of the single trials identified, requires substantial information about the experiences of patients. For example, unlike standard technologies, TTT trials typically have a complex treatment protocol that specifies how drug treatments are to be amended, and how the frequency of visits can be amended, by taking the assessment of patients into account. To estimate resource use that will vary by patient because of these factors requires a level of reporting of results that is typically absent from published papers. Indeed, in most cases such data will not have been collected.

The importance of extrapolation beyond the trial study period is critical in this area. Vermeer *et al.*[85] show how cost-effectiveness estimates vary substantially between their 2- and 3-year analyses. Extrapolation is critical in this area because TTT typically involved higher upfront costs – patients are treated in a more intense fashion and assessments are made more frequently. The expectation is that better control of patients gained from this more intense management will provide benefits both to patients and to the health system in the longer term. This can be achieved because it is often the case that patients in continued remission of LDA can have their drug treatments reduced or eliminated entirely, even if only for a short period.[87] This may not be apparent within the short follow-up periods of clinical trials. It is also the case that better disease control is likely to reduce or eliminate the requirement for joint replacement surgery and hospitalisations.[88] Finally, and critically, the lifetime cost-effectiveness of any treatment strategy is likely to be dominated by the extent to which biologic drugs are used. Current eligibility for biologic drug treatment in the UK NHS requires the failure of at least two cDMARDs. It is not feasible to estimate the rate at which drug failures occur within clinical trials in order to then construct a model that moves patients to biologic drugs in the extrapolation period. Even if it was, such is the importance of the use of biologics on cost-effectiveness that it is entirely feasible that this would dominate any influence of the TTT element of the treatment strategy. In the extreme case, one could imagine a case where biologics themselves were not considered to be cost-effective. In this case, treatment strategies in early RA that resulted in the greatest delay in patients failing two DMARDs (and, therefore, moving to biologics) would become the optimal strategy. This could lead to perverse results.

Owing to the combination of these factors, a standard economic analysis conducted in terms of cost per QALY was not deemed feasible or useful for informing decision-making. Owing to a lack of validity in synthesising the data, an approach of a single model that compares all identified treatment strategies simultaneously was not considered appropriate. Instead, each study identified within the clinical effectiveness review was considered in isolation, with an ICER being extracted if the authors provided a measure of cost-effectiveness, or estimated by the authors of this report, if possible. Where insufficient data were provided to allow an estimate of the ICER, a narrative account of the relative cost-effectiveness of the treatment arms contained within each study is provided. The data provided in the papers were often insufficient to allow a robust estimate of cost–utility. However, cost-effectiveness ratios such as incremental cost per additional patient in remission could typically be calculated and presented. In contrast to results generated by cost–utility analyses, there is no stated threshold to determine whether or not treatments are likely to be deemed to be cost-effective using different metrics. Where the results are sufficiently robust to allow conclusions on likely cost-effectiveness, the authors have done so. Although a more limited approach to cost-effectiveness, our aim was to provide evidence that portrays the limited evidence base in its most useful form.

We adopted a pragmatic approach to costing health resources consumed by patients in the identified studies. Studies rarely report data in a form that would allow an estimate of the timing or dosages of drug change for cDMARDs, steroids, immunosuppressants and anti-inflammatory painkillers. For these types of drugs, it was assumed that the costs would be approximately equal in each treatment strategy arm and, therefore, not included in the cost analysis. This is not believed to introduce significant inaccuracy as a result of the relatively inexpensive unit costs for the drugs, but will be favourable to those treatments that start with combination treatment rather than monotherapy. Where there were differences reported between study arms in terms of hospital inpatient and outpatient care, appointments with rheumatologists and other health-care professionals, or other aids and applications, these were costed at 2014/15 values.[89,90] For studies which allowed the use of bDMARDs, a more precise estimation of the additional drug costs was undertaken as these drugs are markedly more expensive, having been estimated to incur an annual cost of £9200:[91] exact costs could not be used because of the commercial-in-confidence patient access schemes for some bDMARDs.

The following section details the TTT studies identified and the cost-effectiveness ratios reported in the original papers or calculated by the authors of this report. These studies are presented in chronological order of the last paper within the study, with papers relating to the same study grouped together. To avoid repetition, the exact components of the treatment arm have not been detailed. Readers are referred to *Independent economic assessment* for further information.

Results

Estimation of cost-effectiveness for each of the 16 TTT studies identified within the literature review of clinical evidence is provided here. We report results separately for studies considering patients with early, established disease or mixed populations.

Early rheumatoid arthritis populations

Fin-RACo (Mottonen et al.*, 1999)*

The paper by Mottonen *et al.*[46] reports on a 2-year multicentre RCT set in Finland. A total of 199 early RA patients were randomly allocated to one of two treatment arms: four patients did not start treatment. A total of 97 patients, 58% female, with a mean age of 47 year received combination drug therapy. The remaining 98 patients, 66% female, with a mean age of 48 years, received single-drug therapy. The target was remission.

The primary outcomes were the percentages of patients achieving remission after 1 and 2 years. After 1 year, 25% of patients receiving combination drug therapy and 11% of patients receiving single-drug therapy achieved remission ($p = 0.011$). After 2 years, both of these values increased: to 37% of patients receiving combination drug therapy and 18% of patients receiving single-drug therapy ($p = 0.003$). Both the results at 1 year and the results at 2 years are statistically significant.

This study presents the percentage of patients who experienced a drug-induced AE. Seventy per cent of those patients on combination therapy experienced an AE, compared with 71% of those on single therapy ($p = 0.840$). There was a statistically significant difference only in the percentage of patients with alanine aminotransferase and alkaline phosphatase levels double that of normal patients, with fewer events in the combination therapy arm ($p = 0.026$).

From the evidence contained in this paper, it would appear that combination drug therapy is more effective than single-drug therapy in inducing remission without having a significant effect on costs. Thus, in terms of cost-effectiveness it would appear, from the evidence of this study, that combination drug therapy either dominates single-drug therapy or would be highly likely to have a cost per QALY below the values published by NICE,[92] of £20,000–30,000, compared with monotherapy.

CAMERA (Verstappen et al., *2007)*

The paper by Verstappen *et al.* [36] reports on a 2-year randomised open-label prospective trial, which was set in the Netherlands. A total of 299 patients were randomly allocated to one of two treatment arms, with one patient dropping out after randomisation. A total of 151 patients, 69% female, with a mean age of 54 years received intensive therapy. A total of 148 patients, 66% female, with a mean age of 53 years, received routine therapy. During the 2-year duration of the study, 94 patients withdrew, 59 in the intensive therapy arm and 35 in the conventional therapy arm, including 10 shortly after inclusion (two in the intensive therapy arm and eight in the conventional therapy arm). The target was complex and multidimensional in both treatment arms.

Patients receiving conventional therapy attended appointments with their treating rheumatologist every 3 months and were treated in accordance the study protocol, whereas patients receiving intensive therapy attended appointments with their treating rheumatologist every 4 weeks. Rheumatology visits are assumed to cost £128[93] in the UK; thus, intensive therapy will be associated with an additional cost of £2315 per patient completing the study compared with conventional therapy. Intensive therapy also includes performing specific clinical measurements, although these costs were assumed small enough to omit.

The primary outcome was the number of patients who achieved and maintained remission for a period of 3 months during the trial. During the first year, 53 patients (35%) in the intensive therapy arm and 21 patients (14%) in the conventional therapy arm achieved, and maintained, at least one 3-month period of remission ($p < 0.001$). Over 2 years these numbers increased to 76 patients (55%) in the intensive therapy arm and 55 patients (37%) in the conventional therapy arm ($p = 0.029$). The mean duration patients spent in the study until remission was 10.4 months for patients receiving intensive therapy and 14.3 months for patients receiving conventional therapy ($p < 0.001$). The duration of remission was also significantly longer for patients receiving intensive therapy (11.6 months) than for patients receiving conventional therapy (9.1 months) ($p = 0.025$).

After 1 year, 87 patients (58%) receiving intensive therapy and 64 patients (43%) receiving conventional therapy had achieved an ACR 50 response ($p = 0.018$). At 2 years, these numbers were 69 patients (46%) in the intensive therapy arm and 67 patients (45%) in the conventional therapy arm ($p = 1.00$). Results for ESR, morning stiffness, SJC, TJC, VAS scores for general well-being and pain and functional disability (as measured using the HAQ) for participants on an intention-to-treat basis using a last observation carried forward methodology basis are also presented. Patients receiving intensive therapy score significantly better in all measures after 3 months of therapy ($p < 0.01$), except functional disability ($p = 0.8$). After 1 year of therapy statistical significant differences are maintained for SJC, TJC and VAS scores for general well-being and pain. After 2 years of therapy a statistical difference is shown only for the VAS scores for general well-being and pain, with the mean differences in these categories diminishing. Thus, it appears that intensive therapy produces a more rapid response than conventional therapy.

Broadly similar mean AEs per appointment are presented: 0.745 in the intensive therapy arm and 0.771 in the conventional therapy arm (*p*-value not reported).

If it is assumed that all patients completed the study, then the estimated cost per incremental patient in remission would be £36.18 at the end of year 1, increasing to £110.26 at the end of year 2. Dropouts from the study mean that these values should be taken as indicative rather than definitive. However, given the potential for increased patient utility and a reduction in costs for a patient being in remission, we believe that the intensive therapy is likely to have a cost per QALY gained below thresholds published by NICE.[92]

Saunders et al., *2008*[54]

The paper by Saunders *et al.*[54] reports on a 12-month RCT set in the UK. A total of 96 patients with early RA were randomly allocated to one of two treatment arms. A total of 49 patients, 76% female, with a mean age of 55 years, received parallel triple therapy. The remaining 47 patients, 79% female, with a mean age of 55 years, received step-up therapy. The target in both arms was a DAS28 of < 3.2.

The primary study outcome was the mean decrease in DAS28 at 12 months. Secondary outcomes, also measured at 12 months, were based on the percentage of patients in each arm achieving good response (EULAR definition) and the percentage of patients achieving remission (EULAR definition) together with the percentage of patients experiencing an ACR 20, ACR 50 and ACR 70 response. These outcomes are presented in *Table 37*.

These study outcomes indicate that there is no statistically significant difference in the effectiveness of parallel triple therapy compared with step-up therapy in terms of the mean reduction in the DAS28, the percentage of patients achieving a good EULAR response or the percentage of patients achieving remission (as defined by EULAR). The results also indicate that there is no statistically significant difference between the two therapies in terms of the percentage of patients experiencing an ACR 20, ACR 50 or ACR 70 response. The step-up therapy approach has a numerical advantage compared with parallel triple therapy: it is possible that step-up therapy is better, but this was not observed because of the small sample size.

Saunders *et al.*[54] acknowledged in the paper that their results were at odds with previous studies which had demonstrated the superiority of triple therapy in achieving clinical improvement among patients with early RA. However, they state that these results were seen mainly in studies which compared triple therapy with single or dual cDMARD therapy in non-intensive treatment strategies. The authors hypothesise that the outcomes could also be as a result of using a relatively low dose of MTX (7.5 mg per week), SSZ (500 mg twice a day) and HCQ (200 mg daily) in the triple-therapy arm compared with the dose of SSZ used as the first treatment in the step-up therapy arm (40 mg/kg/day or maximally tolerated dose). The authors also state that the outcomes of the FIN-RACo trial,[46] which was the only other published study comparing a triple-therapy treatment regimen with a monotherapy treatment regimen in early RA patients, were measured after 24 months of treatment rather than after just 12 months of treatment. Patients in the triple-therapy arm of the FIN-RACo study[46] were also prescribed oral prednisolone, which was not part of the treatment regimen in this study.

TABLE 37 Study outcomes at 12 months reported by Saunders *et al.*[54]

Outcome	Therapy		*p*-value
	Parallel triple	Step-up	
Number of participants	49	47	–
Mean reduction in the DAS28	–3.3	–4.0	0.16
EULAR good response	41%	60%	0.47
EULAR remission	33%	45%	0.6
ACR 20 response	76%	77%	0.9
ACR 50 response	51%	60%	0.7
ACR 70 response	20%	30%	0.6

From the data in this paper there is no evidence of statistically significant differences in the effectiveness of the two therapies and only a minor difference in terms of the costs of the two therapies. Therefore, no firm conclusion can be drawn between parallel triple-therapy and step-up therapy in terms of cost-effectiveness or cost–utility.

STREAM (van Eijk et al.*, 2011)*

The paper by van Eijk *et al.*[55] reports on a 2-year RCT set in the Netherlands. A total of 82 patients were randomly allocated to one of two treatment arms. Forty-two patients, 58% female, with a mean age of 48 years, received aggressive therapy under a tight control treatment regimen. Forty patients, 79% female, with a mean age of 46 years, received conventional therapy. Patients assigned to aggressive therapy were able to receive ADA; however, patients assigned to the conventional therapy were not. The target was remission, defined as a DAS44 score of < 1.6.

The primary outcome was the Sharp/van der Heijde radiographic score. There was a numerical advantage favouring aggressive therapy, although this was not statistically significant at 2 years ($p = 0.17$).

Secondary outcomes, which were again measured at 2 years, included differences in the DAS28; the percentage of patients in clinical remission (a DAS28 of < 1.6); the percentage of patients in pharmaceutical-free clinical remission; HAQ score; and AEs. A total of 66% of patients in the aggressive therapy group and 49% of patients in the conventional therapy group achieved remission; the authors report that this is not statistically significant, but do not report a *p*-value. In the aggressive therapy group, 17.9% of patients achieved a period of pharmaceutical-free remission, compared with 15.8% of patients in the conventional therapy group ($p = 0.08$). The mean duration of pharmaceutical-free remission in the aggressive therapy group was 6 months and the mean duration of pharmaceutical-free remission in the conventional therapy group was 7.5 months. Analysis of HAQ score changes did not show a clear benefit of either treatment arm.

AE occurrence was recorded, with 62 events among patients receiving aggressive therapy patients, compared with 35 events in the conventional therapy patients within the follow-up period ($p = 0.034$). Thus, there is a statistically significant difference in the AE rate, with patients receiving aggressive therapy more likely to experience an AE than patients receiving conventional therapy.

Based on the evidence contained in this study, aggressive therapy is associated with greater costs than conventional therapy as a result of the use of a bDMARD in 19 out of 42 patients in the aggressive arm and the need to record the DAS28. There is not a statistically significant difference in the efficacy of the two therapies, although a beneficial effect may not have been observed because of the small sample sizes. Therefore, it is possible that the aggressive therapy is dominated by conventional therapy as a result of achieving the same outcomes at a considerably higher cost. However, there remains some uncertainty because of the numerical advantage of patients reaching remission in the aggressive arm: it was not possible to calculate a robust cost per incremental patient reaching remission as a result of the lack of data provided by van Eijk *et al.*[55] on the treatment duration with bDMARDs. Therefore, no definitive conclusion on the cost-effectiveness of the aggressive therapy arm can be made.

The T-4 study (Urata et al.*, 2011; and Urata* et al.*, 2012)*

The more recent paper by Urata *et al.*[57] reports on a 56-week trial set in Japan and supersedes an earlier abstract.[56] A total of 243 patients with early RA were randomly allocated to one of four treatment arms. A total of 62 patients were allocated to routine care, 60 patients were allocated to a regimen in which treatment decisions were made based on DAS28, 60 patients were allocated to a regimen in which treatment decisions were based on MMP-3 scores and 61 patients were allocated to a regimen in which treatment decisions were based on both the DAS28 and MMP-3 scores.

A total of 21 patients dropped out during the trial as a result of AEs. Seven patients dropped out of routine care, leaving 55 patients in the routine care group, 76% female, with a mean age of 62 years. Four patients dropped out of the DAS therapy group, leaving 56 patients in this group, 77% female, with a

mean age of 60 years. Seven patients dropped out of the MMP-3 therapy group, leaving 53 patients, 83% female, and a mean age of 62 years. The remaining three patients dropped out of the combination therapy group, leaving 58 patients, 84% female, with a mean age of 56 years. Baseline patient characteristics were reported for only those patients who completed the study. There was no target for routine care; the target for the DAS28-driven therapy was a DAS28 of < 2.6. The target for the MMP-3-driven therapy was a MMP-3 concentration of < 121 ng/ml in men and < 59.7 ng/ml in women and the targets for both the DAS28 and MMP-3-driven therapies were those for the individual components.

Patients in all the arms of the trial could receive bDMARD pharmaceuticals, which included a first-line anti-TNF, a second-line anti-TNF and TOC. The times of bDMARD initiation in each of the four treatment arms is presented in table 3 of Urata *et al.*,[57] although the numbers provided for each arm (55 for routine care, 59 for DAS28-driven therapy, 59 for MMP-3-driven therapy and 61 for both the DAS28 and MMP-3-driven therapy) do not match either the intention-to-treat population or the numbers who completed the trial. We have assumed that those patients who would be included in the intention-to-treat analysis did not receive a bDMARD.

A number of primary and secondary outcomes were presented for the study; these include clinical remission (defined by a DAS28 of < 2.6), radiographic non-progression [defined by a change in modified total Sharp score (mTSS) of ≤ 0.5], normal physical function (as defined by a mHAQ $= 0$), a combination of all three of the above conditions and clinical remission (as defined by a SDAI of ≤ 3.3). These results are presented in *Table 38*.

There appear to be errors in the marking of statistical significance between groups in figure 2 of the Urata *et al.*[57] paper. The correct markings are not easy to interpret, so no further comment will be made on these. However, it is reported in the results section of the paper's abstract that clinical remission at 56 weeks was achieved by more patients in the DAS28 and MMP-3-driven group than in either the routine therapy group ($p < 0.0005$) or the MMP3-driven group ($p < 0.0005$).

From the numbers in *Table 38* it is seen that the DAS28 and MMP-3-driven group is the most efficacious treatment in all categories bar prevention of radiographic progression.

Table 39 presents the estimated total treatment duration with bDMARD received by patients in each arm of the trial. From this the estimated average cost per patient associated with bDMARDs in each arm of the study could be calculated. It was assumed that the annual cost of all bDMARDs was £9200, which will result in a daily cost of bDMARD treatment of £25.19, in line with a recent publication.[91] The exact costs could not be used because of the commercial-in-confidence patient access schemes. It has been assumed that any costs associated with providing MMP-3-driven therapy and/or DAS28-driven therapy are not excessive and can be ignored for simplicity.

TABLE 38 Outcomes at 56 weeks in the T-4 study[57]

Therapy	Outcome (%)				
	Clinical remission, a DAS28 of < 2.6	Radiographic non-progression	Normal physical functioning	Combination of the first three	Clinical remission, a SDAI of ≤ 3.3
Routine care	21	27	44	6	15
DAS28-driven therapy	38	42	60	15	32
MMP-3-driven therapy	13	62	43	7	13
Both DAS28- and MMP-3-driven therapy	56	59	72	34	46

TABLE 39 Doses of bDMARDs received by patients in the T-4 study[57]

Intervention	Number of patients	Days of bDMARD treatment				Cost of arm per patient (£)
		First TNF	Second TNF	TOC	Total	
Routine care	62	5950	0	0	5950	2417
DAS28-driven therapy	60	5432	560	756	6748	2833
MMP-3-driven therapy	60	5012	0	588	5600	2351
Combined DAS28 and MMP-3-driven therapy	61	10,136	784	784	11,704	4833

From our calculations the most expensive treatment is combined DAS28 and MMP-3-driven therapy, which has a per-patient cost of £4833, followed by DAS28-driven therapy, which has a per-patient cost of £2833, followed by routine care, which has a per-patient cost of £2417, with MMP-3-driven therapy being the cheapest, at £2351 per patient.

The cost per additional patient in remission is approximately £167 when combined DAS28 and MMP-3-driven therapy is used (*Table 40*). Given the long-term benefits associated with remission (in terms of both costs incurred and health-related quality of life accrued), we believe that it is highly likely that the cost per QALY of the strategy would be below those quoted by NICE as thresholds for cost-effectiveness.[92]

COBRA-light (den Uyl et al.*, 2013)*

The paper by den Uyl *et al.*[69] reports on a 6-month randomised controlled non-inferiority study set in the Netherlands. A total of 164 early RA patients were randomly allocated to one of two treatment arms. A total of 81 patients, 67% female, with a mean age of 53 years, were allocated to COBRA therapy. A total of 83 patients, 70% female, with a mean age of 51 years, were allocated to COBRA-light therapy.[44,45] The target was a DAS44 score of < 1.6.

A summary of key outcomes from the study is presented in *Table 41*.

There were no significant differences in any outcome measure presented in *Table 41* and there was no clear indication that one treatment strategy was better than the other. Therefore, no firm conclusion can be made regarding which strategy is the more cost-effective.

The TEAR study

The TEAR study,[58–60] set in the Netherlands, evaluated two treatment options [ETN plus MTX and triple therapy (MTX + SSZ + HCQ)] and two timings regarding the initiation of therapy (immediately or step-up from MTX monotherapy if the DAS28-ESR was ≥ 3.2 at week 24). A total of 755 patients with early RA (symptom duration

TABLE 40 The estimated cost-effectiveness of the treatment strategies in the T-4 study[57]

Therapy arm	Patients achieving clinical remission		Cost (£)		ICER (£)[a]
	Number	Incremental	Per patient	Incremental	
MMP-3-driven therapy	8	–	2351	–	–
Routine care	13	5	2417	66	13
DAS28-driven therapy	22	9	2833	416	46
Combined DAS28 and MMP-3-driven therapy	34	12	4833	2000	167

a This ICER is measured in terms of the incremental cost per patient achieving remission.

TABLE 41 Study outcomes at 26 weeks in the COBRA-light[69] study

Outcome	Therapy		*p*-value
	COBRA	COBRA-light	
Number of participants	81	83	–
Change in the DAS44	2.50	2.18	0.19[a]
Percentage of patients achieving ACR response			
ACR 20 response	74	72	NR[b]
ACR 50 response	57	62	NR[b]
ACR 70 response	38	49	NR[b]
Percentage of patients achieving EULAR response			
Good response	75	65	NR[b]
Moderate response	19	24	NR[b]
Non-response	6	11	NR[b]
Percentage of patients achieving remission (ACR/EULAR definition)	16	20	NR[b]
Percentage of patients achieving minimal disease activity (a DAS44 of < 1.6)	49	41	NR[b]

NR, not reported.
a Once corrected for baseline values (*p*-value of 0.08 uncorrected).
b Although the *p*-value is not reported, the authors do report that the result is not statistically significant.

of < 3 years) were randomly allocated to one of four treatment arms. A total of 245 patients, 74.2% female, with a mean age of 50.7 years, received immediate MTX plus ETN. A total of 132 patients, 76.5% female, with a mean age of 48.8 years, received immediate triple therapy. A total of 255 patients, 69.0% female, with a mean age of 48.6 years, received step-up therapy from MTX monotherapy to MTX plus ETN. The remaining 124 patients, 70.2% female, with a mean age of 49.3 years, received step-up therapy from MTX monotherapy to triple therapy.

The TEAR study: results after 102 weeks (Moreland et al.*, 2010)*

This abstract by Moreland *et al.*[59] provided preliminary data on radiographic scores by treatment type and by the timing of treatment initialisation; these data came from 297 participants. At week 102, the baseline-adjusted change in mTSSs in the ETN plus MTX group was 0.6 (SD 3.3) and for the triple-therapy group was 2.4 (SD 10.1), which was significantly different ($p = 0.0180$). No significant differences were found when analysing the timing of treatment (immediate vs. step-up; $p = 0.8059$), the percentage of patients with no damage ($p = 0.30$ by treatment group), JSN ($p = 0.15$ by treatment group) or the number of patients with no erosions (*p*-value not reported). It is unlikely that the benefit in the reduced progression of mTSSs would warrant the increased costs associated with ETN.

The TEAR study: 2-year results (Moreland et al.*, 2012; and O'Dell* et al.*, 2013)*

At 2 years, 67.9% of participants completed the study, with the authors reporting that there was no differential dropout rate across the treatment arms ($p = 0.73$) or according to the timing of intensive treatment ($p = 0.61$) or medication type (ETN plus MTX or triple therapy) ($p = 0.18$). Of those completing the study, only 476 had sufficient data for the DAS28-ESR to be determined at week 102.

At week 24, 72% of the patients in the step-up group had a DAS28-ESR of ≥ 3.2 and treatment was intensified. In contrast, the proportion of patients with a DAS28-ESR of ≥ 3.2 in the immediate-intensified treatment groups was 59% for those receiving ETN plus MTX and 57% for those receiving triple therapy.

Combining the two immediate treatment groups showed a statistically significant benefit in the DAS28-ESR reduction compared with those in the step-up arms ($p < 0.0001$). However, by week 48 the DAS28-ESR was similar in all groups and there was no significant difference across the four treatment groups between week 48 and week 102 ($p = 0.28$). This conclusion held when the results were analysed by treatment type ($p = 0.48$) and timing of intensified treatment ($p = 0.55$).

There was no difference in those patients achieving clinical remission (defined as a DAS28-ESR of < 2.6) between groups ($p = 0.93$), by timing of intensification ($p = 0.36$) or by type of treatment received ($p = 0.43$). A similar pattern was seen with ACR responses, with both immediate treatment groups achieving better ACR 20/50/70 responses than the step-up groups ($p < 0.0001$), but few results were statistically significant at week 102. The only significant comparison from all tested was an improvement in ACR 70 responses between ETN plus MTX and triple-therapy groups ($p = 0.01$).

With respect to mTSSs, there was no difference in the change between baseline and week 102 when comparing immediate with step-up treatment ($p = 0.74$), although those allocated to ETN plus MTX had better results than those allocated to triple therapy ($p = 0.047$). Using a definition of progression of a radiographic score of > 0.5, 33.6% of patients showed progression, although this did not differ significantly across the groups ($p = 0.33$) or according to the timing of intensified treatment ($p = 0.56$). However, there was a difference between those allocated to ETN plus MTX and those receiving triple therapy ($p = 0.02$), although this became non-significant when an outlier (with a mTSS increase of 78.5) was removed ($p = 0.069$). No significant differences across treatment groups were reported for GC use or for those experiencing AEs or SAEs.

The evidence presented in this study prompted the authors to state that:

> *Initial use of MTX monotherapy with the addition of SSZ plus HCQ (or ETN, if necessary, after 6 months) is a reasonable therapeutic strategy for patients with early RA.*

The authors of this report would concur and additionally point out that the use of ETN is considerably more expensive than SSZ or HCQ, and it is highly unlikely that the costs could justified an improvement in radiographic damage.

O'Dell *et al.*[60] presented very similar results to those provided in Moreland *et al.*[58] It was reported that no statistically significant difference was observed between the percentage of patients in each treatment modality (immediate combination treatment vs. step-up treatment) who discontinued treatment by week 24 ($p = 0.84$). Nor was any statistically significant difference observed between the percentage of patients in each treatment modality (immediate combination treatment vs. patients who stepped up treatment at week 24 vs. patients who remained on MTX monotherapy at week 24) who discontinued treatment between weeks 24 and 102 ($p = 0.86$). At 102 weeks, 159 patients remained in the immediate MTX plus ETN treatment arm, 76 patients remained in the immediate triple-therapy treatment arm, 166 patients remained in the step-up MTX plus ETN treatment arm and 75 patients remained in the step-up triple-therapy treatment arm.

The authors conclude that radiographic outcomes for those who started on MTX monotherapy and then stepped up to combination therapy if the DAS28-ESR was ≥ 3.2 at 24 weeks were 'indistinguishable from week 48 to week 102'. The authors further report that the advantage of initial combination of ETN plus MTX compared with the addition of MTX in those that did not meet the goal of a DAS28-ESR of < 3.2 had 'no clinical or radiographic advantage'. The authors discuss the economic consequences of the results, stating that 28% of those patients started on MTX monotherapy had a very good outcome and thus the expense of ETN need not be incurred. We concur with this view and believe that the use of ETN before intensive treatment with cDMARDs would not be justified economically and the ICER for such a strategy would be significantly higher than published NICE thresholds.[92]

The BehandelStrategieën in Reumatoïde Artritis trial

The BeSt trial[30,33,34,68] is a multicentre RCT set in the Netherlands. A total of 508 patients were randomly allocated to one of four treatment arms. A total of 126 patients, 68% female, with a mean age of 54 years, received sequential monotherapy; 121 patients, 71% female, with a mean age of 54 years, received step-up combination therapy; 133 patients, 65% female, with a mean age of 55 years, received initial combination therapy with PDN; and 128 patients, 66% female, with a mean age of 54 years, received initial combination therapy with IFX. The target was a DAS44 score of ≤ 2.4.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 1 year (Goekoop Ruiterman et al.*, 2005)*

Study outcomes measured at 1 year included the D-HAQ, a lower score on which indicates better patient functioning.[30] Radiological damage was assessed in terms of mean total SHS, mean erosion score and mean JSN. These outcomes are presented in *Table 42*.

These outcomes show a statistically significant difference between patients receiving initial combination therapy with PDN and patients receiving initial combination therapy with IFX compared with patients receiving sequential monotherapy and patients receiving step-up combination therapy for mean total SHS at every time point; mean erosion score at every time point; and mean D-HAQ score at 3, 6 and 9 months. At 12 months, D-HAQ was statistically significant between patients receiving initial combination therapy with PDN and patients receiving initial combination therapy with IFX compared with patients receiving sequential monotherapy.

A statistically significant difference in mean JSN was observed between patients receiving initial combination therapy with PDN or IFX and patients receiving sequential monotherapy and also between patients receiving combination therapy with IFX and patients receiving step-up combination therapy.

TABLE 42 Outcomes at 1 year from the BeSt trial[30]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination therapy	Initial combination with PDN	Initial combination with IFX	
Percentage of patients achieving LDA[a]	53 (50)	64 (60)	71 (65)	74 (70)	[b]
Mean D-HAQ score					
Baseline	1.4	1.4	1.4	1.4	–
3 months	1.0	1.0	0.6	0.6	< 0.001[c]
6 months	0.9	0.9	0.5	0.5	< 0.001[c]
9 months	0.8	0.8	0.6	0.5	< 0.001[c]
12 months	0.7	0.7	0.5	0.5	< 0.009[d]
Progression of radiological damage					
Mean total SHS	7.1	4.3	2.0	1.3	< 0.001[c]
Mean erosion score	3.5	2.6	0.9	0.7	< 0.001[c]
Mean JSN score	3.6	1.6	1.0	0.6	< 0.001[e]

a Percentage of patients achieving LDA as presented in the paper (percentage of patients achieving LDA using the number of patients randomised to each therapy as the denominator).
b *p*-value = 0.004 between groups 1 and 3; *p*-value = 0.001 between groups 1 and 4; and *p*-value not significant for other comparisons.
c *p*-value < 0.05 between groups 1 and 2 vs. groups 3 and 4.
d *p*-value < 0.05 between group 1 vs. 3 and 4.
e *p*-value < 0.05 between group 1 and groups 3 and 4; and between groups 2 and 4.

A statistically significant difference was observed in the D-HAQ scores at 3, 6 and 9 months between patients receiving initial combination therapy with PDN or IFX and patients receiving step-up combination therapy or sequential monotherapy.

Table 43 provides data on AEs observed in the first year of the BeSt trial.[26–34,65,68] No statistically significant difference was observed in the rate of AEs. However, numerically the combination strategies had fewer patients with AEs, although the combination strategy with PDN had the numerically largest number of SAEs.

Given the statistically significant better efficacy results for the strategy of combination therapy with PDN compared with sequential monotherapy and with step-up combination therapy, it is plausible that the first strategy would have a cost per QALY ratio compared with the last two strategies that was below published NICE thresholds,[92] although this would be dependent on the D-HAQ gains being translated into clinically meaningful outcomes.

Given the similar efficacy data observed for the combination with PDN and the combination with IFX therapies, it is anticipated that, because of the relatively large costs of IFX, the cost per QALY gained associated with the use of IFX rather than PDN would be markedly higher than the published NICE thresholds.[92]

The BehandelStrategieën in Reumatoïde Artritis trial: results at 2 years (Allaart et al.*, 2006)*

The results presented in Allaart *et al.*[27] included clinical data at 2 years for each of the four study arms. These data are summarised in *Table 44*.

The results indicate that at 2 years many of the key clinical outcomes are not significantly different between the four arms. The two initial combination arms, however, had a quicker effect on the HAQ score and had less radiographic progression at 2 years than the two remaining arms. Given the significant costs associated with bDMARDs it is anticipated that the initial combination therapy with IFX arm would have a cost per QALY in excess of that published by NICE[92] when compared with initial combination therapy with PDN.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 3 years (Allaart et al.*, 2007)*

The paper by Allaart *et al.*[26] provided information additional to that of the previous year.[27] Data were provided on the HAQ scores, DAS28, ESR and SHSs for the sequential monotherapy arm and the step-up

TABLE 43 Adverse event experience by patients in the first year of the BeSt trial[30]

AE	Therapy (%)				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
SAEs	6	7	13	5	0.438
At least one AE	43	47	37	39	0.367
Gastrointestinal AEs	16	15	8	11	NR
Dermatological AEs	10	12	9	6	NR
Upper RTI AEs	4	7	8	8	NR
Vascular AEs	2	2	6	2	NR
Reaction in infusion	0	0	0	8	NR
Latent tuberculosis	0	0	0	7	NR

NR, not reported; RTI, respiratory tract infection.

TABLE 44 Clinical outcome data at 2 years as reported by Allaart *et al.*[27]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination therapy	Initial combination with PDN	Initial combination with IFX	
HAQ improvement compared with baseline: mean (SD)					
6 months	0.5 (0.7)	0.5 (0.7)	0.9 (0.7)	0.8 (0.6)	< 0.001
12 months	0.7 (0.7)	0.7 (0.7)	0.9 (0.7)	0.9 (0.7)	0.03
18 months	0.7 (0.7)	0.8 (0.7)	0.8 (0.8)	0.9 (0.7)	0.26
24 months	0.7 (0.7)	0.8 (0.7)	0.9 (0.7)	0.9 (0.7)	0.26
Progression of SHS compared with baseline at 2 years: mean (SD)					
Total SHS	9.0 (17.9)	5.2 (8.1)	2.6 (4.5)	2.5 (4.6)	< 0.001
Erosion score	4.7 (9.0)	3.1 (5.0)	1.1 (2.2)	1.3 (2.7)	< 0.001
JSN score	4.3 (9.8)	2.1 (3.8)	1.5 (3.2)	1.2 (2.9)	0.07
Relative risk for SHS progression of radiographic joint at 2 years: mean (95% CI)					
Relative risk	Referent	0.91 (073 to 1.12)	0.74 (0.61 to 0.89)	0.73 (0.61 to 0.88)	–
Patients achieving a DAS44 of < 2.4					
Percentage	75	81	78	82	NS
Patients achieving a DAS44 of < 1.6					
Percentage	46	38	41	42	NS

NS, not significant.

combination therapy arm at 1 year, with a conclusion that the benefits of DAS-adjusted treatment was clear, with statistically significant improvements for all comparisons. Drug-free clinical remission at 3 years was reported: 11% for those started on sequential monotherapy, 6% for those started with step-up combination therapy, 7% for those started with initial combination therapy with PDN and 16% for those started with combination therapy with IFX. The comparison between the IFX combination and both the step-up therapy and PDN combination was statistically significant. Radiological damage progression was significantly lower in the initial combination therapy arms than in the remaining arms. The data provided in this paper are more favourable to an initial IFX combination therapy arm, but would not change our conclusions regarding the likely cost-effectiveness of initial IFX combination therapy compared with initial PDN combination therapy.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 2 years (van der Kooij et al.*, 2009)*

Study outcomes measured at 2 years were patient-reported outcomes, including changes in the McMaster–Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), SF-36 Physical Component score, SF-36 Mental Component score and the VAS scores for pain, disease progression and global general health.[68] These results are presented in *Table 45*.

At 2 years there was no significant difference in SF-36 Physical Component ($p = 0.95$), SF-36 Mental Component ($p = 0.97$), VAS pain ($p = 0.33$), VAS disease activity ($p = 0.19$) and VAS global health ($p = 0.10$), although some scores were statistically significant at 1 year, as was the MACTAR score. However, there is a difference in costs, with those patients in the combination therapy with IFX anticipated to be more expensive and thus unlikely to be cost-effective compared with the remaining arms.

TABLE 45 Changes in patient-reported outcomes at 6 months, 1 and 2 years from the BeSt trial[68]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
SF-36 Physical Component score					
Baseline	32.9	32.9	32.8	33.4	0.93
6 months	8.0	8.5	12.5	12.4	< 0.001[a]
1 year	8.9	11.2	11.9	12.0	0.10
2 years	11.9	12.3	12.3	12.7	0.95
SF-36 Mental Component score					
Baseline	47.5	46.3	47.6	47.6	0.73
6 months	3.1	3.5	1.2	4.1	0.17
1 year	4.3	4.4	3.2	4.3	0.83
2 years	4.3	4.6	4.6	4.0	0.97
VAS pain					
Baseline (0–100)	53.1	53.4	54.1	54.1	0.98
6 months	–17.4	–25.5	–30.3	–30.2	< 0.001[b]
1 year	–21.3	–26.0	–28.9	–30.5	0.05[c]
2 years	–28.2	–27.3	–26.9	–32.6	0.33
VAS disease activity					
Baseline (0–100)	59.2	59.4	59.5	61.8	0.77
6 months	–22.3	–28.0	–32.0	–35.9	0.003[b]
1 year	–27.5	–29.8	–32.8	–38.3	0.03[c]
2 years	–33.2	–33.0	–31.5	–39.0	0.19
VAS global health					
Baseline (0–100)	51.9	51.9	50.6	55.0	0.36
6 months	–17.7	–21.3	–21.5	–28.4	0.01[c]
1 year	–21.7	–23.2	–22.7	–30.0	0.06
2 years	–26.4	–25.6	–23.9	–31.8	0.10
MACTAR					
Baseline	47.5	47.1	47.3	47.0	0.77
6 months	12.6	15.4	16.4	19.1	< 0.001[d]
1 year	15.2	16.3	16.9	19.3	0.02[c]

a $p < 0.05$ between groups 1 and 2 vs. groups 3 and 4.
b $p < 0.05$ between group 1 vs. groups 3 and 4.
c $p < 0.05$ between groups 1 and 4.
d $p < 0.05$ between groups 1 and 2 vs. group 4 and between groups 1 and 3.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 7 years (Dirven et al. *2010)*

This abstract, by Dirven *et al.*,[29] presented clinical results at 7 years. These are summarised in *Table 46*.

It is seen that there is a statistically significant difference neither in the DAS categories nor in SHS progression. Although there has been a statistically significant reduction in mean HAQ score, equating to approximately one HAQ level, this is not believed to provide sufficient clinical benefit to make the use of initial combination with IFX cost-effective given that the number of people using IFX at 7 years is significantly higher in the initial IFX combination therapy arm.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 8 years (Dirven et al. *2011)*

This abstract, by Dirven *et al.*,[28] presented clinical results at 8 years and was very similar to the abstract presented in 2010.[29] The results are summarised in *Table 47*. It is not stated how the number of completers was higher in the 8-year results than in the 7-year results.

The conclusions remain the same as for the 7-year results. Namely, it is seen that there is a statistically significant difference neither in the DAS categories nor in SHS progression. Although there has been a statistically significant reduction in mean HAQ score, equating to approximately one HAQ level, this is not believed to provide sufficient clinical benefit to make the use of initial combination with IFX cost-effective given that the number of people using IFX at 7 years is significantly higher in the initial IFX combination arm.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 5 years (Klarenbeek et al.*, 2011)*

The paper by Klarenbeek *et al.*[31] presented clinical and radiological outcomes at 5 years and focused on functional status, quality of life, joint damage, AEs and the percentage of patients in remission (DAS44 of < 1.6). As previously reported, the beneficial impacts of the two initial combination arms were quicker than for the remaining arms, but these gains did not persist over time. The results are presented in *Table 48*.

TABLE 46 Seven-year results from the BeSt trial as reported by Dirven *et al.*[29]

Analyses	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
Number recruited	126	121	133	128	–
Completers	83	72	79	97	–
Completers analyses					
A DAS of ≤ 2.4 (%)	82	76	82	76	0.64
A DAS of < 1.6 (%)	49	39	53	45	0.35
A DAS of < 1.6 drug free (%)	16	18	17	17	0.96
SHS progression over 7 years: median (mean)	3.8 (15.1)	3.5 (10.7)	2.0 (8.4)	2.0 (5.5)	0.205
Intention-to-treat analyses					
Use of IFX at 7 years	14	6	11	21	< 0.05
Mean HAQ score over 7 years	0.70	0.71	0.63	0.57	< 0.001
Non-completers (%)	26	33	26	17	0.04

TABLE 47 The 8-year results from the BeSt trial, as reported by Dirven *et al.*[28]

Analyses	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
Completers analyses					
Number recruited	126	121	133	128	–
Completers	85	78	86	98	–
A DAS of ≤ 2.4 (%)	79	76	84	76	0.49
A of DAS < 1.6 (%)	49	56	57	47	0.48
A of DAS < 1.6 drug free (%)	18	19	17	15	0.90
SHS progression over 8 years: median (mean)	3.0 (14.6)	4.3 (13.9)	2.0 (8.5)	2.0 (8.3)	0.567
Intention-to-treat analyses					
Use of IFX at 8 years	21	10	13	24	0.06
Mean HAQ score over 8 years	0.69	0.71	0.63	0.57	< 0.05
Non-completers (%)	33	36	35	23	0.13

TABLE 48 The 5-year results from the BeSt trial as reported by Klarenbeek *et al.*[31]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
Drug-free remission (%)	14	16	10	19	0.18
SHS progression over 5 years: median (mean)	3.5 (14.0)	2.5 (11.0)	1.0 (7.6)	1.0 (6.0)	NR
Mean HAQ score over 5 years	0.70	0.70	0.62	0.54	NR
Mean SF-36 Physical Component score over 5 years: area under the curve per month	43.5	43.3	44.1	45.0	NS
Mean SF-36 Mental Component score over 5 years: area under the curve per month	51.8	51.0	50.9	51.2	NS

NR, not reported; NS, not significant.

At 5 years there was no significant difference in HAQ score (mean value 0.58), although there was a significant difference in mean HAQ score over the 5 years for the combination therapy arms compared with the sequential monotherapy and the step-up combination arms ($p < 0.001$) and for the initial combination therapy with IFX arm compared with initial combination therapy with PDN. There was no significant difference in either of the quality of life measurements recorded. Radiological progression was least in the initial combination arms ($p < 0.01$), although after the first year the authors reported no difference between the arms. The authors report that 48% of patients were in clinical remission and were equally distributed between arms, although the initial combination therapy with IFX arm had the greatest proportion (81%) achieving this on the treatment to which they were initially allocated, with the lowest

value being that for sequential monotherapy (46%). No significant difference was observed in the proportion with drug-free remission ($p = 0.18$). The authors report that 86% of patients had at least one AE and 30% of patients had SAEs, which were equally distributed across treatment groups.

The data from this paper do not alter the conclusions that the use of initial IFX treatment is unlikely to be cost-effective.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 7 years (van den Broek et al.*, 2012)*

The paper by van den Broek *et al.*[65] reports clinical results at 7 years of follow-up. It was reported that there was no statistically significant difference between the four treatment arms after the first year, although 36% of patients in the initial combination therapy with PDN arm and 53% of patients in the initial combination therapy with IFX arm had been tapered to monotherapy after year 2 because of persistent low DAS44 score. A statistically significant difference was observed between the initial combination therapy with IFX or PDN groups and the remaining two groups. At the end of the seventh year the percentages of patients across the groups with drug-free remission were similar: 13% for sequential monotherapy; 16% for step-up combination treatment; 16% for initial combination with PDN; and 14% with initial combination therapy with IFX.

The data from this paper do not alter the conclusions that the use of initial IFX treatment is unlikely to be cost-effective.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 5 years (Koevoets et al.*, 2013)*

The paper by Koevoets *et al.*[32] focused on the relationship between erosions and JSN with the D-HAQ. The analysis used generalised estimating equations regression models, as these are relatively robust to violations of normality. Covariates of the DAS44, sex, treatment arm and body mass index were used. In univariate analyses, the effects of erosions and JSN were similar (erosions: $\beta = 0.003$, 95% CI –0.001 to 0.006; JSN: $\beta = 0.004$, 95% CI 0.001 to 0.008), although erosions were not statistically significant whereas JSN was significant. The variables that have the greatest influence on HAQ score when analysed univariately were DAS44, female sex and DAS44 at baseline. Compared with the initial combination treatment with IFX, sequential monotherapy (β 0.176, 95% CI 0.047 to 0.578) and step-up combination treatment (β 0.148, 95% CI 0.017 to 0.279) were associated with significantly worse HAQ scores, although initial combination therapy with PDN was not (β 0.076, 95% CI –0.035 to 0.188). When a multivariate model was used, the impact of both erosions and JSN was reduced and neither was a statistically significant predictor of HAQ score.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 8 years (van den Broek et al.*, 2013)*

The study outcomes measured at 8 years were the percentage of patients achieving LDA (as defined as a DAS28 of ≤ 2.4), the percentage of patients achieving remission (as defined as a DAS28 of < 1.6), the percentage of patients maintaining remission while pharmaceutical free, the percentage of patients in each treatment arm who are still on their initial treatment, the mean HAQ score over the 8-year period of the study, the percentage of patients in each arm who were receiving IFX after 8 years (patients in all arms could progress to treatment with IFX during the 8-year period of the study) and the mean SHS over the 8-year period of the study.[34] These results are presented in *Table 49*.

No statistically significant difference between the groups was observed in any of the DAS28 outcomes or in mean SHS. The mean HAQ score over the 8-year period was statistically significantly different across all groups when analysed simultaneously, with the authors additionally reporting that initial combination therapy with IFX group had statistically significant better results against the step-up combination therapy group and had borderline statistically significantly better results than the sequential monotherapy group. None of the other comparisons were statistically significantly different. Current use of IFX analysed across all groups approached statistical significance, with the greatest use being in the initial combination therapy with IFX group and in the sequential monotherapy group.

TABLE 49 Outcomes from the BeSt trial at 8 years as reported by van den Broek *et al.*[34]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
A DAS28 of ≤ 2.4 (%)	79	76	84	76	0.5
A DAS28 of < 1.6 (%)	49	56	57	47	0.5
A DAS28 of < 1.6 pharmaceutical free (%)	18	19	17	15	0.9
Still on initial treatment step (%)	29	22	45	66	< 0.001
Mean HAQ score over the study period (8 years)	0.69	0.71	0.63	0.57	< 0.05[a]
Current use of IFX (%)	21	10	13	24	0.06
Mean SHS progression (years 0–8)	14.6	13.9	8.5	8.3	0.6

a According to a linear mixed model: group 2 vs. group 4, $p < 0.05$; group 1 vs. group 4, $p = 0.055$; and all others, $p > 0.05$.

Based on van den Broek *et al.*,[34] there is no evidence to suggest that the initial combination with PDN group has worse outcomes than the initial combination with IFX group. Owing to the relatively high price of IFX, it is assumed that the initial combination with IFX group would either be dominated by the initial combination therapy with PDN group or have a cost per QALY ratio greater than those published by NICE.[92]

The use of IFX in the sequential monotherapy group is numerically higher (21%) than for those who began on combination therapy with PDN (13%), although this finding did not reach statistical significance. There was, however, a significant difference in the mean D-HAQ score and radiological progression in the first year (see *Table 42*). No firm conclusions can be made on the relative cost-effectiveness of the sequential monotherapy and the initial combination therapy with PDN group, although it is plausible that initiating combination therapy with PDN is more cost-effective than initiating sequential monotherapy.

The results of those in the step-up combination group and those in the initial combination therapy with PDN were broadly comparable, although there was a significantly quicker change in D-HAQ score at 3 months in the combination therapy with PDN group (see *Table 42*). No firm conclusions can be made regarding which out of the initial step-up combination therapy group and the initial combination therapy with PDN group is more cost-effective.

The BehandelStrategieën in Reumatoïde Artritis trial: results at 10 years (Markusse et al.*, 2014)*

The results at 10 years report only mortality rates[33] and these rates are presented in *Table 50*.

It can be seen that there is a numerical advantage for patients who receive initial combination therapy with PDN and patients who receive initial combination therapy with IFX compared with patients who receive sequential monotherapy and patients who receive step-up combination therapy. However, these differences are not statistically significant ($p = 0.805$) and are contrary to the mean HAQ score over the initial 8 years (see *Table 49*), so this difference is likely to be by chance.

For this reason, the results presented by Markusse *et al.*[33] would not influence the conclusions on cost-effectiveness generated by the data from van den Broek *et al.*[34]

TABLE 50 Mortality outcomes at 10 years as reported by Markusse *et al.*[33]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
Number of patients	126	121	133	128	–
Number of deaths	16	15	21	20	–
Percentage mortality at the years	12.70	12.40	15.79	15.63	0.805

The BehandelStrategieën in Reumatoïde Artritis trial: results at 10 years (Markusse et al.*, 2016)*

The paper by Markusse *et al.*[64] reports on the results at 10 years and comments that there was a significant difference in dropout rates among the four arms, with 28% dropping out of the initial combination therapy with IFX arm, compared with 40–45% in the remaining arms ($p = 0.031$). Of those patients dropping out, 39% were in clinical remission. No significant differences were observed in the number of AEs ($p = 0.159$), SAEs ($p = 0.47$) or deaths ($p = 0.81$). Survival was stated to be comparable to that of the Dutch population. The 10-year results have been included in *Table 51*.

These 10-year results do not change the previously reached conclusions that no firm conclusions can be made regarding which of sequential monotherapy, initial step-up combination therapy and initial combination therapy with PDN group is the most cost-effective. However, initiation with IFX is not likely to be cost-effective.

Hodkinson *et al.*, 2015

The paper by Hodkinson *et al*,[51] reports on a prospective 12-month study set in South Africa. A total of 102 patients, 94% black Africans, 83% female, with a mean symptom duration of 3.0 years and a mean DAS28 of 6.2, were randomly allocated to one of two monitoring methodologies: CDAI or SDAI. This study cites post hoc analyses,[94–96] which have shown both indexes to be valid instruments in monitoring disease activity in patients receiving treatment under a tight control strategy. The target in the SDAI arm was a score of ≤ 11 and the target in the CDAI arm was a score of ≤ 10, both of which represented LDA.

TABLE 51 Clinical outcomes at 10 years as reported by Markusse *et al.*[64]

Outcome	Therapy				*p*-value
	Sequential monotherapy	Step-up combination	Initial combination with PDN	Initial combination with IFX	
Drug-free remission: study completers (%)	8.7	9.1	9.0	10.2	NR
Remission (%)	51	49	53	53	0.94
A DAS28 of ≤ 2.4 (%)	84	77	83	84	0.72
Use of initial treatment at 10 years: intention to treat (%)	17	11	25	41	NR
Use of IFX at 10 years: study completers (%)	18	12	13	25	NR
Mean HAQ score over 10 years	0.69	0.72	0.64	0.58	0.12

NR, not reported.

The authors state that SDAI is based on a summation of five variables and that CDAI is based on a similar summation. However, SDAI requires an acute-phase reactant test at each monitoring visit, whereas CDAI does not. Thus, SDAI will be associated with a marginally greater cost than CDAI.

Two patients were lost to follow-up and two patients died during the study period. The analyses presented by the authors were based predominantly on 98 patients: 57 patients receiving CDAI monitoring and 41 patients receiving SDAI monitoring.

The study outcomes at 12 months are presented in *Table 52*. However, the definitions for remission, LDA, moderate disease activity and high disease activity are not provided. It can be seen from the *p*-values that there is no statistically significant difference between the treatments in terms of the percentage of patients in the four disease categories or the percentage of patients achieving a good response, as defined by EULAR. The *p*-values of 1.00 appear to have been miscalculated, but this would not affect the broad conclusion.

No firm conclusion can be made regarding the cost-effectiveness of the treatments; however, current evidence suggests that the treatment strategies are broadly comparable, but that SDAI will cost more than CDAI. These data would suggest that, in the absence of further data, CDAI would be preferable.

The Care in early Rheumatoid Arthritis trial

The CareRA study[38–43] was a 52-week randomised, pragmatic, open-label, superiority trial set in Belgium. Patients were assigned to either the high- or low-risk group based on the presence of erosions, disease activity, rheumatoid factor and anti-citrullinated protein antibody. The risk for which patients were reported to be high or low was not stated, but we presume it is of RA progression. The target for all patients in all arms was LDA, defined as a DAS28-CRP of ≤ 3.2.

The Care in early Rheumatoid Arthritis trial: results at 16 weeks (De Cock et al.*, 2013)*

The results from this abstract[38] were also reported in a full paper by Verschueren *et al.*,[42] although slight differences were noted. It is assumed that the later, full, paper would contain the correct results. For this reason, no further comment will be provided on this abstract.

The Care in early Rheumatoid Arthritis trial: results at 16 weeks (Verschueren et al.*, 2014)*

The results from this abstract[41] were also reported in a full paper by Verschueren *et al.*[42] We have focused on the full paper.

The Care in early Rheumatoid Arthritis trial: results at 16 weeks (Verschueren et al.*, 2015)*

The results provided in this paper, by Verschureren *et al.*,[42] compared the use of COBRA Classic with COBRA Slim and COBRA Avant-Garde in patients at high risk following 16 weeks of treatment. A total of 98 patients were allocated to COBRA Classic, 65.3% female, with a mean age of 53.2 years; 98 patients were allocated to COBRA Slim, 64.3% female, with a mean age of 51.8 years; and 94 patients were

TABLE 52 Outcomes at 12 months reported by Hodkinson *et al.*[51]

Outcome	Monitoring methodology (%)		*p*-value
	SDAI	CDAI	
Percentage of patients in remission	34.1	33.3	1.00
Percentage of patients with LDA	31.7	29.8	1.00
Percentage of patients with moderate disease activity	31.7	31.6	1.00
Percentage of patients with high disease activity	2.4	5.3	0.64
EULAR good response	56.1	50.9	0.68

allocated to COBRA Avant-Garde, 69.1% female, with a mean age of 51.2 years. Four outcomes were assessed: DAS28-CRP remission defined as a score of < 2.6, cumulative disease activity, HAQ scores and AEs. These results are reported in *Table 53*.

There was only one statistically significant difference among the three groups at 16 weeks, which related to therapy-related AEs with COBRA Slim having fewer events than the remaining arms. Given the comparable costs and efficacy it is likely that COBRA Slim would be the most cost-effective of the three strategies given the 16-week data.

The Care in early Rheumatoid Arthritis trial: results at 16 weeks for low-risk patients (De Cock et al.*, 2014)*

The results from this abstract[39] were also reported in a full paper by Verschueren *et al.*[40] For this reason, no further comment will be provided on this abstract.

The Care in early Rheumatoid Arthritis trial: results at 16 weeks for low-risk patients (Verschueren et al.*, 2015)*

The results provided in the paper[40] by Verschueren *et al.* compared the use of MTX-TSU with COBRA Slim in patients at low risk following 16 weeks of treatment. A total of 47 patients were allocated to MTX-TSU, 80.9% female, with a mean age of 51.02 years, and 43 patients were allocated to COBRA Slim, 76.7% female, with a mean of 51.42 years. Four outcomes were assessed: DAS28-CRP remission defined as a score of < 2.6, cumulative disease activity, HAQ scores and AEs. These results are reported in *Table 54*.

COBRA Slim was observed to have a statistically significant benefit in terms of both the area under the curve of DAS28-CRP in the 16-week period and the proportion of patients with a HAQ score of zero. Although not reaching significance, there were numerical advantages for COBRA Slim in key clinical outcomes such as remission, change in DAS28-CRP, change in HAQ score and EULAR response.

TABLE 53 Clinical outcomes at week 16 as reported by Verschueren *et al.*[42]

Outcome	Therapy			*p*-value
	COBRA Classic (*n* = 98)	COBRA Slim (*n* = 98)	COBRA Avant-garde (*n* = 94)	
Change in DAS28-CRP	2.80	2.60	2.40	0.140
Area under the curve of DAS28-CRP in weeks 0–16	10.66	11.05	10.72	0.521
Remission (%)	70.4	73.5	68.1	0.713
LDA (%)	84.7	86.7	87.2	0.863
Good EULAR response (%)	79.6	79.6	76.6	0.844
Moderate or good EULAR response (%)	98.0	95.9	93.6	0.320
Reduction in HAQ score	0.8	0.6	0.7	0.081
HAQ clinically meaningful change (%)	84.7	76.5	76.6	0.271
HAQ = 0	45.9%	42.9%	48.9%	0.700
	(*n* = 91)	(*n* = 96)	(*n* = 91)	
Patients with therapy-related AEs (%)	61.2	46.9	69.1	0.006
Number of therapy-related AEs per ITT patient	1.63	0.73	1.43	NR
Patients with therapy-related SAEs (%)	2.2	1.0	3.3	NR

ITT, intention to treat; NR, not reported.

TABLE 54 Clinical outcomes at week 16 for low-risk patients as reported by Verschueren *et al.*[40]

Outcome	Therapy		*p*-value
	MTX-TSU ($n = 47$)	COBRA Slim ($n = 43$)	
Change in DAS28-CRP	1.76	2.12	0.192
Area under the curve DAS28-CRP in weeks 0–16	13.84	11.18	0.006
Remission (%)	46.8	65.1	0.081
LDA (%)	72.3	79.1	0.458
Good EULAR response (%)	44.7	58.1	0.202
Moderate or good EULAR response (%)	72.3	86.0	0.111
Reduction in HAQ score	0.40	0.58	0.267
Clinically meaningful reduction in HAQ (%)	53.2	62.8	0.357
HAQ score of 0 (%)	23.4	51.2	0.006
Patients with therapy-related AEs (%)	44.7	39.5	0.622
Number of therapy-related AEs per ITT patient	0.681	0.698	NR
Patients with therapy-related SAEs (%)	0	0	NR

ITT, intention to treat; NR, not reported.

Given the likely comparability of costs for the two arms, but the superior efficacy for the COBRA Slim arm, it is likely that COBRA Slim would be more cost-effective than MTX-TSU given the 16-week data.

The Care in early Rheumatoid Arthritis trial: 52-week results (Verscheuren et al.*, 2015)*

The results from this abstract, by Verscheuren *et al.*,[40] were also reported in a full paper by Verschueren *et al.*,[43] although slight differences were noted. It is assumed that the later, full, paper, would contain the correct results and, therefore, no further comment will be provided on this abstract.

The Care in early Rheumatoid Arthritis trial: 52-week results (Verschueren et al.*, 2016)*

Two analyses were described within this paper by Verscheuren *et al.*:[43] one assessed three interventions for high-risk patients and one assessed two interventions for low-risk patients.

High-risk patients A total of 289 high-risk patients were randomly allocated to one of three treatment strategies. Ninety-eight patients, 65.3% female, with a mean age of 53.2 years, received COBRA Classic therapy; 98 patients, 64.3% female, with a mean age of 51.8 years, received COBRA Slim therapy; and 93 patients, 68.8% female, with a mean age of 51.1 years, received COBRA Avant-Garde therapy. Note that this number of patients is one fewer in the COBRA Avant-Garde arm than previously reported.[38,42]

Study outcomes, measured at 54 weeks, were the percentage of patients achieving LDA, the change in DAS28-CRP, the percentage of patients achieving remission (defined as DAS28-CRP < 2.6), the percentage of patients achieving a good EULAR response and the percentage of patients achieving a moderate EULAR response. The results for these outcomes are presented in *Table 55*.

Study outcomes indicate that there are no statistically significant differences in the efficacy of the three interventions. Indeed, each treatment possesses a numerical advantage in at least one outcome measure.

No firm conclusions can be made regarding the cost-effectiveness of the three treatment strategies. In the absence of other data, it is noted that COBRA Slim was associated with significantly fewer AEs. This conclusion is consistent with the 16-week results.

TABLE 55 Study outcomes at 52 weeks for high-risk patients reported by Verschueren *et al.*[43]

Outcome	Therapy			*p*-value
	COBRA Classic	COBRA Slim	COBRA Avant-Garde	
Number of participants	98	98	93	–
DAS28-CRP reduction	2.5	2.3	2.3	0.329
Remission (%)	64.3	60.2	62.4	0.840
LDA (%)	74.5	75.5	79.6	0.684
Good EULAR response (%)	67.3	68.4	67.7	0.995
Moderate or good EULAR response (%)	84.7	88.8	88.2	0.654
Patients with therapy-related AEs (%)	67.3	66.3	78.5	0.125
Number of therapy-related AEs per ITT patient	1.9	1.3	1.9	0.028
Patients with therapy-related SAEs (%)	2.0	2.0	2.2	NR

ITT, intention to treat; NR, not reported.

Low-risk patients A total of 90 low-risk patients were randomly assigned to one of two treatment strategies. Forty-seven patients, 80.9% female, with a mean age of 51.0 years, received MTX-TSU; and 43 patients, 76.7% female, with a mean age of 51.4 years, received COBRA Slim (low-risk) therapy. The results for low-risk patients are presented in *Table 56*.

There were no statistically significant differences in the efficacy of the two interventions. However, COBRA Slim therapy does possess a numerical advantage in all outcomes except that of obtaining at least a moderate EULAR response. The possibility that a true difference was not observed because of a small sample size cannot be discounted. However, there were two SAEs in the COBRA Slim arm and zero in the MTX-TSU group.

TABLE 56 Study outcomes at 52 weeks for low-risk patients reported by Verschueren *et al.*[43]

Outcome	Therapy		*p*-value
	MTX-TSU	COBRA Slim	
Number of participants	47	43	–
DAS28-CRP change	2.1	2.1	0.990
Remission (%)	57.4	67.4	0.329
LDA (%)	76.6	81.4	0.577
Good EULAR response (%)	57.4	60.5	0.771
Moderate or good EULAR response (%)	78.7	76.7	0.822
Patients with therapy-related AEs (%)	63.8	51.2	0.224
Number of therapy-related AEs per ITT patient	1.2	1.2	0.737
Patients with therapy-related SAEs (%)	0.0	4.3	NR

ITT, intention to treat; NR, not reported.

No firm conclusions can be made regarding which treatment strategy was more cost-effective. COBRA Slim has a numerical advantage on key clinical outcomes and AEs, but not SAEs; however, this was not statistically significant. This conclusion differs from that which was formed when only the results at 16 weeks were known.

The U-Act-Early trial (Bijlsma *et al.*, 2016)

The paper by Bijlsma *et al.*[62] reports on a 2-year RCT which was set in the Netherlands. A total of 317 patients with early RA were randomly allocated to one of three treatment arms. One hundred and six patients, 61% female, with a mean age of 53.0 years, received TOC plus MTX; 103 patients, 76% female, with a mean age of 55 years, received TOC monotherapy; and the remaining 108 patients, 64% female, with a mean age of 53.5 years, received MTX monotherapy. The target was to achieve sustained remission defined as a period of at least 24 weeks with a DAS28 of < 2.6 and a SJC of < 5.

The primary study outcome was the percentage of patients achieving sustained remission at 104 weeks. Secondary outcomes, measured at 24, 52 and 104 weeks, included the percentage of patients achieving a good or moderate EULAR response, the percentage of patients achieving an ACR 20/50/70/90 response and the mean physical function score (the D-HAQ adjusted for centre and baseline). A measure of the progression of radiological joint damage using the SHS was also assessed at 52 and 104 weeks. These outcomes are presented in *Table 57*.

Patients were allowed to add HCQ to their initial allocated treatment. If sustained remission was not achieved, then subsequent treatment regimens were allowed. These included alternative TNFis for those who were initially on TOC treatment, and TOC and an alternative TNFi for those patients who were allocated to MTX monotherapy.

No statistically significant difference was observed between TOC plus MTX and TOC monotherapy in terms of the percentage of patients achieving sustained remission. However, statistically significant differences were observed between both TOC arms compared with patients receiving MTX monotherapy. The same pattern exists in terms of EULAR response and ACR 20/50/70 responses at week 24. However, by week 52 most of these differences had become non-significant and by week 104 no statistically significant differences existed between treatment groups. In terms of physical function, a statistically difference between treatment groups as present at week 24 ($p = 0.0275$). However, again by week 52 this difference had become non-significant (week 52, $p = 0.14$; week 104, $p = 0.06$). In terms of the progression of radiological joint damage, measured by the SHS, there was a statistically significant difference at week 52 (patients receiving TOC + MTX vs. patients receiving MTX monotherapy; $p = 0.0164$) and week 104 [patients receiving TOC + MTX vs. patients receiving MTX monotherapy ($p = 0.0207$) and patients receiving TOC monotherapy vs. patients receiving MTX monotherapy ($p = 0.0381$)].

The study presents the percentage of patients who experienced AEs, SAEs and serious infections. However, there appear to be no statistically significant differences in AE frequency between treatment arms.

The study also reports results for patients at the end of the study, when patients could move on to subsequent treatments. At the end of the study, 88% of the TOC arm, 86% of the TOC plus MTX arm and 77% of the MTX arm had achieved sustained remission, with only the comparison between TOC monotherapy and MTX monotherapy being significant ($p = 0.0356$). It is stated that 'roughly 50%' of patients in the MTX monotherapy arm received TOC.

Without further details on the costs for each patient in each of the allocated treatment arms, it is not possible to estimate a robust cost per QALY for the interventions. What is known is that the use of TOC produces a statistically significantly higher percentage of patients who achieve sustained remission and that TOC is markedly more expensive than MTX. Given that 44% of patients on MTX monotherapy achieved sustained remission without the use of a bDMARD, there can be considerable savings by not starting

TABLE 57 Outcomes reported by Bijlsma *et al.*[62] as measured at 24, 52 and 104 weeks

Outcome	Therapy			*p*-value by therapy		
	TOC and MTX	TOC monotherapy	MTX monotherapy	TOC and MTX vs. MTX	TOC vs. MTX	TOC and MTX vs. TOC
Sustained remission at 104 weeks on initial treatment, *n* (%)	91 (86)	81 (83)	48 (44)	< 0.0001/2.0[a]	< 0.0001/1.86[a]	0.62/1.03[a]
Week 24						
Good EULAR response (%)	89	87	49	< 0.0001	< 0.0001	0.43
Moderate EULAR response (%)	5	11	32			
ACR 20 response (%)	75	75	59	0.0099	0.0343	NS
ACR 50 response (%)	64	59	34	< 0.0001	0.0009	NS
ACR 70 response (%)	44	37	15	< 0.0001	0.0003	NS
ACR 90 response (%)	18	12	5	0.0027	NS	NS
Mean physical function score	0.50	0.63	0.65	0.0275		
Week 52						
Good EULAR response (%)	75	88	72	0.26	0.0074	0.06
Moderate EULAR response (%)	6	4	7			
ACR 20 response (%)	75	72	69	NS	NS	NS
ACR 50 response (%)	62	59	51	NS	NS	NS
ACR 70 response (%)	44	44	33	NS	NS	NS
ACR 90 response (%)	19	21	7	0.0045	0.0026	NS
Mean physical function score	0.46	0.48	0.55	0.14		
SHS[b]	0.50	0.79	0.96	0.0164	0.06	0.49
Week 104						
Good EULAR response (%)	66	76	68	0.87	0.13	0.10
Moderate EULAR response (%)	8	8	8			
ACR 20 response (%)	63	65	61	NS	NS	NS
ACR 50 response (%)	49	55	48	NS	NS	NS
ACR 70 response (%)	36	39	35	NS	NS	NS
ACR 90 response (%)	21	20	14	NS	NS	NS
Mean physical function score	0.48	0.61	0.62	0.06		
SHS[b]	1.18	1.45	1.53	0.0207	0.0381	0.53

NS, not significant.
a Cochran–Mantel–Haenszel test stratified/relative risk; testing sequence for the intention-to-treat analysis defined a priori.
b Change from baseline.

patients on bDMARDs and in potentially increasing the intensity of cDMARDs before progressing to biologic use. It is the opinion of the authors of this report that the use of bDMARDs initially would produce a cost per QALY greater than the thresholds published by NICE.[92]

Established disease rheumatoid arthritis populations

Fransen et al.*, 2005*

The paper by Fransen *et al.*[50] reports on a 24-week multicentre cluster RCT set in the Netherlands. A total of 384 RA patients were included with a subgroup of 142 patients who had DAS28 assessed were included. Twenty-four rheumatology outpatient centres were randomly allocated to provide DAS28-guided care (61 patients) or usual care (81 patients). A summary of the patients' characteristics are tabulated in *Table 58*. The target in the systematic therapy arm was a DAS28 of ≤ 3.2: there was no target in the usual-care arm.

The frequency of appointments with treating rheumatologists was no different between patients receiving systematic therapy and patients receiving usual-care therapy. However, rheumatologists would perform a joint count and calculate the DAS28 during appointments with patients in the systematic monitoring arm, which are likely to be associated with a cost. However, this cost is unlikely to be significant and has been omitted from this analysis.

Outcomes included the percentage of patients achieving LDA (defined as a DAS28 of ≤ 3.2) at 24 weeks and the mean DAS28. These results are also presented in *Table 58*.

The authors state that the difference between the results in terms of the percentage of patients achieving LDA was statistically significant at the 5% level ($p = 0.028$). However, the difference in DAS28 was not statistically significant at the 5% level ($p = 0.36$).

It was found that, in terms of treatment-induced adverse reactions, a statistically significant difference between the treatment arms was observed only for rash or itching, with 4% of patients in the systematic monitoring therapy arm and 11% of patients in the usual-care therapy arm reporting this adverse reaction to treatment. However, it was assumed that this difference would not have a substantial effect on costs.

The evidence in the study appears to indicate that the systematic monitoring of patients is more effective without having a significant effect on costs. Thus, in terms of cost-effectiveness, the evidence in this paper would appear to indicate that usual-care therapy is dominated by the systematic monitoring of patients.

TABLE 58 Baseline patient characteristics in Fransen *et al.*[50]

	Therapy	
Characteristic	Systematic monitoring	Usual care
Mean age (years)	57	58
Patients who are female (%)	62	77
Baseline		
Mean DAS28	4.6	4.5
Patients with LDA (%)	13	12
24 weeks		
Mean DAS28	4.2	4.4
Patients with LDA (%)	31	16

The BROSG trial (Symmons et al.*, 2005)*

This *Health Technology Assessment* (HTA) report[9] presents the methodology and results of the BROSG RCT set in the UK. This study compared a shared-care treatment methodology, with patients treated predominantly within a primary care setting, with a hospital-based treatment modality, with patients treated predominantly within a hospital clinical setting. In the shared-care treatment methodology, the aims were to reduce joint pain, stiffness and related symptoms, whereas in the hospital-based methodology these aims were supplemented by an additional aim, to reduce clinical and laboratory evidence of inflammation.

A total of 466 patients were randomly allocated to one of the two treatment arms. Two hundred and thirty-three of these patients, 68.2% female, with a mean age of 60.4 years and mean duration of symptomatic RA of 12.6 years received shared care. The remaining 233 patients, 67.8% female, with a mean age of 60.8 years and mean duration of symptomatic RA of 12.5 years, received hospital-based care. The target was controlling joint pain, stiffness and related symptoms.

Health-related quality of life values were evaluated using the EQ-5D instrument at baseline and every 4 months, finishing at 36 months. The discounted QALYs were accrued by patients in each cohort of the study for three time periods: baseline to 12 months, 12–24 months and 24–36 months. The QALYs are presented in *Table 59* together with the total QALYs accrued by patients in both arms of the study across the entire study period.

Thus, according to the authors, the incremental QALYs accrued by patients in the shared-care cohort compared with patients in the hospital-based treatment cohort is 0.07 QALYs. A sensitivity analysis was conducted, which adjusted the calculation for differences in baseline utilities between arms.

The undiscounted costs incurred by patients in the shared-care cohort and the hospital-based treatment cohort across the 36-month period of the study are presented in *Table 60*. The authors report an incremental discounted cost of the shared-care treatment compared with hospital-based treatment of £106.

The authors conclude that the ICER of shared-care compared with hospital-based treatment is £1517 per QALY. A sensitivity analysis was conducted in which the calculation was adjusted for baseline utility values and this produced an ICER of £7571.

From the evidence presented in this study, shared-care treatment appears cost-effective when compared with hospital-based care.

The Optimisation of Adalimumab study (Pope et al.*, 2010; and Pope* et al.*, 2013)*

Both of the documents by Pope *et al.*[52,53] report results from the Optimisation of Adalimumab study. The Optimisation of Adalimumab study is an 18-month cluster RCT set in Canada that investigated whether or not TTT produced better results than routine care in established RA. Pope *et al.*[53] was an abstract that has been superseded by a full paper.[52] A total of 308 patients were randomly allocated to one of three treatment arms. One hundred and nine patients, 83.5% female, with a mean age of 56.0 years and mean

TABLE 59 Discounted QALYs accrued by patients in each cohort of the BROSG RCT[9]

	Treatment	
Assessment period	Shared care	Hospital based
Baseline to 12 months	0.60	0.57
12–24 months	0.55	0.53
24–36 months	0.52	0.50
Entire study period	1.67	1.60

TABLE 60 Undiscounted mean costs for the 36-month period of the study in the BROSG RCT[9]

	Treatment (£)	
Cost category	Shared care	Hospital based
Inpatient care	1575	1261
Outpatient care	997	1369
Primary care	502	395
Other health care	98	90
Drug therapy	1475	1403
Aids and appliances	68	76
Total	4700	4581

baseline DAS28 of 5.7 received routine care with no target. One hundred patients, 82.0% female, with a mean age of 55.3 years and mean baseline DAS28 of 5.7 received treatment in which the target was a DAS28 of < 2.6. The remaining 99 patients, 77.8% female, with a mean age of 51.5 years and mean baseline DAS28 of 5.8 received treatment in which the target was to achieve a SJC of 0.

Study outcomes measured at 6, 12 and 18 months were the DAS28, the percentage of patients achieving LDA (defined as a DAS28 of < 3.2), the percentage of patients achieving remission (defined as a DAS28 of < 2.6), the percentage of patients achieving a good/moderate EULAR response (undefined) and the percentage of patients achieving a SJC of 0. Analyses were undertaken using an intention-to-treat basis. These outcomes are presented in *Table 61*.

At all of the time points the strategy of treating to a target of a DAS28 of < 2.6 had a numerical advantage in terms of the percentage of patients achieving the following criteria: achieving remission; LDA; good or moderate EULAR response; and no swollen joints. Statistical significance was not reached given an adjustment in the significance level as a result of multiple testing, but was borderline at 18 months for EULAR response and approached significance at 18 months for remission and for LDA. Thus, there may be a true beneficial effect that has not been observed as a result of the small sample size.

The dose of ADA was not changed across arms, although the paper reports that there were more intensifications of other drugs in the targeted arms. The incremental cost of treatment between the arms of the study was therefore assumed to be negligible. However, the paper reports that there were more physician visits in the targeted groups, 4.3 in the routine care arm and 6.5 in each of the targeted arms. The additional 2.2 visits were assumed to cost £128,[93] resulting in additional costs of £281.60 for the two targeted arms.

Given the numerical advantage of the targeted treatment strategies, which may have failed to reach reached significance only because of small sample sizes, no firm conclusion on the cost-effectiveness or cost–utility of the treatment strategies can be made.

Mixed, early and established disease populations

TIght COntrol for Rheumatoid Arthritis trial (Grigor et al.*, 2004)*

The paper by Grigor *et al.*[61] reports on an 18-month single-blind RCT set in the UK. A total of 111 RA patients were randomly allocated to one of two treatment arms, with one patient dropping out after randomisation. Fifty-five patients, 71% female, with a mean age of 51 years, received intensive therapy. The remaining 55 patients, 69% female, with a mean age of 54 years, received routine therapy. The target in the intensive management arm was a DAS44 score of ≤ 2.4: there was no target in the routine therapy arm.

TABLE 61 Outcomes from the Optimisation of Adalimumab study at 6, 12 and 18 months reported by Pope *et al.*[52]

	Treatment group			
		Target of		
Outcome by time point	Routine care	DAS28 of < 2.6	SJC of 0	*p*-value
Mean DAS28[a]				
6 months	3.26	3.72	3.49	0.460
12 months	3.12	3.38	3.18	0.619
18 months	3.27	3.40	3.16	0.273
Intention-to-treat analyses				
Percentage of patients achieving remission (DAS28 of < 2.6)				
6 months	17.4	24.0	16.2	0.564[b]
12 months	21.1	28.0	26.3	0.697[b]
18 months	15.6	38.0	22.2	0.027[b]
Percentage of patients achieving LDA (DAS28 of < 3.2)				
6 months	28.4	33.0	30.3	0.880[b]
12 months	32.1	39.0	31.3	0.672[b]
18 months	22.9	47.0	27.3	0.022[b]
Percentage of patients achieving a good or moderate EULAR response				
6 months	56.9	62.0	62.5	0.634[b]
12 months	51.4	61.0	50.5	0.508[b]
18 months	35.8	63.0	53.5	0.018[b]
Percentage of patients achieving an SJC of 0				
6 months	22.0	27.0	24.2	0.839[b]
12 months	22.9	29.0	26.3	0.780[b]
18 months	21.1	34.0	26.3	0.331[b]

a Least square mean estimates based on linear mixed model.
b Between-group comparisons were assessed using a chi-squared clustered test with a significance level of 0.017 to account for multiple comparisons.

The primary outcome was the mean reduction in DAS and the proportion of patients with a good EULAR response (a DAS44 of < 2.4 and a fall from baseline of > 1.2) over the 18-month study period. Secondary outcomes included the percentage of patients achieving remission, defined as a DAS28 of < 1.6. These results are presented in *Table 62*. The results indicate that there are statistically significant differences in the effectiveness of intensive care compared with routine care.

Costs, using 2001/2 prices, were taken directly from the paper (*Table 63*). All costs except prescription costs were uplifted to 2014/15 values using inflation indices from *Unit Costs for Health & Social Care 2015*[89] and *Unit Costs for Health & Social Care 2010*[90] (as the 2015 version did not include the inflation index for 2001/2). It was assumed that the annual increase in the cost of pharmaceuticals is not in line with the inflation indices given in the *Unit Costs for Health & Social Care 2015*.[89] Ideally, the total pharmaceutical cost for each arm would have been calculated using current costs; however, the paper did not specify either the total or the individual pharmaceutical use in each arm and so this was not possible. These values were left at their 2001/2 values assuming that the incremental pharmaceutical or prescription cost would not differ considerable between 2001/2 and 2014/15.

TABLE 62 Outcomes of the Grigor *et al.*[61] study at 18 months

Outcome	Treatment group		*p*-value
	Routine care	Intensive care	
Number in study arm	55	55	–
Mean reduction in DAS44	–1.9	–3.5	< 0.0001
Patients achieving a good EULAR response (%)	44	82	< 0.0001
Number achieving remission (%)	16	65	< 0.0001

TABLE 63 Mean cost per patient reported in Grigor *et al.*[61] and their updated equivalents

Cost category	Cost year calculation (£)			
	Original paper (2001/2)		Uplifted to current costs (2014/15)	
	Routine care	Intensive care	Routine care	Intensive care
Outpatient cost	401	698	569	991
Inpatient cost	1611	571	2287	810
Prescription costs	452	649	452	649
Health professional visits	1249	859	1773	1219
Diagnostic tests	341	568	484	806
Total	4054	3345	5565	4476

The incremental mean savings per patient, using 2014/15 values, was £1089. There were 55 participants in both the intensive care arm and the routine care arm of this study and the total savings associated with intensive care were £59,892.

Given that the intensive care arm was associated with better patient outcomes and cost savings, intensive care is estimated to dominate routine care.

van Hulst et al.*, 2010*

The paper by van Hulst *et al.*[63] reports on an 18-month randomised pilot study set in the Netherlands. A total of 248 patients were randomly allocated to one of two treatment arms. One hundred and forty-four patients, 68% female, with a mean age of 60 years, were allocated to a nurse-led intervention. In this intervention, treating rheumatologists were informed of a patient's DAS28 before each consultation with a target of reducing a patient's DAS28 to ≤ 3.2 (mean age 60 years and 68% were female). One hundred and four patients, 60% female, with a mean age of 59 years, were allocated to a usual-care arm. These patients had their DAS28 calculated at each consultation, to allow a comparison of efficacies between arms to be evaluated, but the DAS28 was not communicated to the treating rheumatologists. The target in the intensive management arm was a DAS28 of ≤ 3.2: there was no target in the routine therapy arm.

In this study, participants underwent an assessment by a rheumatology nurse each time they were seen by their treating rheumatologist. In practice, usual-care patients would not be assessed by a rheumatology nurse at each consultation and, therefore, it is anticipated that the nurse-led intervention would be associated with a higher cost.

Study outcomes that were measured at 18 months were based on the change in DAS28 and the percentage of patients exhibiting a good, moderate or no EULAR response. These outcomes are presented in *Table 64*.

TABLE 64 Study outcomes at 18 months reported by van Hulst *et al.*[63]

Outcome	Therapy		*p*-value
	Intervention	Usual care	
Number of participants	144	104	–
Change in DAS28	–0.69	–0.66	0.7
Good EULAR response (%)	21.5	18.3	NR
Moderate EULAR response (%)	22.9	26.9	NR
No EULAR response (%)	55.6	54.8	NR

NR, not reported.

There was no evidence of a statistically significant difference in the effectiveness of a nurse-led intervention compared with usual care. Given the anticipated higher costs, it is highly likely that the nurse-led approach would be dominated by usual care or have an estimated cost per QALY greater than those published by NICE.[92]

Discussion

Literature relating to 16 studies was found. In papers relating to six of these studies [i.e. Saunders *et al.*,[54] van Eijk *et al.*,[55] Pope *et al.*,[52,53] den Uyl *et al.*,[69] Hodkinson *et al.*[51] and CareRA[39,40,43] (low risk, presumably of progression, patient subgroup)], no clear conclusions could be made regarding comparative cost-effectiveness. In the remaining 10 studies and for the high-risk patient subgroup in the CareRA trial,[39,42,43] the authors believe that conclusions could be made with some confidence. In Mottonen *et al.*,[46] combination drug therapy was estimated to be more cost-effective than single-drug therapy; in Grigor *et al.*,[61] intensive care was associated with both better outcomes and lower costs than routine care; in Fransen *et al.*,[50] systematic monitoring produced significantly more patients with LDA than usual care for similar costs; in Symmons *et al.*,[9] the paper concludes that the ICER of shared-care treatment compared with hospital-based treatment is £1517 per QALY or £7571 per QALY when accounting for different baseline utility; in Verstappen *et al.*,[36] it was concluded that intensive therapy would be more cost-effective than conventional therapy; in van Hulst *et al.*,[63] usual care was deemed more cost-effective than a nurse-led approach as the additional resources required were not translated into health benefits; in Urata *et al*,[57] a policy of using both DAS28 and MMP-3 to drive treatment decisions has been estimated by the authors of this report to be < £170 per additional person in remission compared with strategies of MMP-3-driven treatment or DAS28-driven treatment alone or routine care; in the TEAR[58–60] study, the additional costs of immediate ETN, or the use of ETN before triple therapy, would not be justified by any clinical gain; whereas in the BeSt trial,[26–34,42,64,65,68] the additional costs of initial combination therapy with IFX has not been shown to produce health benefits above initial combination therapy with PDN despite the markedly higher costs; in the CareRA trial,[38,42,43] for high-risk (presumably of progression) patients, efficacy was similar across the three arms but there were significantly fewer AEs in the COBRA Slim arm; and in Bijlsma *et al.*,[62] although TOC produced a statistically significantly higher percentage of people who achieved sustained remission, it would likely be associated with markedly higher costs than MTX and it is believed that the cost per QALY of using bDMARDs prior to treatment with intensive cDMARDs would have a cost per QALY greater than those published by NICE.[92]

There were too few studies in established RA to discern a pattern regarding cost-effectiveness: in two studies it was believed that a clear conclusion on cost-effectiveness could be made,[9,50] and in one no clear conclusion could be drawn.[52,53]

As previously stated, the regimens used within the studies were too heterogeneous to draw conclusions that compared all of the tested strategies simultaneously. Furthermore, it is unclear how routine care has changed over time and setting; for example, recent data[97] have shown that the intensity of cDMARD

treatment has increased since the publication of results from the TICORA trial,[61] which indicated that an intensive approach was both more beneficial for patients and saved money. However, there appears to be a pattern that treating intensively with cDMARDs was likely to be more cost-effective than treating with routine practice: the extent and degree to which this result was attributable to treating to a specific target is uncertain. A further pattern was that treating with bDMARDs prior to intensive treatment with cDMARDs would not produce sufficient benefit to justify the additional costs, given published NICE thresholds.[92] Of course, caution in the interpretation of these results is required because of the fact that cost estimates for some papers had to be undertaken on the basis of very limited data and outcomes could not always be expressed in standard metrics.

Chapter 5 Assessment of factors relevant to the NHS and other parties

For people with newly diagnosed RA, NICE clinical guideline number 79,[4] published in 2009, recommends a combination of cDMARDs (including MTX and at least one other DMARD plus short-term GCs) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. In early disease, this element of more intensive treatment of patients is often part of TTT strategies that have been tested in clinical studies. It is therefore the case that some elements of TTT are likely to be already in widespread NHS practice. It is not clear the extent to which other elements of TTT (the setting of explicit treatment goals and more frequent assessments of patients) are practised in the NHS or if such approaches are consistently followed in all areas of the UK.

Treat to target is typically more resource intensive during the early management of disease, until LDA or remission is achieved. There is a requirement for more frequent assessments and monitoring. Therefore, if there was a more widespread adoption of this form of TTT than is currently the case, this may place demands on rheumatology services.

It is also feasible that some patients whose disease progresses rapidly will be identified earlier via TTT management approaches and move to bDMARD therapies more rapidly than would otherwise be the case.

Chapter 6 Discussion

Statement of principal findings

Treat to target refers not to a single concept, but to a spectrum of broad approaches to the treatment of patients. TTT requires, at a minimum, the specification of a treatment objective. However, TTT commonly combines the specifying of a patient target with more frequent assessment of the target and adjustments to treatments by the clinician in response to those assessments. Those treatment adjustments can be entirely at the discretion of the clinician or may be protocolised. Clinical studies included in this report exhibit marked heterogeneity in each of the aforementioned aspects of TTT. Studies also differ in terms of the patient populations they examine, with the distinction between early and established disease being particularly important. Owing to these differences, it was not possible to quantitatively synthesise evidence across the studies and the number of studies where valid comparisons can be made, even qualitatively, is reduced.

Compared with usual care, there is no clear evidence either in favour of, or against, the clinical effectiveness of a TTT approach, in terms of the proportion of patients meeting the target, attaining LDA and attaining remission. In early RA, two studies found evidence in favour of the TTT approach. TTT was more effective in terms of the proportion of patients meeting the target and attaining remission. The T-4 study[56,57] found usual care to be more effective than the MMP-3-targeted arm, but the combined DAS28 of < 2.6- and MMP-3-targeted arm to be more effective than usual care [OR 0.21 (95% CI 0.10 to 0.47) at 1 year in the T-4 study[56,57]], in terms of the proportion of patients attaining remission. In trials with an established RA population, there was evidence in favour of a TTT approach compared with usual care in the Fransen *et al.* trial[50] in terms of the proportion of patients meeting the target or attaining LDA, but no difference between TTT and usual care in the Optimisation of Adalimumab study[52] in terms of the proportion of patients meeting the target or attaining LDA or remission. The TICORA trial[61] demonstrated evidence in favour of a TTT approach in a population containing both early and established RA patients in terms of the proportion of patients attaining remission.

The evidence is also mixed when comparing TTT to usual care in terms of other outcomes (DAS44 response, SJC, TJC, EULAR response, HAQ, erosions and quality of life). In early RA, there were mixed findings for DAS28/DAS44[55,57] and joint erosion,[55,57] and no difference between TTT arms and usual care on HAQ score.[55,57] In established RA, there was evidence in favour of in terms of EULAR response in the Optimisation of Adalimumab study.[52] There was, however, no difference between TTT and usual care in terms of DAS28,[50,52] SJC,[52] TJC[52] or HAQ response. In a mixed population, a TTT approach was favoured compared with usual care in terms of ACR 20/50/70 response in the TICORA[61] trial. The evidence, however, was equivocal for DAS28/DAS44 score,[61,63] SJC,[61,63] TJC,[61,63] EULAR response,[61,63] HAQ response,[61,63] joint erosion[61] and quality of life.[61]

Few differences in outcomes were found in relation to different targets within TTT strategies. Only the T-4 study[56,57] (early RA) found differences between targets: the DAS28 of < 2.6 target was more effective than the MMP-3 target, and the combined DAS28 of < 2.6 and MMP-3 target was more effective than both the DAS28 of < 2.6 target and the MMP-3 target, in terms of the proportion of patients in remission. Among trials examining an early RA population, there was no difference in the clinical effectiveness of different targets on DAS28/DAS44,[51,57,58] TJC,[51,58] EULAR response[51] and HAQ score response.[51,57,58] Findings relating to SJC,[51,58] ACR 20/50/70 response[58] and joint erosion[57,58] were equivocal. In established RA populations, there is evidence in favour of TTT, using a LDA target (DAS28 of ≤ 3.2),[50] but evidence is mixed with regard to remission (DAS28 of < 2.6) and SJC (SJC of 0) targets.[52] For other outcomes, only the Optimisation of Adalimumab study[52] demonstrated the benefit of a DAS28 of < 2.6 target over a SJC of 0 target. Both trials examining populations containing both early and established RA patients (i.e. the

TICORA trial[61] and van Hulst *et al.*[63]) examined a LDA target (DAS44 of ≤ 2.4[61] or DAS28 of ≤ 3.2[63]), and demonstrated evidence in favour of a TTT approach on most outcomes, with ambiguous evidence on some clinical outcomes. It is also important to note that all trials comparing different targets were rated as being at high risk of bias.

Only a small number of studies report data on AEs. Among trials examining an early RA population, there was no difference in the proportion of patients experiencing any AE, SAE, death, withdrawals as a result of AEs or specific AEs, although more events were experienced in the TTT arm compared with the usual-care arm in the STREAM trial.[55] Among trials examining established RA populations, a smaller proportion of patients withdrew as a result of AEs[52] and experienced specific AEs (dermatological and gastrointestinal AEs[50]) in the TTT arm, compared with usual care. The only trial reporting on these outcomes in a population containing both early and established RA patients, the TICORA trial,[61] which was also the only trial examining TTT compared with usual care rated as being at a low risk of bias, reported that a smaller proportion of patients reported any AE and specific AEs (dermatological, gastrointestinal and infectious AEs, significance not reported) in the TTT arm than in the usual-care arm. Overall, comparing trials by target on AEs, there is no clear evidence in favour of any target being more or less safe, compared with usual care.

Overall, we consider that the evidence for TTT is mixed but, in early RA, there does seem to be some limited support for TTT, in general, on some clinical outcomes. This is particularly true if the TICORA trial results, which was the only study in the review considered at low risk of bias, are interpreted as providing evidence relevant to the early RA population. The inclusion criterion for the TICORA trial was that patients had to have a disease duration of < 5 years.

There is also evidence to suggest that, in early RA, the components of care that together constitute TTT are likely to form a cost-effective approach. Conclusions relating to cost-effectiveness could be drawn for 10 studies, and for the high-risk patient subgroup in the CareRA trial. Almost all of the estimates from these studies indicated that TTT would be considered cost-effective other than when the TTT strategy included the use of bDMARDs in early disease. No conclusions could be made in relation to TTT in established disease.

Patient and public involvement representatives stated that if a TTT strategy were to be implemented, it would be beneficial that the patient was explicitly informed of this and made aware of the planned escalation of medication and the proposed target.

Strengths and limitations of the assessment

The current systematic review is the most comprehensive review to date to examine the clinical effectiveness of TTT. We have synthesised findings on TTT compared with usual care and a comparison of different targets. However, TTT is a broad term covering a spectrum of different treatment strategies. Clinical studies test TTT strategies that are heterogeneous. It was not felt justified to pool these strategies and make comparisons based on a synthesis of the evidence base.

Synthesis of different treatment protocols was precluded (even in terms of a narrative synthesis) by heterogeneity and lack of comparability between treatment protocols, although we have provided a comprehensive summary of the findings of trials that compare different treatment protocols. The current review is also the only systematic review to examine findings by population, which is important in this context as the recommendations for TTT differ slightly for early and established RA patients, as the treatment prognosis and implications of TTT may be different in these populations.[17,18] Another strength of the current review is the focus on RCTs, which reduces the impact of selection bias on the review findings.

A further strength of the work undertaken is in assessing the likely cost-effectiveness implications of each study identified in the clinical review. These results, which help inform the conclusions on the cost-effectiveness of TTT, also serve as a source of information for fellow researchers.

The main limitation of the current review is the small number of trials within in each comparison, in each population group. There was much heterogeneity in terms of targets, treatment protocols and frequency of contact between trials, even within each population group, in each comparison. Risk of bias was rated as being high in the majority of included trials.

The heterogeneity in identified studies, inter alia, placed additional constraints on the cost-effectiveness analysis. We adopted a pragmatic approach to estimate costs and outcomes from data reported alongside each clinical study. The required assumptions to optimise the use of limited resource use data and often also required the expression of outcomes in non-standard terms.

Uncertainties

It is unclear from the current review if there are specific elements of TTT that drive clinical effectiveness and cost-effectiveness, as TTT strategies tested in the identified clinical studies are varied and variously include the formal assessment of patients, clear protocols for drug treatment changes in response to patient assessments and more frequent assessment of patients. Existing NICE guidelines, based on systematic review of the literature, already recommend combination non-biologic drug treatment in early disease. This review is unable to establish if the adding in of other elements of TTT represents a cost-effective approach to care.

There is more limited evidence relating to TTT as a concept in established disease.

Chapter 7 Conclusions

Implications for service provision

For people with newly diagnosed RA, NICE Clinical Guideline 79[4] recommends a combination of cDMARDs (including MTX and at least one other DMARD plus short-term GCs) as first-line treatment. For patients with early disease, this element of more intensive treatment for patients is often part of TTT strategies that have been tested in clinical studies. Furthermore, it is likely that rheumatologists would monitor patients more frequently if treating with a more intense drug strategy. It is therefore likely that many rheumatologists, if compliant with NICE guidance, would experience little impact on their services were they to switch to a formal TTT strategy. It is also likely that many are already providing TTT in some form.

It is likely that more widespread adoption of TTT principles, particularly those TTT approaches that combine a treatment target with intensive drug protocols and frequent assessment of patients, would require more intense management of patients with early disease during their initial treatment period. It is also feasible that some patients whose disease progresses rapidly will be identified earlier via TTT management approaches, and move to bDMARD therapies more rapidly than would otherwise be the case.

Suggested research priorities

We highlight substantial uncertainty in the evidence base for TTT in RA. In part, this stems from the relatively low quality of the clinical trials identified. Only one study, the TICORA trial,[61] was rated as having a low risk of bias. However, there is also significant uncertainty that stems from the fact that TTT describes a broad concept, used to describe a spectrum of ways to treat patients, rather than a clearly defined, individual technology. Clinical studies reflect this and exhibit a wide degree of heterogeneity in the types of TTT they seek to examine. This results in a series of studies that cannot feasibly be pooled quantitatively, diminishing the strength of any conclusions. This heterogeneity also means that it is difficult to disentangle the effect of different elements of TTT strategies: the target itself, whether or not there is a treatment protocol to be followed in the light of assessment of the target and the frequency of patient assessment.

The design of any future clinical trials needs to be carefully assessed to ensure that aspects of these uncertainties will be resolved by the data they generate. If such research is to be conducted, there should be a focus on well-conducted trials comparing TTT with usual care and/or different TTT targets, which are adequately blinded (in terms of participants, study personnel and outcome assessment), with low rates of attrition and adequate allocation concealment, reporting on the proportion of patients meeting the target and being in remission. It is imperative that the design of such trials is mindful of the contribution results may make to the overall body of existing evidence on the subject. This requires comparability between trials. For example, remission, defined in a consistent manner, should be the target of choice for future studies. This extends to considerations of cost-effectiveness. As well as conducting cost-effectiveness analyses alongside the trial, methods for ensuring long-term extensions studies, that allow some of the key uncertainties in this area to be addressed, are critical (e.g. the rate at which patients move to bDMARD therapies in the long term).

Patient and public involvement representatives stated that future research into the fatigue that is associated with RA would be beneficial, as it was not only swollen joints and pain that were of concern to the patient.

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Contributions of authors

Allan Wailoo (Professor, Health Economics) oversaw and contributed to all aspects of the project.

Emma S Hock (Research Fellow, Systematic review) undertook the literature review relating to clinical effectiveness, detailed the identified studies and provided the summary of evidence found.

Matt Stevenson (Professor, HTA) undertook the review of cost-effectiveness papers and produced the estimates of cost-effectiveness related to each study identified in the clinical effectiveness review.

Marrissa Martyn St James (Research Fellow, Systematic review) undertook the literature review relating to clinical effectiveness, detailed the identified studies and provided the summary of evidence found.

Andrew Rawdin (Research Assistant, Health Economics) undertook the review of cost-effectiveness papers and produced the estimates of cost-effectiveness related to each study identified in the clinical effectiveness review.

Emma Simpson (Research Fellow, Systematic review) undertook the literature review relating to clinical effectiveness, detailed the identified studies and provided the summary of evidence found.

Ruth Wong (Information Specialist) devised and ran the search strategies.

Naila Dracup (Information specialist) devised and ran the search strategies.

David L Scott (Professor, Clinical rheumatology) provided clinical advice to the project and commented on specific aspects of the clinical evidence.

Adam Young (Consultant Rheumatologist) provided clinical advice to the project and commented on specific aspects of the clinical evidence.

All authors were involved in drafting and commenting on the final report.

Data sharing statement

There are no new data generated from this project beyond those reported in the project report. Further information on any aspects of the study can be addressed to the corresponding author.

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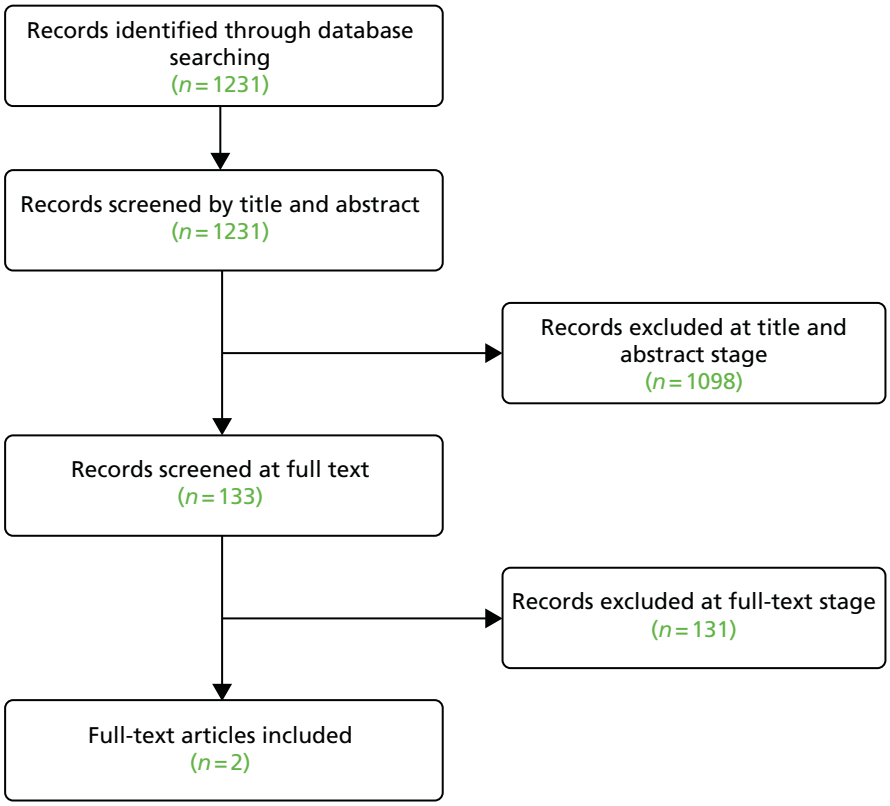
Appendix 1 Cost-effectiveness review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart



Appendix 2 Literature search strategies

Phase I search strategies

MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R)

Date searched: 19 May 2015.

Search strategy

1.	exp Arthritis, Rheumatoid/
2.	rheumatoid arthritis.tw.
3.	or/1-2
4.	Remission Induction/
5.	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$).ti.
6.	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).mp.
7.	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
8.	(adapt$ or titrat$ or adjust$ or response-based).tw.
9.	7 or 8
10.	*Disease Progression/
11.	*Disease Management/
12.	*Disease Outbreaks/
13.	Disease/
14.	10 or 11 or 12 or 13
15.	9 and 14
16.	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).mp.
17.	(remission adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).mp.
18.	(((low$ or moderate or medium or high) and activity) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).mp.
19.	4 or 5 or 6 or 15 or 16 or 17 or 18
20.	3 and 19
21.	randomized controlled trial.pt.
22.	randomized controlled trial.mp.
23.	21 or 22
24.	20 and 23
25.	limit 24 to yr=‘2008 -Current’
26.	MEDLINE.tw.
27.	systematic review.tw.
28.	meta analysis.pt.
29.	or/26-28
30.	20 and 29

31.	limit 30 to yr='2008 -Current'
32.	ec.fs.
33.	cost.tw.
34.	health care costs.sh.
35.	or/32-34
36.	20 and 35
37.	limit 36 to yr='2013 -Current'

EMBASE

Date searched: 19 May 2015.

Search strategy

1.	exp rheumatoid arthritis
2.	rheumatoid arthritis.tw.
3.	1 or 2
4.	remission/
5.	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$).ti.
6.	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
7.	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
8.	(adapt$ or titrat$ or adjust$ or response-based).tw.
9.	7 or 8
10.	*disease course/
11.	*disease management/
12.	*epidemic/
13.	diseases/
14.	or/10-13
15.	9 and 14
16.	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).tw.
17.	(remission adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
18.	(((low$ or moderate or medium or high) and activity) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
19.	4 or 5 or 6 or 15 or 16 or 17 or 18
20.	3 and 19
21.	double-blind:.mp.
22.	placebo:.tw.
23.	blind:.tw.
24.	or/21-23
25.	20 and 24
26.	limit 25 to yr='2008 -Current'

27.	meta-analysis.tw.
28.	systematic review.tw.
29.	27 or 28
30.	20 and 29
31.	limit 30 to yr=‘2008 -Current’
32.	cost.tw.
33.	costs.tw.
34.	32 or 33
35.	20 and 34
36.	limit 35 to yr=‘2013 -Current’

Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Health Technology Assessment Database; Database of Abstracts of Reviews of Effects; and NHS Economic Evaluation Database

Date searched:19 May 2015.

Search strategy

#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2	rheumatoid arthritis:ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Remission Induction] explode all trees
#5	(strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*):ti,ab,kw
#6	((strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) next/2 (treat* or therap*)):ti,ab,kw
#7	(optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*):ti,ab,kw
#8	(adapt* or titrat* or adjust* or response-based):ti,ab,kw
#9	#7 or #8
#10	MeSH descriptor: [Disease Progression] this term only
#11	MeSH descriptor: [Disease Management] this term only
#12	MeSH descriptor: [Disease Outbreaks] this term only
#13	MeSH descriptor: [Disease] explode all trees
#14	#10 or #11 or #12 or #13
#15	#9 and #14
#16	((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) next/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)):ti,ab,kw
#17	(remission next/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)):ti,ab,kw
#18	(((low* or moderate or medium or high) and activity) next/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)):ti,ab,kw
#19	#4 or #5 or #6 or #15 or #16 or #17 or #18
#20	#3 and #19

Web of Science Citation Index Expanded and Web of Science Citation Index and Conference Proceedings Index

Date searched: 19 May 2015.

Search strategy

# 19	#18 AND #13
Indexes=SCI-EXPANDED, CPCI-S Timespan=2013-2015	
# 18	TOPIC: ((cost* and (effective* or utilit* or benefit* or minimi*))) OR TITLE: (costs) OR TOPIC: (((economic* or pharmacoeconomic* or pharmaco-economic*))) OR TITLE: (economic*)
# 17	#16 AND #13
# 16	TS=((meta-analysis or meta analy* or metaanaly*)) OR TS=(systematic review*)
# 15	#14 AND #13
# 14	TS=(randomi* controlled trial*) OR TS=(placebo*)
# 13	#12 AND #1
# 12	#11 OR #10 OR #9 OR #8 OR #3 OR #2
# 11	TS=(((low* or moderate or medium or high) and activity)) AND TS=((strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
# 10	TS=(((remission NEAR/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))))
# 9	TS=(((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) NEAR/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)))
# 8	#7 AND #6
# 7	TOPIC: (disease)
# 6	#5 OR #4
# 5	TOPIC: ((adapt* or titrat* or adjust* or response-based))
# 4	TITLE: ((optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*))
# 3	TS=(((strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) NEAR/2 (treat* or therap*)))
# 2	TITLE: ((strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*))
# 1	TOPIC: (rheumatoid arthritis*)

ClinicalTrials.gov: US National Institutes of Health

URL: http://clinicaltrials.gov/.

Date searched:19 May 2015.

Search strategy

ultrasound l arthritis

ultrasonography l arthritis

sonography l arthritis

echography l arthritis

European League Against Rheumatism Abstract Archive; published in the Annals of the Rheumatic Diseases *and searched via the Web of Science*

URL: www.abstracts2view.com/eular/sessionindex.php

Date searched: 21 May 2015.

Search strategy

# 15	#14 AND #13
Indexes=SCI-EXPANDED, CPCI-S Timespan=2008-2015	
# 14	PUBLICATION NAME: (ann rheum dis)
# 13	#12 AND #1
# 12	#11 OR #10 OR #9 OR #8 OR #3 OR #2
# 11	TS=(((low* or moderate or medium or high) and activity)) AND TS=((strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
# 10	TS=(((remission NEAR/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))))
# 9	TS=(((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) NEAR/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)))
# 8	#7 AND #6
# 7	TOPIC: (disease)
# 6	#5 OR #4
# 5	TOPIC: ((adapt* or titrat* or adjust* or response-based))
# 4	TITLE: ((optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*))
# 3	TS=(((strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) NEAR/2 (treat* or therap*)))
# 2	TITLE: ((strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*))
# 1	TOPIC: (rheumatoid arthritis*)

American College of Rheumatology and Association of Rheumatology Health Professionals; published in Arthritis and Rheumatology *and searched via the Web of Science*

URL: http://acrabstracts.org/

Date searched: 21 May 2015.

Search strategy

# 15	#14 AND #13
Indexes=SCI-EXPANDED, CPCI-S Timespan=2008-2015	
# 14	SO=(ARTHRITIS 'AND' RHEUMATISM)
# 13	#12 AND #1
# 12	#11 OR #10 OR #9 OR #8 OR #3 OR #2
# 11	TS=(((low* or moderate or medium or high) and activity)) AND TS=((strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
# 10	TS=(((remission NEAR/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))))

# 9	TS=(((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) NEAR/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)))
# 8	#7 AND #6
# 7	TOPIC: (disease)
# 6	#5 OR #4
# 5	TOPIC: ((adapt* or titrat* or adjust* or response-based))
# 4	TITLE: ((optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*))
# 3	TS=(((strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) NEAR/2 (treat* or therap*)))
# 2	TITLE: ((strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*))
# 1	TOPIC: (rheumatoid arthritis*)

Phase II randomised controlled trials search strategies

MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R)

Date searched: 8 January 2016.

Search strategy

1	exp Arthritis, Rheumatoid/
2	rheumatoid arthritis.tw.
3	or/1-2
4	Remission induction/
5	(remission adj2 induc$).ti,ab.
6	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$ or optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
7	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
8	(ttt or t2t).tw.
9	(treat$ and target$).ti.
10	((disease activity score or das28) adj3 (driven or step$ or strateg$ or therap$ or treat$)).tw.
11	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
12	(adapt$ or titrat$ or adjust$ or response-based).tw.
13	or/11-12 (1662622)
14	*Disease Progression/
15	*Disease Management/
16	*Disease Outbreaks/
17	Disease/
18	or/14-17
19	13 and 18
20	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).tw.
21	((remission or activ$) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.

22	(((low$ or moderate or medium or high) and activity) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
23	4 or 5 or 6 or 7 or 8 or 9 or 10 or 19 or 20 or 21 or 22
24	3 and 23
25	Randomized controlled trials/
26	Randomized controlled trial.pt.
27	Controlled clinical trial.pt.
28	Random Allocation/
29	Double blind method/
30	Single Blind Method/
31	Clinical trial.pt.
32	exp Clinical Trial/
33	(clin$ adj25 trial$).ti,ab.
34	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
35	Placebos/
36	Placebo$.ti,ab.
37	Random$.ti,ab.
38	or/25-37
39	24 and 38
40	Comment.pt.
41	Letter.pt.
42	Editorial.pt.
43	case report.tw.
44	Historical article.pt.
45	Animal/
46	Human/
47	45 not (45 and 46)
48	or/40-44,47
49	39 not 48

EMBASE

Date searched: 8 January 2016.

Search strategy

1	exp rheumatoid arthritis/
2	rheumatoid arthritis.tw.
3	or/1-2
4	remission/
5	(remission adj2 induc$).ti,ab.
6	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$ or optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.

7	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
8	(treat$ and target$).ti.
9	((disease activity score or das28) adj3 (driven or step$ or strateg$ or therap$ or treat$)).tw.
10	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
11	(adapt$ or titrat$ or adjust$ or response-based).tw.
12	10 or 11
13	*disease course/
14	*disease management/
15	*epidemic/
16	diseases/
17	or/13-16
18	12 and 17
19	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).tw.
20	((remission or activ$) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
21	4 or 5 or 6 or 7 or 8 or 9 or 18 or 19 or 20
22	3 and 21
23	Randomized controlled trial/
24	clinical trial/
25	Randomization/
26	Single blind procedure/
27	Double blind procedure/
28	Crossover procedure/
29	Placebo/
30	randomi?ed controlled trial$.tw.
31	(clin$ adj25 trial$).ti,ab.
32	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
33	placebo$.ti,ab.
34	random$.ti,ab.
35	or/23-34
36	22 and 35
37	Case study/
38	case report.tw.
39	Abstract report/
40	letter/
41	Animal/
42	Human/
43	41 not (41 and 42)
44	37 or 38 or 39 or 40 or 43
45	36 not 44

Cochrane Central Register of Controlled Trials

Date searched: 14 January 2016.

Search strategy

#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2	rheumatoid arthritis:ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Remission Induction] explode all trees
#5	(remission next/2 induc*):ti,ab,kw
#6	(strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*):ti
#7	(strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) next/2 (treat* or therap*):ti,ab,kw
#8	(ttt or t2t):ti,ab,kw
#9	(treat* and target*):ti
#10	((disease activity score or das28) near/3 (driven or step* or strateg* or therap* or treat*)):ti,ab,kw
#11	(optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*):ti
#12	(adapt* or titrat* or adjust* or response-based):ti,ab,kw
#13	#11 or #12
#14	MeSH descriptor: [Disease Progression] this term only
#15	MeSH descriptor: [Disease Management] this term only
#16	MeSH descriptor: [Disease Outbreaks] this term only
#17	MeSH descriptor: [Disease] this term only
#18	#14 or #15 or #16 or #17
#19	#13 and #18
#20	(strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) n3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*):ti,ab,kw
#21	((remission or activ*) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)):ti,ab,kw
#22	(((low* or moderate or medium or high) and activity) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)):ti,ab,kw
#23	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #19 or #20 or #21 or #22
#24	#3 and #23

Web of Science Citation Index Expanded and Web of Science Citation Index and Conference Proceedings Index

Date searched: 26 January 2016.

Search strategy

S1	TOPIC=(Rheumatoid arthritis)
S2	TOPIC=(remission near/2 induc*)
S3	TITLE=(strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)

S4	TS=((strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*) near/2 (treat* or therap*))
S5	TOPIC=(ttt or t2t)
S6	TITLE=(treat* and target)
S7	TOPIC=('disease activity score' or das28)
S8	TI=(optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S9	TOPIC=(adapt* or titrat* or adjust* or response-based)
S10	S9 OR S8
S11	TOPIC=Disease Progression
S12	TOPIC=Disease Management
S13	TOPIC=Disease Outbreaks
S14	TOPIC=Disease
S15	S14 OR S13 OR S12 OR S11
S16	S15 AND S10
S17	TOPIC=((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) near/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*))
S18	TOPIC=((remission or activ*) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S19	TOPIC=((low* or moderate or medium or high) and (activity) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S20	S19 OR S18 OR S17 OR S16 OR S7 OR S6 OR S5 OR S4 OR S3 or S2
S21	S20 AND S1
S22	TOPIC=(randomi?ed controlled trial)
S23	TOPIC=(rct)
S24	TOPIC=(random allocation)
S25	TOPIC=(allocated near/2 random*)
S26	TOPIC=single blind*
S27	TOPIC=(double blind*)
S28	TOPIC=((treble or triple) near/1 (blind*))
S29	TOPIC=(placebo*)
S30	S29 OR S28 OR S27 OR S26 OR S25 OR S24 OR S23 OR S22
S31	S30 AND S21

Bioscience Information Service Previews

Date searched: 14 January 2016.

Search strategy

S1	TOPIC=Rheumatoid arthritis
S2	TOPC=(remission near/2 induc*)
S3	TITLE=(strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S4	TOPIC=((strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control*) near/2 (treat* or therap*))
S5	TOPIC=(ttt or t2t)

S6	TITLE=(treat* and target)
S7	TOPIC=('disease activity score' or das28)
S8	TITLE=(optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S9	TOPIC=(adapt* or titrat* or adjust* or response-based)
S10	#9 OR #8
S11	TOPIC=Disease Progression
S12	TOPIC=Disease Management
S13	TOPIC=Disease Outbreaks
S14	TOPIC=Disease
S15	#14 OR #13 OR #12 OR #11
S16	#15 AND #10
S17	TOPIC=((strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) near/3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*))
S18	TOPIC=((remission or activ*) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S19	TOPIC=((low* or moderate or medium or high) and (activity) near/3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S20	#19 OR #18 OR #17 OR #16 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
S21	#20 AND #1
S22	TOPIC=(randomi?ed controlled trial
S23	TOPIC=(rct)
S24	TOPIC=(random allocation)
S25	TOPIC=(allocated near/2 random*)
S26	TOPIC=(single blind*)
S27	TOPIC=(double blind*)
S28	TOPIC=((treble or triple) near/1 (blind*))
S29	TOPIC=(placebo*)
S30	S29 OR S28 OR S27 OR S26 OR S25 OR S24 OR S23 OR S22
S31	S30 AND S21

Cumulative Index to Nursing and Allied Health Literature

Date searched: 13 January 2016.

Search strategy

S1	(Mesh Heading 'Arthritis, Rheumatoid+')
S2	TX rheumatoid arthritis
S3	(S1 OR S2)
S4	TI (remission n2 induc*) or AB (remission n2 induc*)
S5	TI (strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S6	TX (strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) n2 (treat* or therap*)

S7	TX (ttt or t2t)
S8	TITLE (treat* and target*)
S9	TX (disease activity score or das28) n3 (driven or step* or strateg* or therap* or treat*)
S10	TITLE (optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S11	TX (adapt* or titrat* or adjust* or response-based)
S12	S10 OR S11
S13	(Major concept 'Disease Progression')
S14	(Major concept 'Disease Outbreaks')
S15	(Mesh Heading 'Disease')
S16	S13 OR S14 OR S15
S17	S12 AND S16
S18	TX (strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) n3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)
S19	TX ((remission or activ*) n3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)
S20	TX (((low* or moderate or medium or high) and activity) n3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S21	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S17 OR S18 OR S19 OR S20
S22	S3 AND S21
S23	(Mesh Heading 'Randomized Controlled Trials')
S24	Publication Type Randomized controlled trial
S25	TX clinic* n1 trial*
S26	TX (Singl* n1 blind*) OR TX (singl* n1 mask*) OR TX (doubl* n1 blind*) OR TX (doubl* n1 mask*) OR TX (tripl* n1 blind*) OR TX (tripl* n1 mask*) OR TX (trebl* n1 blind*) OR TX (trebl* n1 mask*)
S27	(Mesh Heading 'Clinical Trials+')
S28	Publication Type Clinical trial
S29	TX Randomi* control* trial*
S30	(MeSH heading 'Random Assignment')
S31	TX Random* allocat*
S32	TX Placebo*
S33	(MeSH heading 'Placebos')
S34	(MeSH heading 'Quantitative Studies')
S35	(S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34)
S36	S22 AND S35
S37	Publication Type commentary
S38	Publication Type Letter
S39	Publication Type Editorial
S40	TX Case report
S41	(MH 'Animals')
S42	S37 OR S38 OR S39 OR S40 OR S41
S43	S36 NOT S42

ClinicalTrials.gov: US National Institutes of Health
URL: http://clinicaltrials.gov/

Date searched: 18 January 2016.

Search strategy
Remission induction l rheumatoid arthritis

'TTT' l rheumatoid arthritis

International Clinical Trials Registry Platform (URL: www.who.int/ictrp/en/)
Date searched: 18 January 2016.

Search strategy
Remission induction l rheumatoid arthritis

'TTT' l rheumatoid arthritis

National Institute for Health and Care Excellence Evidence (URL: www.nice.org.uk/)
Date searched: 18 January 2016.

Search strategy
'TTT' filtered by type of information – commissioning guide

'TTT' filtered by type of information – ongoing trials

'Remission induction' rheumatoid arthritis filtered by type of information – ongoing trials

'Remission induction' rheumatoid arthritis filtered by type of information – commissioning guide

Phase II cost-effectiveness search strategies

MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R)
Date searched: 14 January 2016.

Search strategy

1	exp Arthritis, Rheumatoid/
2	rheumatoid arthritis.tw.
3	or/1-2
4	Remission induction/
5	(remission adj2 induc$).ti,ab.
6	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$ or optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
7	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
8	(ttt or t2t).tw.
9	(treat$ and target$).ti.
10	((disease activity score or das28) adj3 (driven or step$ or strateg$ or therap$ or treat$)).tw.

11	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
12	(adapt$ or titrat$ or adjust$ or response-based).tw.
13	or/11-12
14	*Disease Progression/
15	*Disease Management/
16	*Disease Outbreaks/
17	Disease/
18	or/14-17
19	13 and 18
20	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).tw.
21	((remission or activ$) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
22	(((low$ or moderate or medium or high) and activity) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
23	4 or 5 or 6 or 7 or 8 or 9 or 10 or 19 or 20 or 21 or 22
24	3 and 23
25	Economics/
26	"Costs and cost analysis"/
27	Cost allocation/
28	Cost-benefit analysis/
29	Cost control/
30	Cost savings/
31	Cost of illness/
32	Cost sharing/
33	"Deductibles and coinsurance"/
34	Health care costs/
35	Direct service costs/
36	Drug costs/
37	Employer health costs/
38	Hospital costs/
39	Health expenditures/
40	Capital expenditures/
41	Value of life/
42	exp Economics, hospital/
43	exp Economics, medical/
44	Economics, nursing/
45	Economics, pharmaceutical/
46	exp "fees and charges"/
47	exp budgets/
48	(low adj cost).mp.

49	(high adj cost).mp.
50	(health?care adj cost$).mp.
51	(fiscal or funding or financial or finance).tw.
52	(cost adj estimate$).mp.
53	(cost adj variable).mp.
54	(unit adj cost$).mp.
55	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
56	exp models, economic/
57	or/25-56
58	24 and 57
59	Comment.pt.
60	Letter.pt.
61	Editorial.pt.
62	case report.tw.
63	Historical article.pt.
64	Animal/
65	Human/
66	64 not (64 and 65)
67	or/59-63,66
68	58 not 67

EMBASE

Date searched: 14 January 2016.

Search strategy

1	exp rheumatoid arthritis/
2	rheumatoid arthritis.tw.
3	or/1-2
4	remission/
5	(remission adj2 induc$).ti,ab.
6	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$ or optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
7	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
8	(treat$ and target$).ti.
9	((disease activity score or das28) adj3 (driven or step$ or strateg$ or therap$ or treat$)).tw.
10	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
11	(adapt$ or titrat$ or adjust$ or response-based).tw.
12	10 or 11
13	*disease course/

14	*disease management/
15	*epidemic/
16	diseases/
17	or/13-16
18	12 and 17
19	((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).tw.
20	((remission or activ$) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
21	4 or 5 or 6 or 7 or 8 or 9 or 18 or 19 or 20
22	3 and 21
23	Socioeconomics/
24	Cost benefit analysis/
25	Cost effectiveness analysis/
26	Cost of illness/
27	Cost control/
28	Economic aspect/
29	Financial management/
30	Health care cost/
31	Health care financing/
32	Health economics/
33	Hospital cost/
34	(fiscal or financial or finance or funding).tw.
35	cost minimization analysis/
36	(cost adj estimate$).mp.
37	(cost adj variable$).mp.
38	(unit adj cost$).mp.
39	or/23-38
40	22 and 39
41	Letter.pt.
42	Editorial.pt.
43	Animal/
44	Human/
45	43 not (43 and 44)
46	or/41-42,45
47	40 not 46

NHS Economic Evaluation Database

Date searched: 14 January 2016.

Search strategy

#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2	rheumatoid arthritis:ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Remission Induction] explode all trees
#5	(remission next/2 induc*):ti,ab,kw
#6	(strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*):ti
#7	(strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) next/2 (treat* or therap*):ti,ab,kw
#8	(ttt or t2t):ti,ab,kw
#9	(treat* and target*):ti
#10	((disease activity score or das28) near/3 (driven or step* or strateg* or therap* or treat*)):ti,ab,kw
#11	(optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*):ti
#12	(adapt* or titrat* or adjust* or response-based):ti,ab,kw
#13	#11 or #12
#14	MeSH descriptor: [Disease Progression] this term only
#15	MeSH descriptor: [Disease Management] this term only
#16	MeSH descriptor: [Disease Outbreaks] this term only
#17	MeSH descriptor: [Disease] this term only
#18	#14 or #15 or #16 or #17

Cumulative Index to Nursing and Allied Health Literature

Date searched: 14 January 2016.

Search strategy

S1	(MeSH Heading "Arthritis, Rheumatoid+")
S2	TX rheumatoid arthritis
S3	(S1 OR S2)
S4	TI (remission n2 induc*) OR AB (remission n2 induc*)
S5	TITLE (strateg* or aim* or goal* or target* or tight* or aggressiv* or intens* or control* or optim* or adapt* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S6	TX (strateg* or aim* or goal* or target* or tight* or aggressiv* or control*) n2 (treat* or therap*)
S7	TX (ttt or t2t)
S8	TI (treat* and target*)
S9	TX (disease activity score or das28) N3 (driven or step* or strateg* or therap* or treat*)
S10	TI (optim* or switch* or add* or chang* or expand* or step* or combin* or intensif* or escalat*)
S11	TX (adapt* or titrat* or adjust* or response-based)
S12	S10 OR S11

S13	(MeSH descriptor "Disease Progression")
S14	(MeSH descriptor "Disease Outbreaks")
S15	(Mesh Heading "Disease")
S16	S13 OR S14 OR S15
S17	S12 AND S16
S18	TX (Strateg* or proced* or consequ* or therap* or halt* or stop* or revers* or dela* or arrest* or detain* or slow* or preven* or retard* or avoid*) N3 (structural or functional or erosi* or progre* or disabilit* or invalidity or impediment or disablement or radiograph* or radiolog*)
S19	TX ((Remission or activ*) N3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing)
S20	TX (((Low* or moderate or medium or high) and activity) N3 (strateg* or optimi* or adapt* or control* or frequency or dose* or dosing))
S21	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S17 OR S18 OR S19 OR S20
S22	S3 AND S21
S23	(MeSH Heading "Economics+")
S24	(MeSH Heading "Financial Management+")
S25	(MeSH Heading "Financing, Organized+")
S26	(MeSH Heading "Business+")
S27	S24 OR S25 OR S26
S28	S23 NOT S27
S29	MeSH Heading Health resource allocation
S30	MeSH Heading Health resource utilization
S31	S29 OR S30
S32	S28 OR S31
S33	TX (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)
S34	S32 OR S33
S35	S22 AND S34
S36	Publication Type Editorial
S37	Publication Type letter
S38	(MeSH Heading "Animal Studies")
S39	S36 OR S37 OR S38
S40	S35 NOT S39

American Economic Association's electronic bibliography

Date searched: 14 January 2016.

Search strategy

1	Rheumatoid arthritis.tw.
2	(remission adj2 induc$).ti,ab.
3	(strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$ or optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
4	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).tw.
5	(ttt or t2t).tw.

6	(treat$ and target$).ti.
7	((disease activity score or das28) adj3 (driven or step$ or strateg$ or therap$ or treat$)).tw.
8	(optim$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
9	(adapt$ or titrat$ or adjust$ or response-based).tw.
10	8 or 9
11	disease progression.tw.
12	disease management.tw.
13	disease outbreaks.tw.
14	disease.tw.
15	or/11-14
16	10 and 15
18	((Remission or activ$) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
19	((((low$ or moderate or medium or high) and activity) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).tw.
20	2 or 3 or 4 or 5 or 6 or 7 or 16 or 17 or 18 or 19
21	1 and 20

Appendix 3 Table of excluded studies with rationale

Study	Reason
ACT-RAY[98,99]	Not a trial of TTT
Alemao *et al.*, 2014[100]	Conference abstract: insufficient detail
ARCTIC[101]	Conference abstract: insufficient detail
Bijlsma *et al.*, 2015[102]	No new data (from update search): U-Act-Early[62]
CAMERA II[37,103–106]	Not a trial of TTT
Carubbi *et al.*, 2016[107]	Not a trial of TTT
Charles-Schoeman 2016[108]	No relevant outcomes (from update search): TEAR[58–60]
CIMESTRA[109–111]	Not a trial of TTT
COBRA[112–116]	Not a trial of TTT
Dale 2015[117]	Not a RCT
De Cock *et al.*, 2013;[118] and 2014[119]	Not a RCT
De Cock *et al.*, 2015[120]	No new data (from update search): CareRA[40,42,43]
DRESS[121]	Not a trial of TTT
Dumitru *et al.*, 2016[122]	No study results yet
Emery *et al.*, 2009;[123] 2010;[124,125] and 2011[126]	Not a RCT
Fedorenko *et al.*, 2013[127]	Not a trial of TTT
Ferraccioli *et al.*, 2002[128]	Numbers stepping up not reported
Fiehn *et al.*, 2007[129]	Not a trial of TTT
Galloway *et al.*, 2015[130]	Not a trial of TTT
Giacomelli *et al.*, 2002[131]	Not a trial of TTT
Harrold *et al.*, 2015[132]	No relevant outcomes
Hørslev-Petersen *et al.*, 2011[133]	Not a trial of TTT
Hwang *et al.*, 2016[134]	No relevant outcomes (from update search): TEAR[58–60]
IDEA[135,136]	Not a trial of TTT
IMAGINE-RA[137]	No study results yet
Jalal *et al.*, 2016[138]	Not a RCT
Korthals-de Bos *et al.*, 2004[113]	Unobtainable
Kume *et al.*, 2013[139]	Conference abstract: insufficient detail
Kuusalo *et al.*, 2015[140]	Not a trial of TTT: Neo-RACo (from update search)
Li *et al.*, 2016[141]	Not a trial of TTT
Marchesoni *et al.*, 2002[142]	Not a trial of TTT
Markusse *et al.*, 2015[143]	No new data (from update search): BeSt[26–34,64–66]
Markusse *et al.*, 2016[144]	Not a RCT
MASCOT[145,146]	Not a trial of TTT
Menon *et al.*, 2014[147]	Not a trial of TTT

Study	Reason
Moller-Bisgaard *et al.*, 2015[148]	Not a trial of TTT: CIMESTA (from update search)
Montecucco *et al.*, 2012[149]	Not a trial of TTT
Neo-RACo[140,150–157]	Not a trial of TTT
OPERA[158–162]	Not a trial of TTT
OPTIMA[163–168]	Not a trial of TTT
OSRA[169,170]	Conference abstract: insufficient detail
Pablos *et al.*, 2015[171]	Not a trial of TTT
Pavelka *et al.*, 2015[172]	Not a RCT
Pavelka *et al.*, 2016[173]	Not a trial of TTT
PREMIER[174–186]	Not a trial of TTT
PRESERVE[187–200]	Not a trial of TTT
Proudman *et al.*, 2000[201]	Not a trial of TTT
Scott and Kowalczyk, 2010[202]	Not a RCT
Scott *et al.*, 2016[203]	Not a RCT
Solomon *et al.*, 2016[204]	Not a RCT
STRASS[205–213]	Not a trial of TTT
TaSER[214–216]	No data available for the DAS28-targeted group
Todoerti *et al.*, 2010[217]	Not a trial of TTT
tREACH[218–224]	Not a trial of TTT
Van der Elst *et al.*, 2016[225]	Not a RCT
van Tuyl *et al.*, 2008[226]	Separate data not reported for the two arms
Verschueren *et al.*, 2008[227]	Not a RCT
Verschueren *et al.*, 2015[228]	No new data (from update search): CareRA[40,42,43]
Yoo *et al.*, 2016[229]	Not a trial of TTT

ACT-RAY, ACTemra (tocilizumab) RAdiographic studY; ARCTIC, Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical TIght Control regimen; CAMERA II, Computer Assisted Management in Early Rheumatoid Arthritis trial-II; CIMESTRA, Ciclosporine, Methotrexate, Steroid in RA; DRESS, Dose REduction Strategy of Subcutaneous TNF inhibitors in rheumatoid arthritis; IDEA, Infliximab as Induction Therapy in Early Rheumatoid Arthritis; IMAGINE-RA, An MRI-guided Treatment Strategy to Prevent Disease Progression in Patients With Rheumatoid Arthritis; MASCOT, Methotrexate And Sulfasalazine Combination Therapry; Neo-RACo, Neo Rheumatoid Arthritis Combination Therapy; OPERA, OPtimized treatment algorithm for patients with Early Rheumatoid Arthritis; OPTIMA, Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab; OSRA, Objectives Study Rheumatoid Arthritis; PREMIER, Patients REceiving Methotrexate and Infliximab for the treatment of Early Rheumatoid arthritis; PRESERVE, Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis; STRASS, Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study; TaSER, Targeting Synovitis in Early Rheumatoid Arthritis; tREACH, treatment in the Rotterdam Early Arthritis Cohort.

Appendix 4 Tables of treatment adaptations and drug dosing

TABLE 65 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – early RA population

Trial acronym	Treatment arms	Treatment adaptations	Total dose of each drug given over trial period
STREAM[55]	Aggressive group	NR	NA
	Conventional care	NR	NA
	Aggressive group	29 patients stepped up to 25 mg/week of MTX 19 patients stepped up to 40 mg/2 weeks of ADA + MTX 25 mg/week 15 patients stepped up to 40 mg/week of ADA + 25 mg/week of MTX 11 patients converted to triple cDMARDs 3 patients stepped up to triple cDMARDs + PDN 1 patient converted to LEF	NR
	Conventional care	24 patients started on HCQ: • 5 switched to SSZ (then 1 to MTX and 1 to HCQ) • 6 switched to MTX • 2 started on SSZ and ended up on MTX at 2 years 14 started on MTX: • 1 ended up on no medication • 3 ended up on MTX + SSZ + HCQ at 2 years	Mean dose of MTX among MTX users was 19 mg/week
T-4 study[56,57]	Routine care	Number initiating: • MTX, $n = 36$ • DMARD (except SSZ), $n = 13$ • Triamcinolone acetonide , $n = 65$ • IA GC, $n = 7$ • First TNFi, $n = 20$ • Second TNFi, $n = 0$ • TOC, $n = 0$ ($N = 55$)	NR
	DAS28-driven therapy	Number initiating: • MTX, $n = 40$ • DMARD (except SSZ), $n = 16$ • Triamcinolone acetonide, $n = 72$ • IA GC, $n = 24$ • First TNFi, $n = 22$ • Second TNFi, $n = 2$ • TOC, $n = 3$ ($N = 59$)	NR

continued

TABLE 65 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – early RA population (*continued*)

Trial acronym	Treatment arms	Treatment adaptations	Total dose of each drug given over trial period
	MMP-3-driven therapy	Number initiating: • MTX, $n = 29$ • DMARD (except SSZ), $n = 9$ • Triamcinolone acetonide, $n = 186$ • IA GC, $n = 84$ • First TNFi, $n = 19$ • Second TNFi, $n = 0$ • TOC, $n = 2$ ($N = 59$)	NR
	DAS2- and MMP-3-driven therapy	Number initiating: • MTX, $n = 46$ • DMARD (except SSZ), $n = 8$ • Triamcinolone acetonide, $n = 61$ • IA GC, $n = 26$ • First TNFi, $n = 38$ • Second TNFi, $n = 3$ • TOC, $n = 3$ ($N = 61$)	NR

IA, intra-articular; NA, not applicable; NR, not reported.

TABLE 66 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – established RA population

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose (mg/week) of each drug given over trial period
Fransen *et al.*, 2005[50]	DAS28	% patients with changes to DMARDs: 25.0%[a]	MTX: 14.2[b] SSZ: 2011.83[b] PDN: 48.93[b]
	Usual care	% patients with changes to DMARDs: 6.8%[a]	MTX: 12.4[b] SSZ: 1940.83[b] PDN: 45.30[b]
	DAS28	% patients with changes to DMARDs: 25.9%[a]	MTX: 14.9[b] SSZ: 2047.34[c] PDN: 46.42[c]
	Usual care	% patients with changes to DMARDs: 12.9%[a]	MTX: 12.1[c] SSZ: 1869.82[c] PDN: 40.46[c]
	DAS28	% patients with changes to DMARDs: 18.0%[a]	MTX: 15.3[c] SSZ: 1923.08[c] PDN: 44.64[c]
	Usual care	% patients with changes to DMARDs: 8.8%[a]	MTX: 12.4[c] SSZ: 1754.44[c] PDN: 39.70[c]

TABLE 66 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – established RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose (mg/week) of each drug given over trial period
Optimisation of Adalimumab study[52,53]	Routine care	NR	NR
	DAS28 target	NR	NR
	SJC target	NR	NR
	Routine care	NR	NR
	DAS28 target	NR	NR
	SJC target	NR	NR
	Routine care	Changes per 100 patient-months: 5.1[c,d]	NR
	DAS28 target	Changes per 100 patient-months: 6.2[b,c]	NR
	SJC target	Changes per 100 patient-months: 3.3[c]	NR

NR, not reported.
a More changes occurred in the DAS28 group ($p = 0.013$).
b $p < 0.001$ vs. routine care.
c Mean.
d $p = 0.035$ vs. routine care.

TABLE 67 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – trials with a combined early and established RA population

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
TICORA[61]	Intensive management	Combination DMARD initiation: 37 (67)[a] Numbers receiving by 18 months: • SSZ or MTX monotherapy: 16/53 • Triple therapy (MTX, SSZ, HCQ): 27/53 • MTX + ciclosporin: 2/53 • Other DMARD combinations: 5/53 • Sodium aurothiomalate: 1/53 • Penicillamine: 1/53	MTX: 17.6 mg/week[b] SSZ: 2.9 g/day[b] Triamcinolone acetonide: 28 mg/month[b]
	Routine management	Combination DMARD initiation: 6 (11)[a] Numbers receiving by 18 months: • Triple therapy (MTX, SSZ, HCQ): 2/51 • Other DMARD combinations: 4/51 • DMARD monotherapy: 45/51	MTX: 13.6 mg/week[b] SSZ: 3.0 g/day[b] Triamcinolone acetonide: 8 mg/month[b]
van Hulst *et al.*, 2010[63]	Intervention group	Medication changed in 35% (263/760) clinic visits: • Adding corticosteroid (injections) without DMARD change, 13.5% • Start, add on or switch DMARD, 14% • Increasing dosage of DMARD, 5% • Increasing dosage of corticosteroid, 0.3%	NR

continued

TABLE 67 Treatment adaptations and drug dosing: comparison of TTT vs. usual care – trials with a combined early and established RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
	Usual-care group	Medication changed in 33% (133/406) clinic visits: • Adding corticosteroid (injections) without DMARD changes, 15% • Start, add on or switch DMARD, 11% • Increasing dosage of DMARD, 5% • Increasing dosage of corticosteroid, 0.7%	NR

NR, not reported.
a Number (%).
b Mean.

TABLE 68 Treatment adaptations and drug dosing: comparison of different targets – early RA population

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
Hodkinson *et al.*, 2015[51]	SDAI arm	NR	NR
	CDAI arm	NR	NR
T-4 study[56,57]	Routine care	Number initiating: • MTX, $n = 36$ • DMARD (except SSZ), $n = 13$ • Triamcinolone acetonide, $n = 65$ • IA GC, $n = 7$ • First TNFi, $n = 20$ • Second TNFi, $n = 0$ • TOC, $n = 0$ ($N = 55$)	NR
	DAS28-driven therapy	Number initiating: • MTX, $n = 40$ • DMARD (except SSZ), $n = 16$ • Triamcinolone acetonide, $n = 72$ • IA GC, $n = 24$ • First TNFi, $n = 22$ • Second TNFi, $n = 2$ • TOC, $n = 3$ ($N = 59$)	NR
	MMP-3-driven therapy	Number initiating: • MTX, $n = 29$ • DMARD (except SSZ), $n = 9$ • Triamcinolone acetonide, $n = 186$ • IA GC, $n = 84$ • First TNFi, $n = 19$ • Second TNFi, $n = 0$ • TOC, $n = 2$ ($N = 59$)	NR

TABLE 68 Treatment adaptations and drug dosing: comparison of different targets – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
	DAS28 and MMP-3-driven therapy	Number initiating: • MTX, $n = 46$ • DMARD (except SSZ), $n = 8$ • Triamcinolone acetonide, $n = 61$ • IA GC, $n = 26$ • First TNFi, $n = 38$ • Second TNFi, $n = 3$ • TOC, $n = 3$ ($N = 61$)	NR
TEAR[58–60]	Immediate ETN	NR	NR
	Immediate triple therapy	NR	NR
	Step-up ETN	NR	NR
	Step-up triple therapy	NR	NR
	Immediate ETN	NR	For all four groups, the mean MTX dosage: 19.1 mg/week (for the whole sample; no significant differences between groups)
	Immediate triple therapy	NR	
	Step-up ETN	NR	
	Step-up triple therapy	NR	

IA, intra-articular; NR, not reported.

TABLE 69 Treatment adaptations and drug dosing: comparison of different targets – established RA population

Trial name	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
Optimisation of Adalimumab study[52,53]	Routine care	NR	NR
	DAS28 target	NR	NR
	SJC target	NR	NR
	Routine care	NR	NR
	DAS28 target	NR	NR
	SJC target	NR	NR
	Routine care	Changes per 100 patient-months: 5.1[a,b]	NR
	DAS28 target	Changes per 100 patient-months: 6.2[a,c]	NR
	SJC target	Changes per 100 patient-months: 3.3[a]	NR

NR, not reported.
a Mean.
b $p = 0.035$ vs. routine care.
c $p < 0.001$ vs. routine care.

TABLE 70 Treatment adaptations and drug dosing: other comparisons – early RA population

Trial acronym	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
CAMERA[35,36,67]	Intensive strategy group	NR	NR
	Conventional strategy group	NR	NR
	Intensive strategy group	55 patients converted to subcutaneous MTX as a result of reaching the maximum dose of MTX or toxicity. Ciclosporin given to 38 patients after the maximum MTX dose reached	MTX: 16.1 (14.8 to 17.3) mg/week[a] (in completers)
	Conventional strategy group	12 patients converted to subcutaneous MTX as a result of reaching the maximum dose of MTX or toxicity. Ciclosporin given to four patients after the maximum MTX dose reached	MTX: 14.0 (13.1 to 14.8) mg/week[a] (in completers)

NR, not reported.
a Mean (95% CI).

TABLE 71 Treatment adaptations and drug dosing: other comparisons – established RA population

Trial	Treatment arm	Treatment adaptations	Total dose of each drug given over trial period
BROSG trial[9]	Symptomatic treatment (shared care)	131/234 (56%) of patients had some change in their disease-suppressive treatment [including patients who had the dose changed, but not those who only had joint injection(s)]	NR
	Aggressive therapy (hospital)	179/232 (77%) of patients had some change in their disease-suppressive treatment [including patients who had the dose changed, but not those who only had joint injection(s)]	NR

NR, not reported.

Appendix 5 Quality assessment of the economic papers

As some of the authors of this report were key members of the team undertaking the HTA of bDMARDs, it was deemed that a review of economic models that did not focus on TTT was unnecessary. Systematic reviews that were identified had references checked to see if any of the included studies were assessments of TTT.

TABLE 72 The CHEERS checklist[83,84]

Section/item	Item number	Recommendation
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms, such as 'cost-effectiveness analysis', and describe the interventions compared
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses) and conclusions
Background and objectives		
Background and objectives	3	Provide an explicit statement of the broader context for the study Present the study question and its relevance for health policy or practice decisions
Methods		
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed, including why they were chosen
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen
Time horizon	8	State the time horizon(s) over which costs, and consequences, are being evaluated and say why appropriate
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed
Measurement of effectiveness	11a	Single study-based evaluation: describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data
	11b	Synthesis-based estimates: describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes

continued

TABLE 72 The CHEERS checklist[83,84] (*continued*)

Section/item	Item number	Recommendation
Estimating resources and costs	13a	Single study-based evaluation: describe the approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs
	13b	Model-based evaluation: describe the approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty
Results		
Study parameters	18	Report the values, ranges, references and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report ICERs
Characterising uncertainty	20a	Single study-based economic evaluation: describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)
Incremental costs and outcomes	20b	Model-based economic evaluation: describe the effects on the results of uncertainty for all input parameters and uncertainty related to the structure of the model and assumptions
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information
Discussion		
Discussion	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with the recommendations of the International Committee of Medical Journal Editors

TABLE 73 The CHEERS checklist for the Vermeer *et al.* study[85]

Item number	Response
1	The study is identified in the title as an economic evaluation. However, the names of the interventions being compared were not identified in the title
2	The study includes a structured summary or abstract
3	The study provides a rationale and context for the research question
	The study identifies and clearly states the research question to be answered, but does not state the relevance that answering the research question will have in health policy or practice decisions
4	The cost-effectiveness analysis was based on the results achieved by patients entered into the DREAM registry which began in 2006. Patients who received TTT care ($n = 261$), 61.7% female, had a mean age of 57.9 years (SD = 13.8 years) and a mean DAS28 of 5.0 (SD = 1.1). Patients who received usual care over the same period ($n = 69$), 62.3% female, had a mean age of 53.9 years (SD = 13.0 years) and a mean DAS28 of 4.8 (SD = 1.3). However, the number of patients entered into the usual-care cohort was considered insufficient and thus patients who had received usual care from the year 2000 were entered into a third cohort ($n = 213$). These patients, 62% of whom were female, had a mean age of 56.6 years (SD = 13.4 years) and a mean DAS28 of 4.8 (SD = 1.2). All patients had a symptom duration of < 1 year and had received no previous DMARD treatment
5	The study was set in Denmark
6	The perspective of the study was direct health-care costs
7	The TTT strategy included a standardised, protocol-based treatment regimen targeted at achieving remission. Patients were assessed at weeks 0, 8, 12, 20, 36 and 52 and every subsequent 3 months with doctors informed of each patient's DAS28 measured by a rheumatology nurse. Treatment consisted of initial MTX monotherapy followed by MTX/SSZ combination therapy followed by MTX/anti-TNF combination therapy. Patients achieving remission were maintained on their current treatment for 6 months; if remission persisted beyond 6 months treatment was gradually reduced and discontinued. NSAID medications, prednisolone and intra-articular corticosteroid injections were allowed at the discretion of the doctor
	The usual-care strategy was a non-standard, non-protocol-based regimen. Patients were assessed every 3 months by a rheumatology nurse, but doctors were not informed of a patient's DAS28. Treatment regimen was at the discretion of the doctor, although the usual pathway is MTX monotherapy followed by either SSZ monotherapy, or combination MTX/SSZ therapy followed by two conventional DMARDs and finally an anti-TNF agent. NSAID medications and prednisolone were allowed at the discretion of the doctor
8	The reporting of cost-effectiveness analysis was poor; time horizon and cycle length were not reported
9	The annual discount rate used to discount future costs and benefits was not reported
10	The study used DAS28 to assess if a patient has achieved remission (i.e. a DAS28 of < 2.6). The HAQ was used to assess the heath-related quality of life of registry patients rather than a preference-based measure such as the EQ-5D. However, HAQ scores were converted to EQ-5D scores using model 5 of the mapping methodology derived by Bansback *et al.*[230]
11a	The study was based on the DREAM registry, a quasi-experimental study performed at multiple locations in eastern Denmark. Patients were allocated to the TTT cohort or the usual-care cohort based on their home address. Patient characteristics and resource use were recorded for all patients, with the interim results (at the time of publication the study was ongoing) used to inform this cost-effectiveness analysis
11b	N/A
12	See response to item 4
13a	See response to item 11a
13b	N/A
14	The study states that a cost year of 2011 was used. Costs from other sources were uplifted to 2011 values, if necessary, using the Dutch price index rate
15	The reporting of cost-effectiveness analysis was poor, no model specification or schematic is reported
16	Not reported

continued

TABLE 73 The CHEERS checklist for the Vermeer *et al.* study[85] (*continued*)

Item number	Response
17	Missing data were dealt with through single imputation using a regression method or linear interpolation using the trapezoid method conditional on missing data occurring at random
18	The reporting of cost-effectiveness analysis was poor, the nature and value of the input parameters is not specified
19	The economic results were provided for data after a 2-year follow-up period and data after a 3-year follow-up period 2-year follow-up period: • TTT: mean total cost €4791 (SD = €7436) • Usual care: mean total cost €3727 (SD = €5773) • ICER: €3591 per patient in remission • ICUR = €19,410 per QALY 3-year follow-up period: • TTT: mean total cost €6410 (SD = €10,485) • Usual care: mean total cost €6872 (SD = €11,033) • ICER: TTT dominates ICUR: TTT dominates
20a	The economic answers were based running the model on 1000 bootstrap replicates. However, there is no reporting of the data behind this bootstrapping
20b	N/A
21	A subgroup analysis was performed using usual-care data collected on patients entering since 2006 (see response to item 4). After 2 years' follow-up the ICER was €8709 per patient in remission and after 3 years' follow-up TTT dominates. However, the 3-year results were based on data for only 45 patients in the usual-care cohort)
22	A comprehensive discussion of the conclusion, strengths and limitations of the study was provided
23	The study was funded by an unrestricted education grant from Abbott
24	All 10 authors state that they had no competing interests

ICUR, incremental cost–utility ratio; N/A, not applicable.

TABLE 74 The CHEERS checklist for the van den Hout *et al.* study[86]

Item number	Response
1	The study is identified in the title as a cost–utility appraisal. However, the names of the interventions being compared are not identified in the title
2	The study includes a structured summary or abstract
3	The study provides a rationale and context for the research question The study identifies, and clearly states, the research question to be answered, but does not state the relevance that answering the research question will have in health policy or practice decisions
4	The cost–utility appraisal was based on the results achieved by patients with recent-onset RA who entered into treatment at the 20 included sites in the Netherlands between March 2000 and August 2002. Patients were at least 18 years of age, fulfilled the 1987 criteria of the ACR and had a disease duration of, at most, 2 years. The details of the randomisation groups is as follows: • Randomisation group 1: initially 126 patients were assigned to treatment strategy 1 with a mean age of 54 years (SD 13 years), 68% of the patients were female and their baseline mean disease activity score was 4.5 (SD 0.9)

TABLE 74 The CHEERS checklist for the van den Hout *et al.* study[86] (*continued*)

Item number	Response
	• Randomisation group 2: initially 121 patients were assigned to treatment strategy 2, again with a mean age of 54 years (SD 13 years), 72% of the patients were female and their baseline mean disease activity score was 4.5 (SD 0.8) • Randomisation group 3: initially 133 patients were assigned to treatment strategy 3 with a mean age of 55 years (SD 14 years), 66% of the patients were female and their baseline mean disease activity score was 4.4 (SD 0.9) • Randomisation group 4: initially 128 patients were assigned to treatment strategy 4, with a mean age of 54 years (SD 14 years), 66% of the patients were female and their baseline mean disease activity score was 4.3 (SD 0.9)
5	The study was set in the Netherlands
6	The primary perspective of the study was a societal cost. However, a secondary analysis was conducted with a health-care cost perspective
7	The study compared four treatment strategies: • Strategy 1, sequential monotherapy • Strategy 2, step-up combination therapy • Strategy 3, initial combination therapy with PDN • Strategy 4, initial combination therapy with IFX The actual treatment a patient received was based on their disease activity score, which was measured every 3 months by an experienced research nurse who was unaware of the randomisation group. In addition, all patients receiving IFX had their disease activity score measured 1 week before infusion. If a patient's DAS was > 2.4, the next treatment regimen in their treatment strategy was started; otherwise, patients remained on their current treatment regimen. After 6 months with a disease activity score of ≤ 2.4, treatment was tapered until the treatment regimen contained only a single DMARD Parallel treatment with NSAID containing corticosteroids
8	The time horizon of the analysis was 2 years and the cycle length was 3 months
9	The annual discount rate used to discount future costs and benefits was 3%
10	The study used QALYs to measure the outcome in terms of health-related benefit which was appropriate for a cost–utility appraisal
11a	The study was based on the BeSt trial, which was designed to determine the best treatment regimen for patients with RA, and was populated to ensure a power of 80% at a significance level of 0.05
11b	N/A
12	The study used a number of methods and instruments to elicit health outcomes from the entire study population, as described in item 4. These included measuring patients' quality of life using the British EQ-5D instrument, the Dutch EQ-5D instrument and the SF-6D every 3 months. The time trade-off method was also used to measure patients' quality of life at baseline, and at 6, 12 and 24 months
13a	Resources used, including pharmaceuticals, were obtained from patient's case notes with pharmaceutical and associated unit costs being taken from the Dutch Health Insurance Executive Board. Other health-care unit costs were based on Dutch standard prices, which were designed to reflect societal costs[231,232] The societal cost of absence from paid work was costed using an age- and sex-appropriate standard hourly rate and ranged between €17 and €41 per hour. The friction method[233] was used in the initial 6-month study period and the human capital method over the entire study period, but did not include the cost of lost production or the cost of replacement staff Patients' out-of-pocket expenses were valued using costs reported by patients in their quarterly cost diaries. If costs were not specified in the diary, expenses were costed using published cost prices[234,235] or current market prices Extra time spent by patients on household and voluntary work was estimated by subtracting the average time taken by an age- and gender-matched population for a task from the time spent on that task by patients. This extra time was valued at the cost of informal care taken from van Roijen *et al.*[236]

continued

TABLE 74 The CHEERS checklist for the van den Hout *et al.* study[86] (*continued*)

Item number	Response
13b	N/A
14	A cost year of 2008 was used with all costs converted to euros using the general Dutch price index rate
15	Not reported
16	Not reported
17	A multiple imputation by chained equations method was employed to reduce any bias attributable to missing data
18	In this instance, all that was required was a statistical analysis of study data rather than health economics modelling
19	*Results of the primary analysis:* in the primary analysis, QALY estimates were based on the British EQ-5D instrument and a societal perspective was taken, with the friction method used to estimate cost of absence from work. Strategy 4 resulted in the highest number of QALYs but at a considerably higher cost, indeed the cost–utility ratio of strategy 4 compared with the next best strategy (strategy 3) is €130,000 (95% CI €27,000 to €3,000,000) per QALY. Strategy 3 had the greatest chance of being optimal at willingness-to-pay thresholds between €74,000 per QALY and €130,000 per QALY, with strategy 2 having the greatest change of being optimal at willingness-to-pay thresholds < €74,000 per QALY. Strategy 1 was dominated by strategies 2 and 3 *Results of the secondary analysis:* the cost–utility ratio of strategy 4 compared with strategy 3 using the other utility estimates were: • Dutch EQ-5D instrument €140,000 (95% CI €30,000 to €2,300,000) per QALY • SF-6D instrument €250,000 (95% CI €50,000 to €15,000,000) per QALY • TTO instrument €320,000 (95% CI €40,000 to ∞) per QALY *Costs of pharmaceuticals:* the following costs are the mean pharmaceutical costs (SD) for the four strategies over the 2-year study period: • Strategy 1: €5202 (SD €8094) • Strategy 2: €1941 (SD €4723) • Strategy 3: €3126 (SD €5317) • Strategy 4: €20,075 (SD €13,491)
20a	No deterministic or stochastic sensitivity analyses were performed
20b	N/A
21	No subgroup analyses were performed
22	A comprehensive discussion of the conclusion was provided
23	The study was funded by a grant from the Dutch Health Insurance Board. However, additional funding was also provided by Schering-Plough B.V. and by Centocor Inc.
24	A number of the authors state that they have competing interests

N/A, not applicable; SF-6D, Short Form questionnaire-6 Dimensions; TTO, time trade off.

Appendix 6 Tables of treat to target and disease activity outcomes for the comparison of different treatment protocols

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
BeSt[26–34,64–66] (12-month randomised phase)	Sequential monotherapy	126	12 months[30]	122/126 (97)	• Patient refusal, *n* = 1 • Revised diagnosis, *n* = 3	A DAS44 of ≤ 2.4	63/118 (53)[b,c]	63/118 (53)[b,c] (DAS44 of ≤ 2.4)	NR	NR	NR
	Step-up combination therapy	121	12 months	115/121 (95)	• Patient refusal, *n* = 4 • AE, *n* = 1 • Other, *n* = 1		72/112 (64)	72/112 (64) (DAS44 of ≤ 2.4)	NR	NR	NR
	Initial combination therapy with PDN	133	12 months	128/133 (96)	• Patient refusal, *n* = 4 • Other, *n* = 1		87/122 (71)	87/122 (71) (DAS44 of ≤ 2.4)	NR	NR	NR
	Initial combination therapy with IFX	128	12 months	126/128 (98)	• Revised diagnosis, *n* = 2		89/121 (74)	89/121 (74) (DAS44 of ≤ 2.4)	NR	NR	NR
	Sequential monotherapy	126	5 years[31]	111/126 (88)	• Patient refusal, *n* = 7 • Revised diagnosis, *n* = 3 • Died, *n* = 3 • Other, *n* = 5		NR	NR	NR	25% still on initial treatment; 41% started delayed IFX and 21% were still on it at 5 years	NR
	Step-up combination therapy	121	5 years	94/121 (78)	• Patient refusal, *n* = 16 • Revised diagnosis, *n* = 2 • Died, *n* = 3 • Other, *n* = 5[d]		NR	NR	NR	21% still on initial treatment; 12% started delayed IFX and 5% were still on it at 5 years. 26% started PDN and 6% were still on it at 5 years	NR
	Initial combination therapy with PDN	133	5 years	113/133 (85)	• Patient refusal, *n* = 6 • Revised diagnosis, *n* = 1 • Died, *n* = 2 • Other, *n* = 1		NR	NR	NR	45% still on initial treatment; 21% started delayed IFX and 11% were still on it at 5 years; 46% had successfully tapered and stopped PDN	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	Initial combination therapy with IFX	128	5 years	116/128 (91)	• Patient refusal, $n = 2$ • Revised diagnosis, $n = 2$ • Died, $n = 4$ • Other, $n = 4$		NR	NR	NR	65% still on initial treatment; 19% were still taking delayed IFX at 5 years; 50% had permanently discontinued IFX	NR
	Sequential monotherapy	126	7 years[29]	83/126 (66)	NR		68/83 (82)	68/83 (82) (DAS44 of ≤ 2.4)	41/83 (49) (DAS44 of < 1.6)	Still on initial treatment step, 17/83 (21%); IFX current use, 12/83 (14%)	NR
	Step-up combination therapy	121	7 years	72/121 (60)	NR		55/72 (76)	55/72 (76) (DAS44 of ≤ 2.4)	28/72 (39) (DAS44 of < 1.6)	Still on initial treatment step, 12/72 (16%); IFX current use, 4/72 (6%)	NR
	Initial combination therapy with PDN	133	7 years	79/133 (59)	NR		59/79 (82)	59/79 (82) (DAS44 of ≤ 2.4)	42/79 (53) (DAS44 of < 1.6)	Still on initial treatment step, 16/79 (20%); IFX current use, 9/79 (11%)	NR
	Initial combination therapy with IFX	128	7 years	97/128 (76)	NR		74/97 (76)	74/97 (76) (DAS44 of ≤ 2.4)	44/97 (45) (DAS44 of < 1.6)	Still on initial treatment step, 53/97 (55%) $p < 0.001$; IFX current use, 20/97 (21%)	NR
	Sequential monotherapy	126	8 years[28]	85/126 (67)	NR		67/85 (79)	67/85 (79) (DAS44 of ≤ 2.4)	42/85 (49) (DAS44 of < 1.6)	Still on initial treatment step, 25/85 (29%); IFX current use, 18/85 (21%)	NR
	Step-up combination therapy	121	8 years	78/121 (64)	NR		59/78 (76)	59/78 (76) (DAS44 of ≤ 2.4)	44/78 (56) (DAS44 of < 1.6)	Still on initial treatment step, 17/78 (22%); IFX current use, 8/78 (10%)	NR
	Initial combination therapy with PDN	133	8 years	86/133 (65)	NR		72/86 (84)	72/86 (84) (DAS44 of ≤ 2.4)	49/86 (57) (DAS44 of < 1.6)	Still on initial treatment step, 39/86 (45%); IFX current use, 11/86 (13%)	NR
	Initial combination therapy with IFX	128	8 years	98/128 (77)	NR		74/98 (76)	74/98 (76) (DAS44 of ≤ 2.4)	46/98 (47) (DAS44 of < 1.6)	Still on initial treatment step, 65/98 (66%) $p < 0.001$; IFX current use, 24/98 (24%)	NR

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
CareRA: high-risk patients[40,42,43] (52-week randomised phase)	COBRA Classic	98	4 weeks	NR	NR	A DAS28-CRP of ≤ 3.2	NR	NR	63/98 (64) (DAS28-CRP < 2.6)	NR	NA
	COBRA Slim	98	4 weeks	NR	NR		NR	NR	60/98 (61) (DAS28-CRP < 2.6)	NR	NA
	COBRA Avant-Garde	94	4 weeks	NR	NR		NR	NR	60/94 (70) (DAS28-CRP < 2.6)	NR	NA
	COBRA Classic	98	8 weeks	NR	NR		NR	NR	64/98 (65) (DAS28-CRP < 2.6)	NR	NA
	COBRA Slim	98	8 weeks	NR	NR		NR	NR	61/98 (62) (DAS28-CRP < 2.6)	NR	NA
	COBRA Avant-Garde	94	8 weeks	NR	NR		NR	NR	65/94 (74) (DAS28-CRP < 2.6)	NR	NA
	COBRA Classic	98	16 weeks	91/98 (93)	• Withdrew consent, *n* = 2 • Lost to follow-up, *n* = 1 • Safety failure, *n* = 2 • Efficacy failure, *n* = 2		83/98 (84.7)	83/98 (85) (DAS28-CRP ≤ 3.2)	69/98 (70) (DAS28-CRP < 2.6)	Adaptations in 19 out of 98 (19.4%) patients over the first 16 weeks	NR
	COBRA Slim	98	16 weeks	96/98 (98)	• Withdrew consent, *n* = 1 • Death, *n* = 1		85/98 (86.7)	85/98 (87) (DAS28-CRP ≤ 3.2)	72/98 (74) (DAS28-CRP < 2.6)	Adaptations in 22 out of 98 (22.4%) patients over the first 16 weeks	NR
	COBRA Avant-Garde	94	16 weeks	91/94 (97)	• Withdrew consent, *n* = 2 • Efficacy failure, *n* = 1		82/94 (87.2)	82/94 (87) (DAS28-CRP ≤ 3.2)	64/94 (68) (DAS28-CRP < 2.6)	Adaptations in 14 out of 94 (14.9%) patients over the first 16 weeks	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	COBRA Classic	98	52 weeks[43]	90/98 (92)	• Death, *n* = 1 • Lost to follow-up, *n* = 4 • Patient withdrawal, *n* = 3		73/98 (74.5)	73/98 (75) (DAS28-CRP ≤ 3.2)	NR (64%) (63/98). No treatment failures, 9/62 (79%); treatment failures, 12/28 (43%); DAS28-ESR[e] remission, NR (58%); SDAI remission, NR (38%); Boolean remission, NR (27%)	One treatment adaptation: 21 (21.4%)	Cumulative PDN dose (mg) mean 2597.2 (SD 666.8)
	COBRA Slim	98	52 weeks	89/98 (91)	• Death, *n* = 1 • Lost to follow-up, *n* = 4 • Patient withdrawal, *n* = 3 • Logistical reason (not described), *n* = 1		74/98 (76)	74/98 (76) (DAS28-CRP ≤ 3.2)	NR (60%) (59/98). Not treatment failures 52/75 (69%); treatment failures 2/14 (14%); DAS28-ESR[e] remission NR (52%); SDAI remission NR (31%); Boolean remission NR (17%)	Two treatment adaptations: 3 (3.1%)	Average daily PDN dose (mg) mean 6.5 (SD 2.7)
	COBRA Avant-Garde	93	52 weeks	85/93 (91)	• Lost to follow-up, *n* = 6 • Patient withdrawal, *n* = 2		74/93 (80)	74/93 (80) (DAS28-CRP ≤ 3.2)	62% (58/93). Not treatment failures, 45/60 (75%); treatment failures, 11/25 (44%); DAS28-ESR[e] remission, NR (55%); SDAI remission, NR (45.2%); Boolean remission, 30.1%	One treatment adaptation: 38 (39%)	Patients with GC injections: 15 (15%)

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
CareRA: low-risk patients[40,43] (52-week randomised phase)	MTX-TSU	47	8 weeks	NA	NR	DAS28-CRP ≤ 3.2	NR	NR	NR	Adaptations in 16 out of 47 (34%) patients over the first 8 weeks	NR
	COBRA Slim	43	8 weeks	NA	NR		NR	NR	NR	Adaptations in 10 out of 43 (23%) patients over the first 8 weeks	NR
	MTX-TSU	47	16 weeks	Unclear	• Patient withdrew their consent, *n* = 1 • Other reasons, NR		34/47 (72)	34/47 (72) (DAS28-CRP ≤ 3.2)	22/47 (47) (DAS28-CRP < 2.6)	Adaptations in 11 out of 47 (21%) patients over the first 16 weeks[i] Intra-articular GC injections in 10 out of 47 (21%) patients (1 patient received 2 injections)	NR
	COBRA Slim	43	16 weeks	Unclear	• Patients withdrew consent, *n* = 3 • Other reasons, NR		34/43 (79)	34/43 (79) (DAS28-CRP ≤ 3.2)	28/43 (65) (DAS28-CRP < 2.6)	Adaptations in 7 out of 43 (16%) patients over the first 16 weeks[i] One patient considered as efficacy failure. Intra-articular GC injections in 3 out of 43 (7.0%) patients	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	MTX-TSU	47	52 weeks[43]	44/47 (93.6)	• Lost to follow-up, *n* = 2 • Logistical reason (not described), *n* = 1		36/47 (77)	36/47 (77) (DAS28-CRP ≤ 3.2)	27/47 (57%). Not considered treatment failures 24/36 (67%); treatment failures 3/8 (38%); DAS28-ESR[e] remission NR (55%); SDAI remission NR (30%); Boolean remission NR (21)%	Two treatment adaptations:16 (16%)	Cumulative PDN dose (mg) mean 36.3 (SD 49.6) Average daily PDN dose (mg) mean 0.1 (SD 0.1) Patients with GC injections: 17 (36%)
	COBRA Slim	43	52 weeks	38/43 (88.4)	• Lost to follow-up, *n* = 1 • Patient withdrawal, *n* = 4		33/43 (77)	33/43 (77) (DAS28-CRP ≤ 3.2)	29/43 (67%). Not treatment failures, 25/30 (83%); treatment failures, 4/8 (50%); DAS28-ESR remission,[e] 63%; SDAI remission, NR (44%); Boolean remission, 37%	One treatment adaptation: 22 (24%)	Cumulative PDN dose (mg) mean 1554.0 (SD 307.6) Average daily PDN dose (mg) mean 3.8 (SD 1.6) Patients with GC injections: 6 (14%)

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
COBRA-light[44,45] (12-month randomised phase)	COBRA	81	13 weeks	NA	NR	A DAS44 of < 1.6	35/81 (43)	NR	35/81 (43) (DAS44 of < 1.6)	Treatment intensified in 46/81 (57%) patients[f]	NR
	COBRA-light	83	13 weeks	NA	NR		36/81 (44)	NR	36/81 (44) (DAS44 of < 1.6)	Treatment intensified in 45/81 (56%) patients[f]	NR
	COBRA	81	6 months	80/81 (99)	• AE (myocardial infarction), *n* = 1		NR (49)[e]	NR	NR (49)[e] (DAS44 of < 1.6)	NR	Mean MTX dose: 15.6 mg/week
	COBRA-light	83	6 months	78/81 (96%) 2/83 did not start treatment (withdrew informed consent immediately after randomisation), not included in ITT population, *n* = 81	• AE (manic episode), *n* = 1		NR (41)[e]	NR	NR (41)[e] (DAS44 of < 1.6)	NR	Mean MTX dose: 24.0 mg/week
	COBRA	81	12 months	78/81 (96)	• AE (myocardial infarction), *n* = 1 • Intolerance of medication, *n* = 1 • Bilateral pulmonary embolism, *n* = 1		38/81 (47)	NR	38/81 (47) (DAS44 of < 1.6) 12/81 (15) (ACR/ Boolean remission)	Started ETN: 27/81 (57%)[f] 16 patients received ETN for 26 weeks	NR
	COBRA-light	83	12 months	77/81 (95)	• Poor compliance with treatment), *n* = 2 • Manic episode), *n* = 1 • Desire to become pregnant), *n* = 1		31/81 (38)	NR	31/81 (38) (DAS44 of < 1.6) 14/81 (17) (ACR/ Boolean remission)	Started ETN: 40/81 (66%)[f] 30 patients received ETN for 26 weeks	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
FIN-RACo[47–49,70] (2-year randomised phase)	Combination treatment	99 (97 in ITT)	2 years[46]	87/97 (90)	• Refused, *n* = 3 • Protocol violation, *n* = 4 • Intercurrent illness, *n* = 1 • Loss to follow-up, *n* = 1 • Loss of efficacy, *n* = 1	Remission: modified version of ACR 1981 defined remission	36/NR (37)[g]	NR	36/NR (37)[g] (modified ACR 1981 criteria)	NR	NR
	Single-drug treatment	100 (98 in ITT)	2 years	91/98 (93)	• Refused, *n* = 5 • Protocol violation, *n* = 2		18/NR (18)[g]	NR	18/NR (18)[g] (modified ACR 1981 criteria)	NR	NR
	Combination treatment	99 (97 in ITT)	5 years[47]	78 (80)	• Remission, *n* = 4 • Refused, *n* = 3 (1 died after 9 years – unclear what this means) • Moved, *n* = 1 • Death, *n* = 1		18, 41[i]/NR (29)[h]	NR	18, 41[i]/NR (29)[h] (modified ACR 1981 criteria)	NR	NR
	Single-drug treatment	100 (98 in ITT)	5 years	82/NR (84)	• Remission, *n* = 5 • AE, *n* = 1 • Refused, *n* = 1 (1 died after 6 years – unclear what this means) • Moved, *n* = 1 • Death, *n* = 5		13, 33[i]/NR (22)[h]	NR	13, 33[i]/NR (22)[h] (modified ACR 1981 criteria)		NR

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	Combination treatment	99 (97 in ITT)	11 years[47]	68/NR (70)	• Centre discontinuation, $n = 2$ • Refused, $n = 4$ • Died, $n = 4$ (unclear if this includes the 1 died at 9 years)		26, 49[j]/ NR (37)[k]	NR	26, 49[j]/NR (37)[k] (modified ACR 1981 criteria); NR (57) (DAS28 of < 2.6)	At some time between the 2- and 11-year visits, a combination-DMARD strategy had been used by 62 (91%) patients 22 (32%) patients had been able to discontinue all DMARDs, at least temporarily, from year 2 to year 11	NR
	Single-drug treatment	100 (98 in ITT)	11 years	70/NR (71)	• Centre discontinuation, $n = 2$ • Refused, $n = 4$ • Died, $n = 4$ (unclear if this includes the 1 died at 9 years)		11, 29[j]/ NR (19%)	NR	11, 29[j]/NR (19)[k] (modified ACR 1981 criteria); NR (49) (DAS28 of < 2.6)	At some time between the 2- and 11-year visits, a combination-DMARD strategy had been used by 56 (80%) of patients 27 (39%) of patients had been able to discontinue all DMARDs, at least temporarily, from year 2 to year 11	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
Saunders *et al.*, 2008[54] (12-month randomised phase)	Parallel triple therapy	49	12 months	47/49 (96)	• Died, *n* = 1 • Lost to follow-up, *n* = 2	A DAS28 of < 3.2	20/49 (41)	20/49 (41) (EULAR good response, defined by a DAS28 of < 3.2)	16/49 (33) (EULAR remission)	15/49 (31%) drug withdrawals as a result of AEs: • SSZ withdrawn in eight patients • MTX withdrawn in two patients • HCQ withdrawn in three patients • SSZ/MTX/HCQ withdrawn in two patients	NR
	Step-up therapy	47	12 months	44/47 (94)	• Lost to follow-up, *n* = 3		28/47 (60)	28/47 (60) (EULAR good response, defined by a DAS28 of < 3.2)	21/47 (45) (EULAR remission)	18/47 (39%) drug withdrawals as a result of AEs: • SSZ withdrawn in 17 patients • MTX withdrawn in one patient	NR

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
TEAR[58–60] (102-week randomised phase)	Immediate ETN	244	24 weeks	See below	See below	No target	100/244 (41)	100/244 (41) (DAS28-ESR of ≤ 3.2)	NR	NR	NR
	Immediate triple therapy	132	24 weeks				65/152 (43)	65/152 (43) (DAS28-ESR of ≤ 3.2)	NR	NR	NR
	Step-up ETN	255	24 weeks			A DAS28-ESR of < 3.2	105/376 (28)	105/376 (28) (DAS28-ESR of ≤ 3.2)	NR	NR	NR
	Step-up triple therapy	124	24 weeks						NR	NR	NR
	Immediate ETN	244	102 weeks	168/244 (69) (159 with DAS28)	• Patient decision, *n* = 33 • Lost to follow-up, *n* = 19 • SAE, *n* = 8 • Other non-medical reason, *n* = 7 • Physician decision, *n* = 6 • AE, *n* = 3 • Death, *n* = 1	No target	90/159 (57)[l]	NR	90/159 (57%)[l] (DAS28-ESR of ≤ 2.6)	NR	Mean MTX dosage: 19.1 mg/ week (for the whole sample; no significant differences between groups)
	Immediate triple therapy	132	102 weeks	82/132 (62) (76 with DAS28)	• Patient decision, *n* = 25 • Lost to follow-up, *n* = 9 • SAE, *n* = 2 • Other non-medical reason, *n* = 4 • Physician's decision, *n* = 4 • AE, *n* = 4 • Death, *n* = 1		45/76 (59)[l]	NR	45/76 (59)[l] (DAS28-ESR of ≤ 2.6)	NR	

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	Step-up ETN	255	102 weeks	182/255 (71) (166 with DAS28)	• Patient decision, $n = 33$ • Lost to follow-up, $n = 18$ • SAE, $n = 2$ • Other non-medical reason, $n = 10$ • Physician's decision, $n = 7$ • AE, $n = 5$ • Death, $n = 2$	A DAS28-ESR of < 3.2	88/166 (53)[l]	NR	88/166 (53)[l] (DAS28-ESR of ≤ 2.6)	NR	
	Step-up triple therapy	124	102 weeks	81/124 (65) (75 with DAS28)	• Patient decision, $n = 19$ • Lost to follow-up, $n = 15$ • SAE, $n = 2$ • Other non-medical reason, $n = 3$ • Physician's decision, $n = 2$ • AE, $n = 2$ • Death, $n = 0$		42/75 (57)[l]	NR	42/75 (57)[l] (DAS28-ESR of ≤ 2.6)	NR	

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
U-Act-Early[62] (104-week randomised phase)	TOC + MTX	106	24 weeks	100/106 (94)	• AE, $n = 4$ • Insufficient response, $n = 1$ • Other, $n = 1$	A DAS28 of < 2.6 and a SJC of ≤ 4 of the 28 joints assessed	NR	NR	NR	NR	NR
	TOC + PBO–MTX	103	24 weeks	101/103 (98)	• AE, $n = 1$ • Other, $n = 1$		NR	NR	NR	NR	NR
	MTX + PBO–TOC	108	24 weeks	98/108 (91)	• AE, $n = 1$ • Insufficient response, $n = 7$ • Withdrew consent, $n = 1$ • Other, $n = 1$		NR	NR	NR	NR	NR
	TOC + MTX	106	52 weeks	87/106 (82)	Weeks 24–52: • AE, $n = 3$ • Insufficient response, $n = 5$ • Withdrew consent, $n = 3$ • Other, $n = 3$		NR	NR	NR	NR	NR

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n*/*N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	TOC + PBO–MTX	103	52 weeks	92/103 (89)	Weeks 24–52: • AE, $n = 4$ • Insufficient response, $n = 2$ • Withdrew consent, $n = 1$ • Other, $n = 2$		NR	NR	NR	NR	NR
	MTX + PBO–TOC	108	52 weeks	92/108 (85)	Weeks 24–52: • AE, $n = 3$ • Insufficient response, $n = 4$ • Withdrew consent, $n = 1$ • Other, $n = 2$		NR	NR	NR	NR	NR
	TOC + MTX	106	104 weeks	78/106 (74)	Weeks 52–104: • AE, $n = 2$ • Insufficient response, $n = 3$ • Withdrew consent, $n = 1$ • Other, $n = 2$		91/106 (86)[m]	NR	91/106 (86)[m] [a DAS28 of < 2.6 and a SJC of (28 joints) ≤ 4]	Switch to subsequent regimen, 9/106 (8.5%) (by week 104)	NR

continued

TABLE 75 Treat-to-target outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym; first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Number completing, *n/N* (%) (randomised phase)	Reasons for withdrawal	Definition of study target	Number (%)			Treatment adaptations	Total dose of each drug given over trial period
							Meeting study target	Attaining LDA (criteria)	Attaining remission (criteria)		
	TOC + PBO–MTX	103	104 weeks	81/103 (79)	Weeks 52–104 • AE, $n = 5$ • Insufficient response, $n = 2$ • Withdrew consent, $n = 2$ • Other, $n = 2$		91/103 (88)[m]	NR	91/103 (88)[m] [a DAS28 of < 2.6 and a SJC of (28 joints) ≤ 4]	Switch to subsequent regimen, 13/103 (13%) (by week 104)	NR
	MTX + PBO–TOC	108	104 weeks	78/108 (72)	• Weeks 52–104: • AE, $n = 4$ • Insufficient response, $n = 2$ • Withdrew consent, $n = 1$ • Other, $n = 3$		83/108 (77)[m]	NR	83/108 (77)[m] [a DAS28 of < 2.6 and a SJC (28 joints) of ≤ 4]	Switch to subsequent regimen, 50/108 (46%) (by week 104)	NR

ITT, intention to treat; NA, not applicable; NR, not reported.
a Randomised.
b $p = 0.004$ vs. group 3.
c $p = 0.001$ vs. group 4.
d Discrepancy in flow-chart: total number withdrawing reported as 27.
e *n* not reported.
f *n/N* (%).
g $p = 0.003$.
h Converted from graphical data.
i Data from the Verschueren *et al.*[40] paper have been used; data on treatment adaptations presented within the De Cock *et al.*[39] abstract are discrepant.
j 95% CI.
k $p = 0.017$.
l Assuming proportion of completers with DAS28.
m Sustained remission during whole study.

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
BeSt[26–34,64–66] (12-month randomised phase)	Sequential monotherapy	126	3 months[30]	NR	NR	NR	NR	NR	ACR 20: 29.2%[b] ACR 70: 24.2%[b]	D-HAQ: 1.0 (0.7)[c,d]	NR	SF-36 PCS improvement: 5.8[e,f] SF-36 MCS improvement: 2.1[e]
	Step-up combination therapy	121	3 months	NR	NR	NR	NR	NR	ACR 20: 36.9%[b] ACR 70: 24.2%[b]	D-HAQ: 1.0 (0.6)[c,d]	NR	SF-36 PCS improvement: 3.9[e,f] SF-36 MCS improvement: 2.5[e]
	Initial combination therapy with PDN	133	3 months	NR	NR	NR	NR	NR	ACR 20: 70.1%[b] ACR 70: 20.2%[b]	D-HAQ: 0.6 (0.6)[c,d]	NR	SF-36 PCS improvement: 11.2[e,f] SF-36 MCS improvement: 0.4[e]
	Initial combination therapy with IFX	128	3 months	NR	NR	NR	NR	NR	ACR 20: 60.2 %[b] ACR 70: 19.3%[b]	D-HAQ: 0.6 (0.6)[c,d]	NR	SF-36 PCS improvement: 9.6[e,f] SF-36 MCS improvement: 3.1[e]
	Sequential monotherapy	126	6 months[30]	NR	NR	NR	NR	NR	ACR 20: 49.4%[b] ACR 70: 15.7%[b]	D-HAQ: 0.9 (0.7)[c,d]	NR	SF-36 PCS improvement: 8.0[e,f] SF-36 MCS improvement: 3.1[e]
	Step-up combination therapy	121	6 months	NR	NR	NR	NR	NR	ACR 20: 60.2%[b] ACR 70: 11.8%[b]	D-HAQ: 0.9 (0.7)[c,d]	NR	SF-36 PCS improvement: 8.5[e,f] SF-36 MCS improvement: 3.5[e]
	Initial combination therapy with PDN	133	6 months	NR	NR	NR	NR	NR	ACR 20: 70.6%[b] ACR 70: 26.6%[b]	D-HAQ: 0.5 (0.5)[c,d]	NR	SF-36 PCS improvement: 12.5[e,f] SF-36 MCS improvement: 1.2[e]

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Initial combination therapy with IFX	128	6 months	NR	NR	NR	NR	NR	ACR 20: 74.2%[b] ACR 70: 31.2%[b]	D-HAQ: 0.5 (0.5)[c,d]	NR	SF-36 PCS improvement: 12.4[e,f] SF-36 MCS improvement: 4.1[e]
	Sequential monotherapy	126	9 months[30]	NR	NR	NR	NR	NR	ACR 20: 62.8%[b] ACR 70: 16.3%[b]	D-HAQ: 0.8 (0.7)[c,d]	NR	NR
	Step-up combination therapy	121	9 months	NR	NR	NR	NR	NR	ACR 20: 72.0%[b] ACR 70: 18.4%[b]	D-HAQ: 0.8 (0.7)[c,d]	NR	NR
	Initial combination therapy with PDN	133	9 months	NR	NR	NR	NR	NR	ACR 20: 70.2%[b] ACR 70: 23.6%[b]	D-HAQ: 0.6 (0.6)[c,d]	NR	NR
	Initial combination therapy with IFX	128	9 months	NR	NR	NR	NR	NR	ACR 20: 77.7%[b] ACR 70: 34.4%	D-HAQ: 0.5 (0.6)[c,d]	NR	NR
	Sequential monotherapy	126	12 months[30]	NR	NR	NR	NR	NR	ACR 20: 63.4%[b] ACR 70: 19.6%[b]	D-HAQ: 0.7 (0.7)[c,g]	Progression of SHS: • Erosion score (0–280): 3.5 (8.2)[f,h,i] • JSN score (0–168): 3.6 (8.4)[h,i,j] • Total score (0–448): 7.1 (15.4)[f,h,i]	SF-36 PCS improvement: 8.9[e] SF-36 MCS improvement: 4.3[e]

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Step-up combination therapy	121	12 months	NR	NR	NR	NR	NR	ACR 20: 63.3%[b] ACR 70: 22.0%[b]	D-HAQ: 0.7 (0.6)[c]	Progression of SHS: • Erosion score (0–280): 2.6 (4.7)[f,h,i] • JSN score (0–168): 1.6 (2.9)[h,i,j] • Total score (0–448): 4.3 (6.5)[f,h,i]	SF-36 PCS improvement: 11.2[e] SF-36 MCS improvement: 4.4[e]
	Initial combination therapy with PDN	133	12 months	NR	NR	NR	NR	NR	ACR 20: 77.3%[b] ACR 70: 29.9%[b]	D-HAQ: 0.5 (0.5)[c,g]	Progression of SHS: • Erosion score (0–280): 0.9 (1.9)[f,h,i] • JSN score (0–168): 1.0 (2.4)[h,i,j] • Total score (0–448): 2.0 (3.6)[f,h,i]	SF-36 PCS improvement: 11.9[e] SF-36 MCS improvement: 3.2[e]
	Initial combination therapy with IFX	128	12 months	NR	NR	NR	NR	NR	ACR 20: 79.1%[b] ACR 70: 40.2%[b]	D-HAQ: 0.5 (0.5)[c,g]	Progression of SHS: • Erosion score (0–280): 0.7 (2.1)[f,h,i] • JSN score (0–168): 0.6 (2.6)[h,i,j] • Total score (0–448): 1.3 (4.0)[f,h,i]	SF-36 PCS improvement: 12.0[e] SF-36 MCS improvement: 4.3[e]
	Sequential monotherapy	126	2 years[26,68]	NR	NR	NR	NR	NR	NR	NR	Progression of SHS from baseline: • Erosion score (0–280): 4.7 (9.4)[f,h] • JSN score (0–168): 4.3 (9.8)[h] • Total score (0–448): 9.0 (17.9)[f,h]	SF-36 PCS improvement: 11.9[e] SF-36 MCS improvement: 4.3[e]

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Step-up combination therapy	121	2 years	NR	NR	NR	NR	NR	NR	NR	Progression of SHS from baseline: • Erosion score (0–280): 3.1 (5.0)[f,h] • JSN score (0–168): 2.1 (3.8)[h] • Total score (0–448): 5.2 (8.1)[f,h]	SF-36 PCS improvement: 12.3[e] SF-36 MCS improvement: 4.6[e]
	Initial combination therapy with PDN	133	2 years	NR	NR	NR	NR	NR	NR	NR	Progression of SHS from baseline: • Erosion score (0–280): 1.1 (2.2)[f,h] • JSN score (0–168): 1.5 (3.2)[h] • Total score (0–448): 8.1 (2.6)[f,h]	SF-36 PCS improvement: 12.3[e] SF-36 MCS improvement: 4.6[e]
	Initial combination therapy with IFX	128	2 years	NR	NR	NR	NR	NR	NR	NR	Progression of SHS from baseline: • Erosion score (0–280): 1.3 (2.7)[f,h] • JSN score (0–168): 1.2 (2.9)[h] • Total score (0–448): 2.5 (4.2)[f,h]	SF-36 PCS improvement: 12.7[e] SF-36 MCS improvement: 4.0[e]
	Sequential monotherapy	126	3 years[26]	NR	NR	NR	NR	NR	NR	NR	Increase in total SHS: 3.8[k,l,m]	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Step-up combination therapy	121	3 years	NR	NR	NR	NR	NR	NR	NR	Increase in total SHS: 3.0[k,n]	NR
	Initial combination therapy with PDN	133	3 years	NR	NR	NR	NR	NR	NR	NR	Increase in total SHS: 1.8[k]	NR
	Initial combination therapy with IFX	128	3 years	NR	NR	NR	NR	NR	NR	NR	Increase in total SHS: 1.5[k,l,m,n]	NR
	Sequential monotherapy	126	5 years[31]	NR	NR	NR	NR	NR	NR	0.70[o,s]	SHS progression:[i] 14.0[p]/3.5[k]	NR
	Step-up combination therapy	121	5 years	NR	NR	NR	NR	NR	NR	0.70[o,p]	SHS progression:[i] 11.0[p]/2.5[k]	NR
	Initial combination therapy with PDN	133	5 years	NR	NR	NR	NR	NR	NR	0.62[o,p]	SHS progression:[i] 7.6[p]/1.0[k]	NR
	Initial combination therapy with IFX	128	5 years	NR	NR	NR	NR	NR	NR	0.54[o,p]	SHS progression:[i] 6.0[p]/1.0[k]	NR
	Sequential monotherapy	126	7 years[29]	NR	NR	NR	NR	NR	NR	0.70;[p,q] $n = 83$	SHS progression: 15.1[p]/3.8,[k] $n = 83$	NR
	Step-up combination therapy	121	7 years	NR	NR	NR	NR	NR	NR	0.71;[p,q] $n = 72$	SHS progression: 10.7[p]/3.5;[k] $n = 72$	NR
	Initial combination therapy with PDN	133	7 years	NR	NR	NR	NR	NR	NR	0.63;[p] $n = 79$	SHS progression: 8.4[p]/2.0;[k] $n = 79$	NR
	Initial combination therapy with IFX	128	7 years	NR	NR	NR	NR	NR	NR	0.57;[p,q] $n = 97$	SHS progression: 5.5[p]/2.0;[k] $n = 97$	NR

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Sequential monotherapy	126	8 years[28]	NR	NR	NR	NR	NR	NR	0.69;[p] $n = 85$	SHS progression: 14.6[p]/3.0;[k] $n = 85$	NR
	Step-up combination therapy	121	8 years	NR	NR	NR	NR	NR	NR	0.71;[p,r] $n = 78$	SHS progression: 13.9[p]/4.3;[k] $n = 78$	NR
	Initial combination therapy with PDN	133	8 years	NR	NR	NR	NR	NR	NR	0.93;[p] $n = 86$	SHS progression: 8.5[p]/2.0;[k] $n = 86$	NR
	Initial combination therapy with IFX	128	8 years	NR	NR	NR	NR	NR	NR	0.57;[p,r] $n = 98$	SHS progression: 8.3[p]/2.0;[k] $n = 86$	NR
	Sequential monotherapy	126	10 years[64]	NR	NR	NR	NR	NR	NR	0.69 (during 10 years)	Change in SHS: 2.0 (0–11.0)[s] SHS estimate corrected for baseline SHS: 14.2[p]	NR
	Step-up combination therapy	121	10 years	NR	NR	NR	NR	NR	NR	0.72 (during 10 years)	Change in SHS: 2.5 (0–13.5)[s] SHS estimate corrected for baseline SHS: 14.1[p]	NR
	Initial combination therapy with PDN	133	10 years	NR	NR	NR	NR	NR	NR	0.64 (during 10 years)	Change in SHS: 3.0 (0.3–11.3)[s] SHS estimate corrected for baseline SHS: 14.6[p]	NR
	Initial combination therapy with IFX	128	10 years	NR	NR	NR	NR	NR	NR	0.58 (during 10 years)	Change in SHS: 1.5 (0.0–6.0)[s] SHS estimate corrected for baseline SHS: 8.9[p]	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
CareRA: high-risk patients[40,42,43] (52-week randomised phase)	COBRA Classic	98	16 weeks	Change from baseline (DAS28-CRP): 2.8 (1.2)	NR	NR	NR	Good response: 78/98 (79.6%) Moderate response: 96/98 (98.0%)	NR	Clinically meaningful HAQ response: 83/98 (84.7%) HAQ = 0: 45/98 (45.9%)	NR	NR
	COBRA Slim	98	16 weeks	Change from baseline (DAS28-CRP): 2.6 (1.2)	NR	NR	NR	Good response: 78/98 (79.6%) Moderate response: 94/98 (95.9%)	NR	Clinically meaningful HAQ response: 85/98 (86.7%) HAQ = 0: 42/98 (42.9%)	NR	NR
	COBRA Avant-Garde	94	16 weeks	Change from baseline (DAS28-CRP): 2.4 (1.3)	NR	NR	NR	Good response: 72/94 (76.6%) Moderate response: 87/94 (93.6%)	NR	Clinically meaningful HAQ response: 72/94 (76.6%) HAQ = 0: 46/94 (48.9%)	NR	NR
	COBRA Classic	98	52 weeks[43]	DAS28-CRP change: 2.5 (1.5) Mean (SD) AUC from baseline 35.0 (11.6)	NR	NR	NR	Good response: 67.3% Moderate response: 84.7%	NR	HAQ change: 0.7 (0.7)[i] Clinically meaningful HAQ change: 68.4% HAQ = 0: 37.8%	Change in SHS: 0.3 (0.5), (*n*) X-ray pairs = 74	NR

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	COBRA Slim	98	52 weeks	DAS28-CRP change: 2.3 (1.4)	NR	NR	NR	Good response: 68.4%	NR	HAQ change: 0.5 (0.7) Clinically meaningful HAQ change: 70.4%	Change in SHS: 0.4 (1.1), (*n*) X-ray pairs = 68	NR
				Mean (SD) AUC from baseline 35.3 (10.6)				Moderate response: 88.8%		HAQ = 0: 36.7%		
	COBRA Avant-Garde	93	52 weeks	DAS28-CRP change: 2.3 (1.5)	NR	NR	NR	Good response: 67.7%	NR	HAQ change: 0.6 (0.7)[j] Clinically meaningful HAQ change: 71.7%	Change in SHS: 0.3 (0.6), (*n*) X-ray pairs = 68	NR
				Mean (SD) AUC from baseline 33.9 (8.6)				Moderate response: 88.2%		HAQ = 0: 44.1%		

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
CareRA: low-risk patients[40,43] (52-week randomised phase)	MTX-TSU	47	16 weeks	Change from baseline (DAS28-CRP): 1.76 (1.68)	NR	NR	NR	Good response: 21/47 (44.7%)	NR	HAQ change: 0.40 (0.62) Clinically meaningful HAQ change: 25/47 (53.2%)	NR	NR
								Moderate response: 34/47 (72.3%)		HAQ = 0: 11/47 (23.4%)[t]		
	COBRA Slim	43	16 weeks	Change from baseline (DAS28-CRP): 2.12 (1.41)	NR	NR	NR	Good response: 25/43 (58.1%)	NR	HAQ change: 0.58 (0.64) Clinically meaningful HAQ change: 27/43 (62.8%)	NR	NR
								Moderate response: 34/43 (86.0%)		HAQ = 0: 22/43 (51.2%)[t]		
	MTX-TSU	47	52 weeks[43]	DAS28-CRP change: 2.1 (1.7)	NR	NR	NR	Good response: 57.4%	NR	HAQ change: 0.5 (0.6) Clinically meaningful HAQ change: 59.6%	Change in SHS: 0.2 (0.3), (*n*) X-ray pairs = 31	NR
				Mean (SD) AUC from baseline to week 52: 42.0 (13.1)[u]				Moderate response: 78.7%		HAQ = 0: 29.8%		
	COBRA Slim	43	52 weeks	DAS28-CRP change: 2.1 (1.9)	NR	NR	NR	Good response: 60.5%;	NR	HAQ change: 0.6 (0.7) Clinically meaningful HAQ change: 55.8%	Change in SHS 0.3 (0.5), (*n*) X-ray pairs = 28	NR
				Mean (SD) AUC from baseline to week 52: 5.8 (14.1)[u]				Moderate response: 76.7%		HAQ = 0: 48.8%		

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
COBRA-light[44,45] (12-month randomised phase)	COBRA	81	13 weeks	NR	NR	NR	NR	Good response: 63%[i] Non-response: 4%[i]	NR	0.52[b,o]	NR	NR
	COBRA-light	83	13 weeks	NR	NR	NR	NR	Good response: 47%[i] Non-response: 11%[i]	NR	0.62[b,o]	NR	NR
	COBRA	81	6 months	NR	1.62 (0.96)[h] Change from baseline: –2.50 (1.21)[h] DAS44-CRP change from baseline: –2.15 (1.09)[h]	NR	NR	Good response: 75%[i] Non-response: 6%[i]	NR	0.47[b,o]	NR	NR
	COBRA-light	83	6 months	NR	1.78 (1.13)[h] Change from baseline: –2.18 (1.10)[h] DAS44-CRP change from baseline: –2.10 (1.09)[h]	NR	NR	Good response: 65%[i] Non-response: 11%[i]	NR	0.56[b,o]	NR	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	COBRA	81	12 months	2.49 (1.3)	1.70 (1.0) DAS44-CRP: 1.71 (1.2) DAS44-CRP change from baseline: −2.41 (1.2)[h]	2.6 (3.6)	5.3 (7.2)	NR	ACR 70: 25/81 (31%)	0.57 (0.5)	6% erosive disease SHS: • Change in erosion score: 0.18 (0.4)[h] • Change in JSN score: 0.31 (1.5)[h] • Change in total score: 0.49 (1.6)[h]	NR
	COBRA-light	83	12 months	2.71 (1.3)	1.88 (1.0) DAS44-CRP: 1.69 (1.1) DAS44-CRP change from baseline: −2.02 (1.1)	2.3 (2.6)	5.0 (6.0)	NR	ACR 70: 28/81 (35%)	0.61 (0.6)	5% erosive disease SHS: • Change in erosion score: 0.30 (0.8)[h] • Change in JSN score: 0.27 (0.8)[h] • Change in total score: 0.59 (1.4)[h]	NR
FIN-RACo[47–49,70] (2-year randomised phase)	Combination treatment	99 (97 in ITT)	3 months[46]	NR	NR	NR	NR	NR	ACR 50: 60.6% (95% CI 49.7% to 70.2%)[b]	NR	NR	NR
	Single-drug treatment	100 (98 in ITT)	3 months	NR	NR	NR	NR	NR	ACR 50: 40.2% (95% CI 30.8% to 51.2%)[b]	NR	NR	NR
	Combination treatment	99 (97 in ITT)	6 months[46]	NR	NR	NR	NR	NR	ACR 20: (95% CI 71 to 88) ACR 50: 69.6% (95% CI 58.9% to 78.1%)[b]	NR	NR	NR

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Single-drug treatment	100 (98 in ITT)	6 months	NR	NR	NR	NR	NR	ACR 20: 78% (95% CI 69% to 86%) ACR 50: 55.4% (95% CI 45.2% to 65.6%)[b]	NR	NR	NR
	Combination treatment	99 (97 in ITT)	12 months[46]	NR	NR	NR	NR	NR	ACR 50: 74.7% (95% CI 64.0% to 82.9%)[b]	NR	NR	NR
	Single-drug treatment	100 (98 in ITT)	12 months	NR	NR	NR	NR	NR	ACR 50: 58.6% (95% CI 48.6% to 69.7%)[b]	NR	NR	NR
	Combination treatment	99 (97 in ITT)	2 years[46]	2.23 (0.33)[b,w,x]	NR	Change from baseline: –10 (95% CI –12 to –9)[y]	Change from baseline: –13 (95% CI –15 to –11)[y]	NR	ACR 20: 78% (95% CI 69/% to 80%) ACR 50: 57.1% (95% CI 46.3% to 67.3%)[b]	0.27 (0.11)[b,w] Stanford HAQ score change from baseline: –0.6 (95% CI –0.7 to –0.4)[y]	Number of eroded joints: 2 (IQR 0–5)[s,t] Larsen score: 4 (IQR 0–4)[s,z]	NR
	Single-drug treatment	100 (98 in ITT)	2 years	3.11 (0.28)[b,w,x]	NR	Change from baseline: –10 (95% CI –12 to –8)[y]	Mean change from baseline: –14 (95% CI –16 to –12)[y]	NR	ACR 20: 84% (95% CI 75% to 90%) ACR 50: 76.0% (95% CI 65.5%–84.4%)[b,p]	0.30 (0.10)[b,w] Stanford HAQ change from baseline: –0.6 (95% CI –0.8 to –0.5)[y]	Number of eroded joints: 4 (IQR 2–7)[s,t] Larsen score: 12 (IQR 4–20)[s,z]	NR
	Combination treatment	99 (97 in ITT)	5 years[47]	2.51 (0.28)[b,w,x]	NR	NR	NR	NR	NR	0.27 (0.11)[b,w]	NR	NR
	Single-drug treatment	100 (98 in ITT)	5 years	2.94 (0.28)[b,w,x]	NR	NR	NR	NR	NR	0.33 (0.12)[b,w]	NR	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Combination treatment	99 (97 in ITT)	11 years[48,49]	2.48 (1.22)[x]	NR	0 (0–3)[s]	1 (0–5)[s]	NR	NR	0.34 (0.54) HAQ score of 0: 56% HAQ score of > 1: 10%	Change from baseline in Larsen score: 17 (95% CI 12–26);[y,aa] 87% (95% CI 74% to 94%) patients in had no erosive changes in large joints	NR
	Single-drug treatment	100 (98 in ITT)	11 years	2.73 (1.23)[x]	NR	2 (IQR 0–4)[s]	2 (IQR 0–5)[s]	NR	NR	0.38 (0.58) HAQ score of 0: 43% HAQ score of > 1: 9%	Change from baseline in Larsen score: 27 (95% CI 22–33);[y,aa] 72% (95% CI 58% to 84%) patients in had no erosive changes in large joints	NR
Saunders *et al.*, 2008[54] (12-month randomised phase)	Parallel triple therapy	47	12 months	Change from baseline: –3.3 (1.6)	NR	NR	NR	Good response: 20/49 (41%)	ACR 20: 37/49 (76%) ACR 50: 25/49 (51%) ACR 70: 10/49 (20%)	Change from baseline: –0.8 (0.7)	SHS change from baseline: • Erosion score: 1.7 (2.4)[h] • JSN score: 4.8 (6.4)[h] • Total score: 6.6 (7.0)[h]	SF-12 change from baseline: 9 (SD 13)[h]
	Step-up therapy	49	12 months	Change from baseline: –4.0 (1.8)	NR	NR	NR	Good response: 28/47 (60%)	ACR 20: 36/47 (77%) ACR 50: 28/47 (60%) ACR 70: 14/47 (30%)	Change from baseline: –0.9 (0.7)	SHS change from baseline: • Erosion score: 1.1 (1.8)[h] • JSN score: 4.9 (3.9)[h] • Total score: 6.0 (5.3)[h]	SF-12 change from baseline: 10 (SD 11)

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
TEAR[58–60] (102-week randomised phase)	Immediate ETN	244	6 months	NR	NR	NR	NR	NR	ACR 20: 56.28%[b,ab] ACR 50: 32.14%[b,ab] ACR 70: 11.13%[b,ab]	NR	NR	NR
	Immediate triple therapy	132	6 months	NR	NR	NR	NR	NR	ACR 20: 55.88%[b,ab] ACR 50: 31.33%[b,ab] ACR 70: 7.97%[b,ab]	NR	NR	NR
	Step-up ETN	255	6 months	NR	NR	NR	NR	NR	ACR 20: 40.12%[b,ab] ACR 50: 19.51%[b,ab] ACR 70: 2.84%[b,ab]	NR	NR	NR
	Step-up triple therapy	124	6 months	NR	NR	NR	NR	NR	ACR 20: 39.32%[b,ab] ACR 50: 17.53%[b,ab] ACR 70: 3.62%[b,ab]	NR	NR	NR
	Immediate ETN	244	2 years	NR	NR	NR	NR	NR	ACR 20: 51.10%[b] ACR 50: 37.18%[b] ACR 70: 20.52%[b]	NR	NR	NR
	Immediate triple therapy	132	2 years	NR	NR	NR	NR	NR	ACR 20: 45.97%[b] ACR 50: 31.27%[b] ACR 70: 10.66%[b]	NR	NR	NR

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	Step-up ETN	255	2 years	NR	NR	NR	NR	NR	ACR 20: 49.11%[b] ACR 50: 32.44%[b] ACR 70: 15.77%[b]	NR	NR	NR
	Step-up triple therapy	124	2 years	NR	NR	NR	NR	NR	ACR 20: 47.92%[b] ACR 50: 37.15%[b] ACR 70: 11.43%[b]	NR	NR	NR
	Immediate ETN	244	102 weeks	3.0 (1.4); $n = 159$ (DAS28-ESR)	NR	2.2 (3.9); $n = 159$	3.3 (5.5)	NR	NR	mHAQ: 1.0 (0.3); $n = 15$	SHS: • Erosions: 3.6 (7.4);[h] $n = 159$ • JSN: 3.7 (9.8);[h] $n = 159$ • Total SHS: 7.0 (16.6);[h] $n = 159$	NR
	Immediate triple therapy	132	102 weeks	2.9 (1.5); $n = 76$ (DAS28-ESR)	NR	2.3 (3.3); $n = 76$	2.6 (4.5); $n = 76$	NR	NR	mHAQ: 1.0 (0.3); $n = 73$	SHS: • Erosions: 3.3 (3.9);[h] $n = 76$ • JSN: 3.9 (10.6);[h] $n = 76$ • Total SHS: 7.3 (13.3);[h] $n = 76$	NR
	Step-up ETN	255	102 weeks	3.0 (1.4); $n = 166$ (DAS28-ESR)	NR	4.4 (3.1); $n = 166$	3.6 (5.8); $n = 166$	NR	NR	mHAQ: 0.9 (0.3); $n = 154$	SHS: • Erosions: 3.0 (3.9);[h] $n = 166$ • JSN: 2.1 (4.4);[h] $n = 166$ • Total SHS: 4.8 (7.2);[h] $n = 166$	NR
	Step-up triple therapy	124	102 weeks	2.8 (1.3); $n = 75$ (DAS28-ESR)	NR	4.4 (2.8); $n = 75$	2.6 (4.4); $n = 75$	NR	NR	mHAQ: 0.9 (0.3); $n = 71$	SHS: • Erosions: 3.3 (4.4);[h] $n = 75$ • JSN: 2.6 (5.0);[h] $n = 75$ • Total SHS: 6.2 (8.9);[h] $n = 75$	NR

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
U-Act-Early[62] (104-week randomised phase)	TOC + MTX	108	24 weeks	Decrease from baseline: median 3.6 (range 0.75–7.48)[ac]	NR	1.0 (2.1); $n = 98$	2.8 (4.9); $n = 98$[ad]	Good response: 93/105 (89%)[ae]	ACR 20: 79/105 (75%)[af] ACR 50: 67/105 (64%)[af]	D-HAQ: 0.50 (0.55); $n = 94$[ag]	NR	NR
								Moderate response: 5/105 (5%)[ae]	ACR 70: 46/105 (44%)[af] ACR 90: 19/105 (18%)[af]			
	TOC + PBO–MTX	106	24 weeks	Decrease from baseline: 3.6 (range 0.45–7.64)[ac,ah]	NR	1.6 (2.8); $n = 96$[ac]	3.0 (3.9); $n = 96$[ad]	Good response: 84/97 (87%)[ae]	ACR 20: 77/102 (75%)[af] ACR 50: 60/102 (59%)[af]	D-HAQ: 0.63 (0.66); $n = 96$[ag]	NR	NR
								Moderate response: 11/97 (11%)[ae]	ACR 70: 38/102 (37%)[af] ACR 90: 12/102 (12%)[af]			
	MTX + PBO–TOC	103	24 weeks	Decrease from baseline: 2.1 (range 1.67–5.11)[ac,ah]	NR	3.0 (4.4); $n = 96$[ac]	3.7 (4.8); $n = 96$[ad]	Good response: 50/103 (49%)[ae]	ACR 20: 63/106 (59%)[af] ACR 50: 36/106 (34%)[af]	D-HAQ: 0.65 (0.54); $n = 87$[ag]	NR	NR
								Moderate response: 33/103 (32%)[ae]	ACR 70: 16/106 (15%)[af] ACR 90: 5/106 (5%)[af]			
	TOC + MTX	108	52 weeks	Decrease from baseline: 3.3 (range 1.02–7.48)[ah]	NR	0.6 (1.5); $n = 84$	2.4 (4.3); $n = 84$	Good response: 75/100 (75%)	ACR 20: 74/99 (75%) ACR 50: 61/99 (62%)	D-HAQ: 0.46 (0.50); $n = 83$[ag]	Change in SHS: 0.50 (1.495)[h,j]	NR
								Moderate response: 6/100 (6%)[ai]	ACR 70: 44/99 (44%) ACR 90: 19/99 (19%)[xl]			

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	TOC + PBO–MTX	106	52 weeks	Decrease from baseline: 3.4 (range 0.28–7.66)[ah]	NR	1.0 (1.7); *n* = 91	1.9 (3.6); *n* = 91	Good response: 85/96 (88%) Moderate response: 4/96 (4%)[ai]	ACR 20: 71/99 (72%) ACR 50: 58/99 (59%) ACR 70: 44/99 (44%) ACR 90: 21/99 (21%)[ak]	D-HAQ: 0.48 (0.55); *n* = 82%	Change in SHS: 0.79 (3.242)[h,j]	NR
	MTX + PBO–TOC	103	52 weeks	Decrease from baseline: 3.3 (range 0.74–6.13)[ah]	NR	0.8 (1.6); *n* = 84	2.7 (4.2); *n* = 84	Good response: 71/99 (72%) Moderate response: 7/99 (7%)[ai]	ACR 20: 71/103 (69%) ACR 50: 53/103 (51%) ACR 70: 34/103 (33%) ACR 90: 7/103 (7%)[ak]	D-HAQ:[al] 0.55 (0.51); *n* = 84%	Change in SHS: 0.96 (2.870)[h,j]	NR
	TOC + MTX	108	104 weeks	Decrease from baseline: 3.3 (range 0.73–6.07)[ah]	NR	0.8 (1.6), median 0; *n* = 76	2.5 (5.0); *n* = 76	Good response: 63/96 (66%) Moderate response: 8/96 (8%)[am]	ACR 20: 61/96 (63%) ACR 50: 47/96 (49%) ACR 70: 35/96 (36%) ACR 90: 20/96 (21%)	D-HAQ:[al] 0.48 (0.55); *n* = 70[an]	Change in SHS: 1.18 (3.919)[h,o]	NR

continued

TABLE 76 Disease activity outcomes: comparison of different treatment protocols – early RA population (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Number of participants[a]	Follow-up time point	Outcome								
				Mean DAS28 (SD)	DAS44 (SD)	Mean SJC (0–66) (SD)	Mean TJC (0–68) (SD)	EULAR good/ moderate/none	ACR 20/50/70	Mean HAQ score (SD)	Joint erosion	Quality of life
	TOC + PBO–MTX	106	104 weeks	Decrease from baseline: 3.3 (range 0.1–6.8)[ah]	NR	0.7 (1.7); *n* = 82	2.0 (3.3); *n* = 82	Good response: 72/95 (76%)	ACR 20: 62/95 (65%) ACR 50: 52/95 (55%)	D-HAQ:[al] 0.61 (0.61); *n* = 77[an]	Change in SHS: 1.45 (4.272)[h,o]	NR
								Moderate response: 8/95 (8%)[am]	ACR 70: 37/95 (39%) ACR 90: 19/95 (20%)			
	MTX + PBO–TOC	103	104 weeks	Decrease from baseline: 3.2 (range 0.79–7.52)[ah]	NR	1.1 (2.3); *n* = 75	2.5 (4.4); *n* = 75	Good response: 65/96 (68%)	ACR 20: 60/99 (61%) ACR 50: 48/99 (48%)	D-HAQ:[al] 0.62 (0.50); *n* = 73[an]	Change in SHS: 1.53 (2.421)[h,o]	NR
								Moderate response: 8/96 (8%)[am]	ACR 70: 35/99 (35%) ACR 90: 14/99 (14%)			

AUC, area under the curve; ITT, intention to treat; MCS, Mental Components score; NR, not reported; PCS, Physical Components Score.
a Randomised.
b Converted from graphical data.
c *n* not reported.
d $p < 0.05$, groups 1 and 2 vs. groups 3 and 4.
e Mean change from baseline.
f $p < 0.05$, groups 1 and 2 vs. groups 3 and 4.
g $p < 0.05$, group 1 vs. groups 3 and 4.
h Mean (SD).
i *n* not reported.
j $p < 0.05$, group 1 vs. groups 3 and 4 and group 2 vs. group 4.
k Median.
l $p = 0.007$ group 1 vs. group 4.
m $p < 0.001$ group 1 vs. group 4.
n $p = 0.004$ group 2 vs. group 4.
o $p < 0.05$.
p Mean.
q $p < 0.05$, groups 1 and 2 vs. group 4.
r $p < 0.05$, group 2 vs. group 4.

s Median (IQR).
t $p = 0.006$.
u $p = 0.017$ across low-risk groups.
v $p = 0.05$.
w Not reported if variance is SD or SE.
x Significant treatment effect over time, $p = 0.0022$.
y Mean (95% CI).
z $p = 0.002$.
aa $p = 0.037$.
ab $p < 0.0001$, groups 1 and 2 vs. groups 3 and 4.
ac $p < 0.0001$ across groups.
ad $p = 0.0176$ across groups.
ae TOC + MTX vs. MTX, $p < 0.0001$; TOC vs. MTX, $p < 0.0001$; TOC + MTX vs. TOC, $p = 0.43$.
af ACR 20: TOC + MTX vs. MTX, $p = 0.0099$; TOC vs. MTX, $p = 0.0343$; ACR 50: TOC + MTX vs. MTX, $p < 0.0001$; TOC vs. MTX, $p = 0.0009$; ACR 70: TOC + MTX vs. MTX, $p < 0.0001$; TOC vs. MTX, $p = 0.0003$; ACR 90: TOC + MTX vs. MTX, $p = 0.0027$.
ag $p = 0.0275$ across groups.
ah Median (range).
ai OC + MTX vs. MTX, $p = 0.26$; TOC vs. MTX, $p = 0.0074$; TOC + MTX vs. TOC, $p = 0.06$.
aj TOC + MTX vs. MTX, $p = 0.0164$; TOC vs. MTX, $p = 0.06$; TOC + MTX vs. TOC, $p = 0.49$.
ak ACR 90: TOC + MTX vs. MTX, $p = 0.0045$; TOC vs. MTX, $p = 0.0026$.
al Adjusted for centre and baseline HAQ score and DAS28.
am TOC + MTX vs. MTX, $p = 0.87$; TOC vs. MTX, $p = 0.13$; TOC + MTX vs. TOC, $p = 0.10$.
an $p = 0.06$ across groups.
ao TOC + MTX vs. MTX, $p = 0.0207$; TOC vs. MTX, $p = 0.0381$; TOC + MTX vs. TOC, $p = 0.53$.

Appendix 7 Tables of specific adverse events

TABLE 77 Specific AEs: comparison of TTT vs. usual care – early RA population

				AEs, *n*/*N* (%)[a]								
Trial acronym	Treatment arm	Safety population, *n*	Follow-up time point	Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
STREAM[55]	Aggressive group	NR	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Conventional care	NR	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
T-4 study[56,57]	Routine care	61	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR
	DAS28-driven therapy	59	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR
	MMP-3-driven therapy	59	56 weeks	NR	NR	NR	NR	NR	NR	1 (1.7)[b]	NR	NR
	DAS28 and MMP-3-driven therapy	61	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR

NR, not reported.
a Refers to numbers of patients unless otherwise specified.
b Serious infection.

TABLE 78 Specific AEs: comparison of TTT vs. usual care – established RA population

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
Fransen *et al.*, 2005[50]	DAS28	205	24 weeks	NR	NR	NR	Rash or itching 4%[b]	NR	Nausea or vomiting 4%[b]	NR	NR	NR
	Usual care	179	24 weeks	NR	NR	NR	Rash or itching 11%[b]	NR	Nausea or vomiting 9%[b]	NR	NR	NR
Optimisation of Adalimumab study[52,53]	Routine care	100	18 months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	DAS28 target	109	18 months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SJC target	99	18 months	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported.
a Refers to numbers of patients unless otherwise specified.
b $p < 0.05$.

TABLE 79 Specific AEs: comparison of TTT vs. usual care – studies with a combined early and established RA population

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
TICORA[61]	Intensive management	55	18 months	NR	NR	NR	10 AEs	NR	18 AEs	5 AEs	NR	• Abnormal liver function, *n* = 8 • CNS, *n* = 1 • Haematological, *n* = 2 • Others, *n* = 2
	Routine management	55	18 months	NR	NR	NR	15 AEs	NR	25 AEs	7 AEs	NR	• Abnormal liver function, *n* = 16 • CNS, *n* = 9 • Haematological, *n* = 6 • Others, *n* = 7
Van Hulst *et al.*, 2010[63]	Intervention group	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Usual-care group	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

CNS, central nervous system; NR, not reported.
a Refers to the number of patients unless otherwise specified.

TABLE 80 Specific AEs: early RA population – comparison of different targets

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
Hodkinson *et al.*, 2015[51]	SDAI arm	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CDAI arm	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
T-4 study[56,57]	Routine care	61	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR
	DAS28-driven therapy	59	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR
	MMP-3-driven therapy	59	56 weeks	NR	NR	NR	NR	NR	NR	1 (1.7)[b]	NR	NR
	DAS28 and MMP-3-driven therapy	61	56 weeks	NR	NR	NR	NR	NR	NR	0 (0)[b]	NR	NR
TEAR[58–60]	Immediate ETN	244	102 weeks	1 AE	0	• Cardiac, $n = 5$ • Vascular, $n = 0$	1 AE	0	2 AEs[c]	9 AEs[c]	3 AEs[c]	• Blood and lymphatic system, $n = 1$ • Immune system, $n = 1$ • Injury and poisoning, $n = 2$[c] • Neoplasms, benign and malignant, $n = 5$[c] • Nervous system, $n = 2$[c] • Respiratory, thoracic and mediastinal, $n = 5$[c] • Surgical and medical procedures, $n = 6$[c]

continued

TABLE 80 Specific AEs: early RA population – comparison of different targets (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]							
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Immediate triple therapy	132	102 weeks	0	0	• Cardiac, $n = 2$[c] • Vascular, $n = 3$[c]	0	0	5 AEs[c]	4 AEs[c]	0	• Blood and lymphatic system, $n = 1$ • Neoplasms AE, benign and malignant, $n = 1$ • Nervous system, $n = 1$ • Pregnancy, puerperium and perinatal, $n = 1$ • Surgical and medical procedures, $n = 5$[c]
	Step-up ETN	255	102 weeks	4 AEs[c]	0	• Cardiac, $n = 4$[c] • Vascular, $n = 3$[c]	2 AEs[c]	0	0	7 AEs[c]	0	• Injury and poisoning, $n = 1$ • Nervous system, $n = 2$ • Pregnancy, puerperium and perinatal, $n = 1$ • Reproductive system and breast, $n = 3$[c] • Respiratory, thoracic and mediastinal, $n = 3$[c] • Surgical and medical procedures, $n = 7$[c]

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Step-up triple therapy	124	102 weeks	0	2 AEs[c]	• Cardiac, *n* = 0 • Vascular, *n* = 0	0	1 AE	0	3 AEs[c]	1 AE	• Blood and lymphatic system, *n* = 1 • Injury and poisoning, *n* = 1 • Neoplasms, benign and malignant, *n* = 1 • Nervous system, *n* = 2[c] • Respiratory, thoracic and mediastinal, *n* = 1 • Surgical and medical procedures, *n* = 1

NR, not reported.
a Refers to number of patients unless otherwise specified.
b Serious infection.
c Number of patients not reported.

TABLE 81 Adverse events: early RA population – comparison of different treatment protocols

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
BeSt[30,31,33]	Sequential monotherapy	126	1 year[30]	≥ 1 AE: 54 (43%)	8/126 (6.3) defined as life-threatening condition or death, a significant or permanent disability, a malignancy, hospitalisation or prolongation of hospitalisation, a congenital abnormality, or a birth defect Hospitalised, *n* = 8: • Hypertension, *n* = 1 • Transient ischaemic attack, *n* = 1 • Pulmonary embolism, *n* = 1 • Pneumonia, *n* = 1 • Herpes simplex encephalitis, *n* = 1 • Hip prosthesis operation, *n* = 1 • Fever associated with SSZ, *n* = 1 • For active arthritis with revision of diagnosis to gout, *n* = 1	NR	NR
	Step-up combination therapy	121	1 year	≥ 1 AE: 57 (47%)	9/121 (7.4) Hospitalised, *n* = 10: • Peripheral bypass operation, *n* = 1 • Pacemaker implantation, *n* = 1 • A prolapsed vertebral disk, *n* = 1 • Neuropathy, *n* = 1 • Hip prosthesis operation, *n* = 1 • Diffuse peritonitis, *n* = 1 • Exacerbations of RA, *n* = 2 • Malignancy (bladder carcinoma), *n* = 1	NR	NR

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]

	Initial combination therapy with PDN	133	1 year	≥ 1 AE: 49 (37%)	17/133 (12.8)
					
					Hospitalised, *n* = 20:
					
					• Myocardial infarction, *n* = 3
					• Heart failure, *n* = 1
					• Oral herpes simplex infection, *n* = 1
					• Hip fracture, *n* = 1
					• Hip pain, *n* = 1
					• Granulocytopenia, *n* = 1
					• Urinary tract stone, *n* = 1
					• Temporal arteritis, *n* = 1
					• Exacerbation of RA, *n* = 2
					• Excision of benign microcalcifications viewed on mammography, *n* = 1
					• Appendectomy, *n* = 2
					• Malignancies, *n* = 2:
					  ○ Breast cancer, *n* = 1
					  ○ Lymphoma, *n* = 1
						NR	NR

	Initial combination therapy with IFX	128	1 year	≥ 1 AE: 50 (39%)	6/128 (4.7) Hospitalised, *n* = 6: • Transient cardiac ischemia, *n* = 1 • Pulmonary embolism, *n* = 1 • Peripheral vascular disease, *n* = 1; • Pneumonia, *n* = 1 • Septic arthritis, *n* = 1 • MTX pneumonitis, *n* = 1	Transient cardiac ischaemia, pulmonary embolism NR	NR
	Sequential monotherapy	126	5 years[31]	110 (87%)	42 (33)	3/126 (2.38%): • Pneumonia • Pneumonia/encephalitis • Non-small cell lung • Carcinoma	NR

continued

TABLE 81 Adverse events: early RA population – comparison of different treatment protocols (*continued*)

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
	Step-up combination therapy	121	5 years	103 (85)	34 (28)	3/121 (2.48): • Cerebrovascular accident • Bronchial carcinoma • Myocardial infarction	NR
	Initial combination therapy with PDN	133	5 years	112 (84)	37 (28)	2/133 (1.5): • Ovarian carcinoma • Cerebrovascular accident	NR
	Initial combination therapy with IFX	128	5 years	112 (88)	37 (31)	4/128 (3.1): • Disseminated tuberculosis • Myocardial infarction • Septic arthritis • Cerebrovascular accident	NR
	Sequential monotherapy	126	10 years[33]	NR	NR	16 (12.7)	NR
	Step-up combination therapy	121	10 years	NR	NR	15 (12.4)	NR
	Initial combination therapy with PDN	133	10 years	NR	NR	21 (15.8)	NR
	Initial combination therapy with IFX	128	10 years	NR	NR	20 (15.6)	NR

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
CareRA: high-risk patients[42,43]	COBRA Classic	91	16 weeks	56/91 (61.2)[c] (therapy related)	2 AEs[d]	0/91 (0)	2/91 (2)
	COBRA Slim	96	16 weeks	45/96 (46.9)[c] (therapy related)	1 AE	1/96 (1)	0/96 (0)
	COBRA Avant-Garde	91	16 weeks	63/91 (69.1)[c] (therapy related)	3 AEs[d]	0/91 (0)	0/91 (0)
	COBRA Classic	98	52 weeks	66/98 (67.3) (therapy related); mean *n* AEs per patient = 1.9 (2.0)[e]	2 AEs (therapy related)[d]	1/98 (1)	0
	COBRA Slim	98	52 weeks	65/98 (66.3) (therapy related); mean *n* AEs per patient = 1.3 (1.4)[e]	2 AEs (therapy related)[d]	1/98 (1)	0
	COBRA Avant-Garde	93	52 weeks	73/93 (78.5) (therapy related); mean *n* AEs Per patient = 1.9 (1.6)[e]	2 AEs (therapy related)[d]	0/93 (0)	0
CareRA: low-risk patients[40,43]	MTX-TSU	47	16 weeks	32 (68.1) (therapy related)	0/47	NR	NR
	COBRA Slim	43	16 weeks	30 (69.8) (therapy related)	0/43	NR	NR
	MTX-TSU	47	52 weeks	30/47 (63.8) (therapy related); mean *n* AEs per patient 1.2 (1.2)	0	0/47 (0)	0
	COBRA Slim	43	52 weeks	22/43 (51.2) (therapy related); mean *n* AEs per patient 1.2 (1.5)	2 AEs (therapy related)[d]	0/43 (0)	0

continued

TABLE 81 Adverse events: early RA population – comparison of different treatment protocols (*continued*)

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n/N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
COBRA-light[44,45]	COBRA	81	6 months[44]	≥ 1 AE: 94%	*n* = 3: • Myocardial infarction, *n* = 1 • Planned cataract operation, *n* = 1 • Planned operation of the cervical spine, *n* = 1	NR	1 manic episode
	COBRA-light	81	6 months	≥ 1 AE: 90%	• *n* = 6: • Planned knee replacement, *n* = 1 • Planned hallux valgus surgery, *n* = 1 • Planned varicose vein surgery, *n* = 1 • planned control colonoscopy for diverticulosis, *n* = 1 • Hospitalisation for arrhythmia, *n* = 1 • Manic episode, *n* = 1	NR	1 myocardial infarction
	COBRA	81	12 months[45]	NR	*n* = 9: • Myocardial infarction, *n* = 1 • Pulmonary embolism, *n* = 1 • Hospitalisation for pneumonia, *n* = 1 • Planned cataract surgery on both eyes (2×), *n* = 2 • Planned surgery of the cervical spine, *n* = 1 • Attempted suicide because of depression, *n* = 1 • Fibula fracture caused by MTX osteopathy, *n* = 1 • Pelvis fracture, *n* = 1 Numbers of SAEs or patients not reported. Patient numbers not reported	NR	NR

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
	COBRA-light	81	12 months	NR	*n* = 16: • Lung carcinoma, *n* = 2 • Planned knee replacement surgery, *n* = 2 • Planned hallux valgus surgery, *n* = 1 • Planned varicose vein surgery, *n* = 1 • Planned control colonoscopy for diverticulitis, *n* = 1 • Hospitalisation for arrhythmia, *n* = 1 • Manic episode, *n* = 1 • Replacement and hospitalisation for a retina bleeding, *n* = 1 • Planned surgery for cyst removal, *n* = 1 • Hospitalisation for anaemia caused by duodenal ulcers, *n* = 1 • Planned cholecystectomy, *n* = 1 • Surgery for an inguinal hernia, *n* = 1 • Hospitalisation and surgery for a hip fracture after a fall, *n* = 1 • Surgery for chronic synovitis, *n* = 1 Patient numbers not reported	NR	NR
FIN-RACo[46]	Combination treatment	97	2 years	68 (70)	SAEs (necessitating hospital admission, life-threatening, fatal or malignant disease), *n* = 3 (3%)	0	0
	Single-drug treatment	98	2 years	70 (71)	SAEs (necessitating hospital admission, life-threatening, fatal or malignant disease), *n* = 5 (5%)	0	0
Saunders 2008[54]	Parallel triple therapy	NR	12 months	141 AEs, *n* patients not reported	NR	NR	0 withdrawal from trial (15 drug withdrawals)
	Step-up therapy	NR	12 months	135 AEs, *n* patients not reported	NR	NR	0 withdrawal from trial (18 drug withdrawals)

continued

TABLE 81 Adverse events: early RA population – comparison of different treatment protocols (*continued*)

Trial	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n/N* (%)			
				Any AE[a]	Any SAE[a,b]	Death	Withdrawals as a result of an AE[a]
TEAR[58]	Immediate ETN	244	102 weeks	193 (79.1)	35 (14.3)	1	12 (4.9): • SAE, *n* = 8 • AE, *n* = 3 • Death, *n* = 1
	Immediate triple therapy	132	102 weeks	101 (76.5)	18 (13.6)	1	7 (5.3): • SAE, *n* = 2; • AE, *n* = 4 • Death, *n* = 1
	Step-up ETN	255	102 weeks	187 (73.3)	32 (12.5)	2	9 (3.5): • SAE, *n* = 2 • AE, *n* = 5 • Death, *n* = 2
	Step-up triple therapy	124	102 weeks	92 (74.2)	16 (12.9)	0	4 (3.2): • SAE, *n* = 2 • AE, *n* = 2 • Death, *n* = 0

NR, not reported.
a Refers to the number of patients, unless otherwise specified.
b Defined in the trial as a SAE.
c Between-group difference $p = 0.006$.
d Patient *n* not reported.
e $p = 0.028$ across high-risk groups.

TABLE 82 Specific AEs: early RA population – comparison of different treatment protocols

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
BeSt[30,31,33]	Sequential monotherapy	126	1 year[30]	NR	NR	3 (2)	12 (10)	NR	20 (16)	5 (4)	NR	NR
	Step-up combination therapy	121	1 year	NR	NR	2 (2)	15 (12)	NR	18 (15)	8 (7)	NR	NR
	Initial combination therapy with PDN	133	1 year	NR	NR	8 (6)	12 (9)	NR	11 (8)	10 (8)	NR	NR
	Initial combination therapy with IFX	128	1 year	NR	NR	2 (2)	8 (6)	NR	14 (11)	10 (8)	NR	NR
	Sequential monotherapy	126	5 years[31]	NR	NR	20 (16)	Dermal/mucosal: 34 (27)	NR	56 (44)	56 (44). Serious infection: 13 (10.3)	NR	Malignancies: 5 (4) Neurological: 27 (21) Infusion reactions 3/52 infusions
	Step-up combination therapy	121	5 years	NR	NR	21 (17)	Dermal/mucosal: 36 (30)	NR	55 (46)	51 (42). Serious infection: 5 (4.1)	NR	Malignancies: 4 (3.3) Neurological: 30 (25) Infusion reactions: 0/15 infusions
	Initial combination therapy with PDN	133	5 years	NR	NR	36 (27)	Dermal/mucosal: 39 (29)	NR	48 (36)	53 (40). Serious infection: 7 (5.3)	NR	Malignancies: 6 (4.5) Neurological: 22 (17) Infusion reactions: 3/28 infusions

continued

TABLE 82 Specific AEs: early RA population – comparison of different treatment protocols (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Initial combination therapy with IFX	128	5 years	NR	NR	26 (20)	Dermal/mucosal: 24 (19)	NR	57 (45)	61 (48). Serious infection: 9 (7.0)	NR	Malignancies: 4 (3.1) Neurological: 25 (20) Infusion reactions: 11/120 infusions
CareRA: high-risk patients[42,43]	COBRA Classic	91	16 weeks	NR	NR	NR	Discomfort: 111 AEs[b]	NR	NR	5 AEs[b]	NR	Toxicity: 27 AEs[b] Others: 4 AEs[b] Surgery: 1 AE
	COBRA Slim	96	16 weeks	NR	NR	NR	Discomfort: 50 AEs[b]	NR	NR	3 AEs[b]	NR	Toxicity: 10 AEs[b] Others: 7 AEs[b]
	COBRA Avant-Garde	91	16 weeks	NR	NR	NR	Discomfort: 96 AEs[b]	NR	NR	5 AEs[b]	NR	Toxicity: 23 AEs[b] Others: 6 AEs[b]
	COBRA Classic	98	52 weeks	NR	NR	NR	Itch and rash: 4 AEs[b]	0	45 AEs[b]	11 AEs[b]	NR	Malaise: 52 AEs[b] Liver function abnormalities: 17 AEs[b] Hair loss: 7 AEs[b] Changed in appetite related: 18 AEs[b] GC related: 9 AEs[b] Blood level related: 7 AEs[b] Diabetes related: 2 AEs[b] Visual impairment related: 0 AEs[b] Kidney function abnormalities: 1 AE[b] Miscellaneous: 11 AEs[b]

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	COBRA Slim	98	52 weeks	NR	NR	NR	Itch and rash: 3 AEs[b]	Visual impairment related: 1 AE[b]	48 AEs[b]	8 AEs[b]	NR	Malaise: 22 AEs[b] Liver function abnormalities: 17 AEs[b] Hair loss: 10 AEs[b] Changed appetite related: 3 AEs[b] GC related: 5 AEs[b] Blood level related: 3 AEs[b] Diabetes related: 1 AE[b] Visual impairment related: 1 AE[b] Kidney function abnormalities: 0 AEs Miscellaneous: 10 AEs[b]
	COBRA Avant-Garde	93	52 weeks	NR	NR	NR	Itch and rash: 1 AE [b]	0	67 AEs[b]	7 AEs[b]	NR	Malaise: 30 AEs[b] Liver function abnormalities: 22 AEs[b] Hair loss: 16 AEs[b] Change in appetite related: 9 AEs[b] GC related: 7AEs[b] Blood level related: 4 AEs[b] Diabetes related: 2 AEs[b] Visual impairment related: 0 AEs[b] Kidney function abnormalities: 0 AEs[b] Miscellaneous: 10 AEs[b]

continued

TABLE 82 Specific AEs: early RA population – comparison of different treatment protocols (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
CareRA: low-risk patients[40,43]	MTX-TSU	47	16 weeks	NR	NR	NR	NR	NR	11/47 (23.4)	1/47 (2)	NR	NR
	COBRA Slim	43	16 weeks	NR	NR	NR	NR	NR	10/43 (23.3)	0/43 (0)	NR	NR
	MTX-TSU	47	52 weeks	NR	NR	NR	Itch and rash: 3 AEs[b]	Visual impairment related: 1 AE[b]	20 AEs[b]	7 AEs[b]	NR	Malaise: 11 AEs[b] Liver function abnormalities: 6 AEs[b] Hair loss: 3 AEs[b] Change in appetite in related: 0 AEs[b] GC related: 0 AEs[b] Blood level related: 0 AEs[b] Diabetes related: 1 AE[b] Visual impairment related: 1 AE[b] Kidney function abnormalities: 2 AEs[b] Miscellaneous: 0 AEs[b]
	COBRA Slim	43	52 weeks	NR	NR	NR	Itch and rash: 2 AEs[b]	Visual impairment related: 2 AEs[b]	15 AEs[b]	2 AEs[b]	NR	Malaise: 12 AEs[b] Liver function abnormalities: 3 AEs[b] Hair loss: 5 AEs[b] Change in appetite related: 4 AEs[b] GC related: 0 AEs[b] Blood level related: 2 AEs[b] Diabetes related: 0 AEs[b]

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
												Visual impairment related: 2 AEs[b] Kidney function abnormalities: 0 AEs[b] Miscellaneous: 4 AEs[b]
COBRA-light[44,45]	COBRA	81	6 months	NR	NR	0	37%	NR	42%	42%	NR	≥ 5-kg gain in weight, reported as *n* = 7 (9%) (suggests safety *n* of 78). New diagnosis of type 2 diabetes, reported as *n* = 2. Hypertension reported as *n* = 1
	COBRA-light	81	6 months	NR	NR	1 (myocardial infarction)	43%	NR	42%	40%	NR	≥ 5-kg gain in weight, reported as *n* = 14 (18%) (suggests safety *n* of 78)
FIN-RACo[46]	Combination treatment	97	2 years	23 (24)	NR	NR	NR	NR	29 (30)	NR	NR	• Hypertension, *n* = 2 • Respiratory, *n* = 14 (14) • Central nervous system, *n* = 12 (12) • Alanine aminotransferase and alkaline phosphatase > 2 × normal concentration, *n* = 11 (11) • Urogenital, *n* = 8 (8) • Haematological, 7 (8)

continued

TABLE 82 Specific AEs: early RA population – comparison of different treatment protocols (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Single-drug treatment	98	2 years	16 (16)	NR	NR	NR	NR	30 (31)	NR	NR	• Respiratory, *n* = 14 (14) • Central nervous system, *n* = 9 (9) • Alanine aminotransferase and alkaline phosphatase > 2 × normal, *n* = 23 (23) • Urogenital, *n* = 10 (10) • Haematological, *n* = 7 (7)
Saunders *et al.*, 2008[54]	Parallel triple therapy	NR	12 months	NR	NR	NR	19 mucocutaneous AEs[b]	NR	52 gastrointestinal AEs;[b] 5 abnormal liver function tests[b]	29 infective AEs[b]	NR	• Haematological, *n* =8[b] • Neurological, *n* = 6[b] • Other, *n* = 22[b]
	Step-up therapy	NR	12 months	NR	NR	NR	16 mucocutaneous AEs[b]	NR	48 gastrointestinal AEs;[b] and 6 abnormal liver function tests[b]	27 infective AEs[b]	NR	• Haematological, *n* =8[b] • Neurological, *n* = 13[b] • Other, *n* = 17[b]

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
TEAR[58]	Immediate ETN	244	102 weeks	1 AE	0	• Cardiac, *n* = 5[b] • Vascular, *n* = 0	1 AE	0	2 AEs[b]	9 AEs[b]	3 AEs[b]	• Blood and lymphatic system, *n* = 1 • Immune system, *n* = 1 • Injury and poisoning, *n* = 2[b] • Neoplasms, benign and malignant, *n* = 5[b] • Nervous system, *n* = 2[b] • Respiratory, thoracic and mediastinal, *n* = 5[b] • Surgical and medical procedures, *n* = 6[b]
	Immediate triple therapy	132	102 weeks	0	0	• Cardiac, *n* = 2[b] • Vascular, *n* = 3[b]	0	0	5 AEs[b]	4 AEs[b]	0	• Blood and lymphatic system, *n* = 1 • Neoplasms, benign and malignant, *n* = 1 • Nervous system, *n* = 1 • Pregnancy, puerperium and perinatal, *n* = 1 • Surgical and medical procedures, *n* = 5[b]

continued

TABLE 82 Specific AEs: early RA population – comparison of different treatment protocols (*continued*)

Trial acronym or first author and year of publication	Treatment arm	Safety population, *n*	Follow-up time point	AEs, *n*/*N* (%)[a]								
				Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Step-up ETN	255	102 weeks	4 AEs[b]	0	• Cardiac, *n* = 4[b] • Vascular, *n* = 3[b]	2 AEs[b]	0	0	7 AEs[b]	0	• Injury and poisoning, *n* = 1 • Nervous system, *n* = 2[b] • Pregnancy, puerperium and perinatal, *n* = 1, • Reproductive system and breast, *n* = 3[b] • Respiratory, thoracic and mediastinal, *n* = 3[b] • Surgical and medical procedures, *n* = 7[b]
	Step-up triple therapy	124	102 weeks	0	2 AEs[b]	• Cardiac, *n* = 0 • Vascular, *n* = 0	0	1 AE	0	3 AEs[b]	1 AE	• Blood and lymphatic system, *n* = 1 • Injury and poisoning, *n* = 1 • Neoplasms, benign and malignant, *n* = 1 • Nervous system, *n* = 2[b] • Respiratory, thoracic and mediastinal, *n* = 1 • Surgical and medical procedures, *n* = 1

NR, not reported.
a Refers to the number of patients, unless otherwise specified.
b Patient *n* not reported.

TABLE 83 Specific AEs: early RA population – other comparisons

				AEs, *n*/*N* (%)[a]								
Trial acronym	Treatment arm	Safety population, *n*	Follow-up time point	Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
CAMERA[35]	Intensive strategy group	149	2 years	NR	NR	• 4 (2.7) patients experienced 6 AEs in 3191 evaluations	• 80 (53.7) patients experienced 373 mucocutaneous AEs in 3191 evaluations[b]	NR	• 99 (66.4) patients experienced 576 gastrointestinal AEs in 3191 evaluations[c] • 3 (2.0) patients experienced 7 gastrointestinal AEs in 3191 evaluations	NR	NR	• 88 (59.1) patients experienced 453 CNS AEs in 3191 evaluations[d] • 82 (55.0) patients experienced 550 hepatic AEs in 3191 evaluations[d] • 58 (38.9) patients experienced 326 renal AEs in 3191 evaluations • 38 (25.5) patients experienced 178 haematological AEs in 3191 evaluations[d] • 21 (14.1) patients experienced 44 lung symptom AEs in 3191 evaluations • 4 (2.7) patients experienced 4 lung finding AEs in 3191 evaluations; 27% patients experienced general AE[e]

continued

TABLE 83 Specific AEs: early RA population – other comparisons (*continued*)

				AEs, *n*/*N* (%)[a]								
Trial acronym	Treatment arm	Safety population, *n*	Follow-up time point	Musculoskeletal	Endocrine and metabolic	Cardiovascular	Dermatological	Ophthalmological	Gastrointestinal	Infectious	Psychological	Other
	Conventional strategy group	140	2 years	NR	NR	0	• 56 (40.0) patients experienced 161 mucocutaneous AEs in 1132 evaluations[b]	NR	• 75 (53.6) patients experienced 215 GI symptom AEs in 1132 evaluations[c] • 1 (0.7) patient experienced 2 GI finding AEs in 1132 evaluations	NR	NR	• 54 (38.6) patients experienced 169 CNS AEs in 1132 evaluations[d] • 49 (35.0) patients experienced 163 hepatic AEs in 1132 evaluations[d] • 62 (44.3) patients experienced 178 renal AEs in 1132 evaluations • 15 (10.7) patients experienced 38 haematological AEs in 1132 evaluations[d] • 19 (13.6) patients experienced 33 lung symptoms AEs in 1132 evaluations • 3 (2.1) patients experienced 3 lung finding AEs in 1132 evaluations • 15% patients experienced general AE[e]

CNS, central nervous system; NR, not reported.
a Refers to the number of patients, unless otherwise specified.
b $p = 0.025$.
c $p = 0.030$.
d $p = 0.001$.
e $p = 0.015$.

EME
HS&DR
HTA
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